International Journal of Research in Medical Sciences
Rasool S et al. Int J Res Med Sci. 2019 Oct;7(10):3882-3886
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20194326

Original Research Article

Fungal infections in patients with chronic liver disease: mortality and associated risk factors

Shahid Rasool[1]*, Ahmad N. Babar[1], Umair Shafquat[1], Salman Azhar[2], Rizwan R. Khan[2]

[1]Department of Gastroenterology, Madina Teaching Hospital, Faisalabad, Pakistan
[2]Department of Medicine, Madina Teaching Hospital, Faisalabad, Pakistan

Received: 03 August 2019
Accepted: 05 September 2019

***Correspondence:**
Dr. Shahid Rasool,
E-mail: drshrasool@yahoo.com

ABSTRACT

Background: Patients with chronic liver disease are immunocompromised and prone to different opportunistic infections. Fungal infections in patients admitted with liver cirrhosis are not rare and they may increase mortality and morbidity of these patients. Aims of the study is to determine the mortality and its risk factors associated with fungal infections in patients with chronic liver disease.
Methods: In this retrospective study, patients admitted with chronic liver disease during the last four years on this hospital were studied for diagnosed fungal infections. A matched control group of cirrhosis patients with a ratio of 1:2 admitted without fungal infections was also studied and mortality was compared between the two groups.
Results: Seventy admitted patients of liver cirrhosis with microbial and histopathological evidence of fungal infection were found while 140 patients of the control group had no evidence of fungal infection. Hepatitis C virus infection was the major cause of cirrhosis (65%) and most of the patients were in child class C(63%). Urinary tract infection, esophageal candidiasis, and mucormycosis were major fungal infections. Mortality was much higher in the fungal infections group (34.3%) as compared to the non-infectious group (16%). On multivariate analysis, high WBCs count, hypo-albuminemia and high creatinine levels were the worst factors affecting mortality.
Conclusions: Fungal infections are a significant cause of morbidity and mortality in patients with decompensated cirrhosis. Advanced cirrhosis, renal insufficiency, and leucocytosis are independent predictors of fatal outcome in these patients.

Keywords: Chronic liver disease, Fungal infection, Liver cirrhosis, Mortality

INTRODUCTION

Patients with chronic liver disease are immunocompromised which makes them prone to a wide range of infections.[1] Epidemiological data of hospitalized cirrhotic patients reveals that about one third have at least one infection during hospitalization which increases mortality and hospital stay.[2,3] Rates of infection in hospitalized cirrhotic patients are much higher (32-34%)[4,5] as compared to hospitalized general patients (5-7%), Fungal infections are commonly diagnosed in immunocompromised patients. Different fungi can cause systemic life-threatening infections and can present dilemmas in diagnosis and management. Liver cirrhosis is defined as a state of immune dysfunction which impairs the ability of the body's natural defense system to clear microorganisms, cytokines, and endotoxins from the circulation. The pathogenesis of this immune dysfunction in cirrhosis is multifactorial. The liver has 90% of the reticuloendothelial cells in the form of kupffer and sinusoidal endothelial cells that play a key role in clearing organisms.[6] In cirrhosis of the liver, there is

shunting of the portal blood flow away from the liver and a reduced number of reticuloendothelial cells resulting in fewer bacteria and endotoxin clearing from the circulation.[7] Cirrhotic patients have reduced neutrophil mobilization, their phagocytic activity and antigen-presenting HLA-DR molecules on monocytes.[8,9] Additional factors that add to this immunodeficiency in cirrhotic patients include malnutrition, immunosuppressive drugs and the use of alcohol.[10]

Common pathogens such as Mycobacterium tuberculosis, Cryptococcus neoformans, Clostridium difficile, Listeria monocytogenes and Vibrio vulnificus are more virulent in patients with cirrhosis as compared to the general population.[11] About one-third of non-human immunodeficiency virus, cryptococcoma cases are seen in patients having chronic liver disease and is proven to be an independent predictor for 30 days mortality as compared to those having acquired immunodeficiency syndrome.[12] The clinical significance of fungal organisms isolated from cirrhotic patients is still not fully known. Fungal infections may increase the morbidity and mortality in liver cirrhosis and using potent antifungal drugs in these patients is difficult due to compromised hepatic and renal functions. Prevention, early detection and proper management of these infections in cirrhotic patients can help in improving survival. This study was aimed to determine the mortality and its risk factors associated with fungal infections in patients with chronic liver disease.

METHODS

It was an observational comparative case control study conducted at the Department of Gastroenterology and Hepatology Madina Teaching hospital Faisalabad. Case records of patients admitted from January 2015 to December 2018 with chronic liver disease were retrieved for diagnosed fungal infections. Cirrhotic patients secondary to any etiology, of any age and either gender admitted with any indication in the ward were enrolled in the study. Exclusion criteria included Infection with human immunodeficiency virus, previous transplantation or any other type of immunodeficiency, multi-microbial infections, secondary bacterial peritonitis, peritoneal or hemodialysis. Urine culture for bacteria and fungus was performed if there was any clue of urinary tract infection on routine urinary examination. Diagnostic ascitic paracentesis and inoculation of ascitic fluid into culture bottles for aerobic, anaerobic bacteria was done. Ascitic fungal culture in Sabouraud's dextrose broth was done in only those cases where routine antibiotics fail to control ascetic fluid infection. A matched control group of cirrhosis patients with a ratio of 1:2 admitted without fungal infections was also studied and mortality was compared between the two groups. The study was approved by the ethical review committee of the University of Faisalabad.

Statistical Package for Social Sciences (SPSS) version 19 was used to analyze the study data. The t-test and chi-square tests were used to determine the statistical difference between the two groups. T-test was used to find the difference between age of two groups. Chi square test was used to compare basic demographic like age and gender, causes of CLD, Child class, spontaneous bacterial peritonitis and hepatocellular carcinoma in fungal and without fungal infection groups. Chi square test was used to measure effect of co-morbid like extra-hepatic malignancy, IHD, HTN and DM on mortality with fungal infection and without fungal infection and odds ratio was also calculated. All p-values were two sided and considered as statistically significant if <0.05.

RESULTS

There were 70 patients with microbiological or histopathological evidence of fungal infections were found, while 140 patients of the control group had no evidence of fungal infection. So, a total of 210 patients were studied. Hepatitis C virus infection was the major cause of liver cirrhosis in both groups (65%) and most of the patients had Child-Pugh class C (63%). Both the groups were comparable concerning basic characteristics as shown in Table 1.

Table 1: Basic characteristics of patients with CLD and fungal infection and control groups.

Factors		CLD and Fungal Inf. N (70)	CLD without Fungal Inf. N (140)	p-value
Gender	Male	37 (53%)	75 (54%)	NS
	Female	33 (47%)	65 (46%)	NS
Age (in years)		51.7±11.5	50.7±10.2	NS
Cause of CLD	HCV	45/70 (64%)	92/140 (66%)	NS
	NAFLD	11/70 (16)	19/140 (13.5%)	NS
	HBV	8/70 (12%)	18/140(13%)	NS
	HCV+HBV	2/70(3%)	5/140(3.5%)	NS
	ALD	4/70 (6%)	6/140 (4%)	NS
Child Class A/B/C (%)		9/24/67	10/25/65	NS
SBP		22/70(31%)	42/140(30%)	NS
HCC		11/70(14%)	25/140(18%)	NS

NS: not significant, SBP: spontaneous bacterial peritonitis, HCC: Hepatocellular carcinoma

Urinary tract infections (56.5%) followed by esophageal candidiasis, mucormycosis, tracheo-pulmonary, intraperitoneal fluid were the major infections found in fungal infection group (Figure 1). The mortality was higher in the fungal infections group, about 24/70 (34.3%) patients died in the index admission while in the control group 11/140 (16%) patients died (Figure 2).

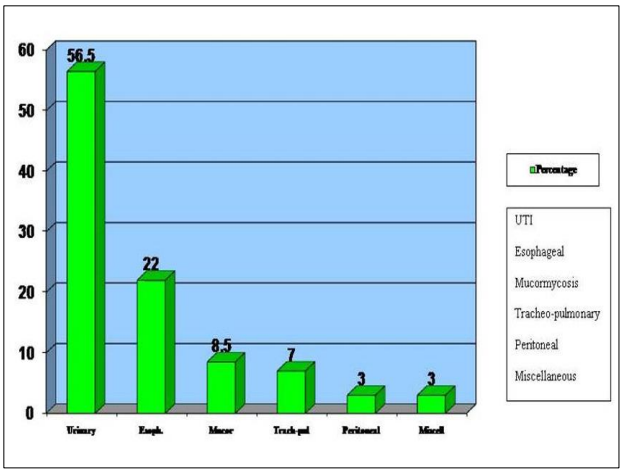

Figure 1: Frequency of fungal infections in CLD (N=70).

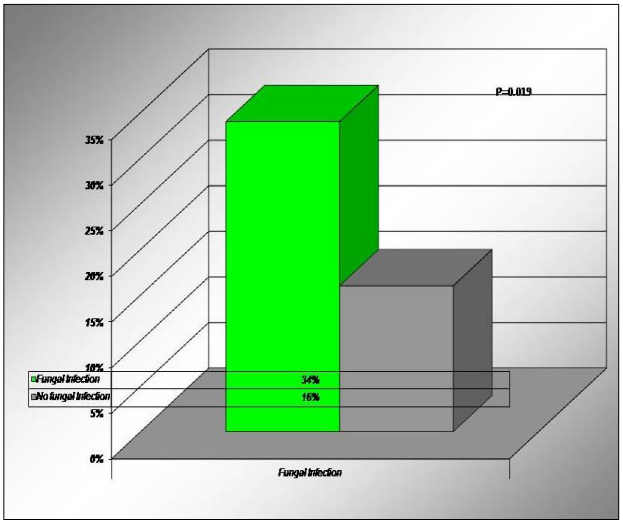

Figure 2: Mortality CLD patients with and without fungal infections.

Table 2: Effect of co-morbids on Mortality in CLD with Fungal Infection. (N=70).

Co-morbid (n)	Mortality % Present	Mortality % Absent	p-value
HCC (10)	4/10 (40%)	20/60 (30%)	0.71
Extra-hepatic malignancy(5)	3/5 (60%)	21/65 (32%)	0.31
IHD (6)	2/6 (33%)	22/64 (34%)	<0.99
HTN (26)	6/26 (23%)	18/44 (40%)	0.24
DM (32)	6/32 (19%)	18/38 (47%)	0.03

In the subgroup analysis of the cirrhotic patients with fungal infections, it was noted that patients having co-morbidities like diabetes mellitus, systemic hypertension, and ischemic heart disease and malignancy had higher mortality as compared to the patients having no co-morbidities, but the difference found was not statistically significant (Table 2).

In the multivariate analysis of the factors associated with mortality it was noted that the odds ratio was highest in patients having advanced cirrhosis (Child-Pugh class C) followed by white cell count >17 x 10 E/L, serum Albumin <2.8 mg/dl and serum creatinine >1.4 mg/dl (Table 3).

Table 3: Factors associated with mortality in univariate and multivariate analysis in CLD.

Factors	OR (95% C.I)	Adjusted OR (95% C.I)
Child class C	4.5(1.2-17.4)	3.5(0.9-14.3)
WBC (>17x10E/L)	3.5(1.1-10.8)	2.8(0.9-4.5)
Creatinine (>1.4mg/dl)	3.3(1.1-9.5)	2.8(0.9-8.6)
Albumin (<2.8gm/dl)	3.5(0.9-13.5)	2.5(0.5-8.7)

OR = Odds ratio, C.I. = Confidence interval

DISCUSSION

This topic of the effect of fungal infections on mortality in cirrhosis of liver patients is rarely discussed. In this study, fungal infections were associated with higher mortality in patients having chronic liver disease. Importantly it was seen that this effect was independent of the co-morbidities in these patients. This finding signifies the importance of performing fungal cultures and maintaining a low threshold in patients having liver cirrhosis.

Ascites, urinary tract, and lungs are the major sites of infection in patients with liver cirrhosis.[13] On thisstudy population, we found the fungal infections mostly in urinary tract followed by esophageal, mucormycosis, Tracheo-pulmonary, ascitic fluid and miscellaneous. In a retrospective study from Germany, researchers have found most of the fungal infections in the lungs followed by urine, blood cultures, and ascitic fluid.[14] Results from a recently published trial were compatible with our study showing that the most fungal infections were in the urinary tract followed by ascites and blood cultures.[15] We found fungal infections mostly in advance stages of cirrhosis which is comparable to the international data.[14]

Any infection in cirrhotic patients has prognostic importance. The mortality after any infection in cirrhosis is very high as compared to non-infectious mortality (43.5% vs 13.6%).[3] Our study data showed very high mortality in patients having a fungal infection (34.3% vs 16%). Our data is in line with previously published studies identifying the greater impact of fungal infections on mortality in cirrhotic patients (78% vs 35%).[3] One

month mortality rates of fungal infections as compared to bacterial infections were 58% and 29% respectively (p=0.001).[16] Bassetti et al, analyzed 169 episodes of candidemia and 72 intra-abdominal candidiasis in cirrhotic patients, showing high rates of ICU admission (50%) and the occurrence of septic shock (35%). Thirty-day mortality was 35.3% and it was independently associated with candidemia (OR=2.2, 95% CI:1.2-4.5) and septic shock (OR=3.2, 95% CI:1.7-6).[17] A study specifically evaluated the impact of Cryptococcus neoformans infection in cirrhotic patients and found that peritonitis found in 45% of the patients was the most common presenting feature and the overall mortality rate was 81% in this study.[18] Karvellas et al, studied critically ill patients having acute on chronic liver failure and found mortality of 56% due to fungal infections in these patients.[19]

When we studied the impact of co-morbid diseases on the mortality of cirrhotic patients with fungal infections we found that fungal infection was an independent risk factor for mortality, and this was also found in previously published German trial.[14]

Patients in this study population were hospitalized and were mostly having an advanced stage of cirrhosis. Research has shown that risk factors for fungal infections in cirrhotic patients include prolonged hospital stay and intensive care unit admission with vascular and abdominal devices, abdominal surgery and antibiotics in the recent past.[20] The signs and symptoms of the fungal disease mainly depend on three things, the organ of the body involved type of fungus and response of the patient to the infection. The most common symptoms are fever and chills not improving after antimicrobial therapy and especially in cirrhotic patients new onset hepatic encephalopathy without any identifiable cause.[17,21]

Due to impaired host immune response in liver cirrhosis, the course is highly variable from inflammation to multiple organ failure, so interpretation of these findings to be a result of fungal infection is difficult.[22] The treating physician must have a high index of suspicion for early diagnosis of fungal infection in cirrhotic patients.[23] Timely starting the antifungal treatment with source control is of critical importance in all critically ill patients including chronic liver disease.[24] On thisstudy antifungal treatment was started as well as source control measures were taken but their impact was not studied on the mortality.

Our study has some limitations, including the retrospective observational nature of the study with potential bias in data collection and the impact of antifungal therapy. The choice of antifungal drugs and timing of initiation of the therapy could have a possible impact on the overall mortality. In conclusion, patients with liver cirrhosis have higher rates of fungal infections and these patients have significantly higher mortality rates. In the light of these findings, it is suggested to have a very high index of suspicion for prompt diagnosis and early initiation of therapy for a better outcome.

CONCLUSION

Fungal infections are a significant cause of morbidity and mortality in patients with decompensated cirrhosis. Advanced cirrhosis, renal insufficiency, and leukocytosis are independent predictors of fatal outcome in these patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Alexopoulou A, Vasilieva L, Agiasotelli D, Dourakis SP. Fungal infections in patients with cirrhosis. J Hepatol 2015 Oct;63(4):1043-5.
2. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterol. 2010 Oct 1;139(4):1246-56.
3. Bajaj JS, Liu EJ, Kheradman R, Fagan A, Heuman DM, White M, et al. Fungal dysbiosis in cirrhosis. Gut. 2018 Jun 1;67(6):1146-54.
4. Bassetti M, Peghin M, Carnelutti A, Righi E, Merelli M, Ansaldi F, et al. Clinical characteristics and predictors of mortality in cirrhotic patients with candidemia and intra-abdominal candidiasis: a multicenter study. Intensive Care Med. 2017 Apr 1;43(4):509-18.
5. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. Clinical gastroenterology and hepatology. 2011 Sep 1;9(9):727-38.
6. Borzio M, Salerno F, Piantoni L, Cazzaniga M, Angeli P, Bissoli F, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Digest Liver Dis. 2001 Feb 1;33(1):41-8.
7. Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol. 2007 Jul;102(7):1510.
8. Fernández J, Acevedo J, Castro M, Garcia O, Rodríguez de Lope C, Roca D, Pavesi M, Sola E, Moreira L, Silva A, Seva-Pereira T. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatol. 2012 May;55(5):1551-61.
9. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatol. 2002 Jan;35(1):140-8.
10. Ferri C, Antonelli A, Mascia MT, Sebastiani M, Fallahi P, Ferrari D, et al. HCV-related autoimmune

and neoplastic disorders: the HCV syndrome. Digest Liver Dis. 2007 Sep 1;39:S13-21.
11. Garcia-Tsao G, Wiest R. Gut microflora in the pathogenesis of the complications of cirrhosis. Best Practice Res Clin Gastroenterol. 2004 Apr 1;18(2):353-72.
12. Ghassemi S, Garcia-Tsao G. Prevention and treatment of infections in patients with cirrhosis. Best Practice Res Clin Gastroenterol. 2007 Jan 1;21(1):77-93.
13. Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. Hepatol. 2009 Dec;50(6):2022-33.
14. Jean SS, Fang CT, Shau WY, Chen YC, Chang SC, Hsueh PR, Hung CC, Luh KT. Cryptococcaemia: clinical features and prognostic factors. Qjm. 2002 Aug 1;95(8):511-8.
15. Karvellas CJ, Pink F, McPhail M, Austin M, Auzinger G, Bernal W, et al. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill non transplanted patients with acute on chronic liver failure. Crit Care Med. 2010 Jan 1;38(1):121-6.
16. Lahmer T, Messer M, Mayr U, Saugel B, Noe S, Schultheiss C, et al. Fungal "colonisation" is associated with increased mortality in medical intensive care unit patients with liver cirrhosis. Mycopathologia. 2015 Feb 1;179(1-2):63-71.
17. Marchetti O, Eggimann P, Calandra T. Invasive candidiasis in critically ill patients: does progressing knowledge improve clinical management and outcome?. Curr Opinion Criti Care. 2010 Oct 1;16(5):442-4.
18. O'donohue J, Workman MR, Rolando N, Yates M, Philpott-Howard J, Williams R. Urinary tract infections in primary biliary cirrhosis and other chronic liver diseases. Eur J Clin Microbiol Infect Dis. 1997 Oct 1;16(10):743-6.
19. Puig-Asensio M, Pemán J, Zaragoza R, Garnacho-Montero J, Martín-Mazuelos E, Cuenca-Estrella M, Almirante B. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. Crit Care Med. 2014 Jun 1;42(6):1423-32.
20. Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis 1996;16(4): 389-402.
21. Singh N, Husain S, de Vera M, Gayowski T, Cacciarelli TV. Cryptococcus neoformans infection in patients with cirrhosis, including liver transplant candidates. Med. 2004 May 1;83(3):188-92.
22. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 2008;28(1):26-42.
23. Tascini C, Menichetti F, Merelli M, Farese A, Sozio E, Scarparo C, Viaggi B, Rossolini GM, Bassetti M. Variable incidence of candidemia in patients admitted to ICUs or medical wards of large tertiary-care Italian hospitals. Clin Microbiol Infect. 2015 Sep 1;21(9):e71-2.
24. Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, et al. Patients with acute on chronic liver failure display 'sepsis-like'immune paralysis. J Hepatol. 2005 Feb 1;42(2):195-201.

Cite this article as: Rasool S, Babar AN, Shafquat U, Azhar S, Khan RR. Fungal infections in patients with chronic liver disease: mortality and associated risk factors. Int J Res Med Sci 2019;7:3882-6.