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Predictors for oesophageal candidiasis in patients with liver cirrhosis

Siddheesh Rajpurohit[1], Balaji Musunuri[1], Pooja Basthi Mohan[1], R Vani Lakshmi[2], Ganesh Bhat[1], Shiran Shetty[1]

[1]Department of Gastroenterology and Hepatology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India;
[2]Department of Data Science, Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, Karnataka, India

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SUMMARY

Background and aim: Oesophageal candidiasis (OC) is one of the most common infections among patients with liver cirrhosis. The present study evaluates the potential predictors for OC among liver cirrhosis patients.
Methodology: This retrospective study was conducted in the tertiary care centre of coastal Karnataka from January 2016 to April 2022. Patients aged 18 and above with a confirmed diagnosis of liver cirrhosis were selected. Patients were equally divided into two groups, *i.e.*, case and control, based on the presence and absence of OC.
Results: A total of 1513 patients with cirrhosis underwent upper gastrointestinal endoscopy. Of these, 50 (3.3%) were diagnosed with OC and taken into case group. An equal number of patients were selected in control group and matched for gender, age and etiology. Most participants were male (94%), with a mean age of 48.46±11.82 years. A lower serum creatinine value was noted among patients with OC. Binary logistic regression identified serum creatinine as an independent predictor for OC (OR: 7.65, 95% CI: 2.012-29.08; p-value: 0.003). The receiver operating characteristic curve for serum creatinine showed the highest significance with a cut-off of <0.86 mg/dL (AUC: 0.722).
Conclusion: Serum creatinine is the independent predictor for OC among liver cirrhosis patients. The possible mechanism is that cirrhosis is a catabolic state in which muscle protein breakdown exceeds synthesis, resulting in decreased muscle mass and low creatinine levels. However, more prospective studies are required to evaluate the role of sarcopenia with OC among liver cirrhosis patients.

Keywords: Creatinine, oesophageal candidiasis, liver cirrhosis, sarcopenia.

INTRODUCTION

Liver cirrhosis is one of the leading causes of morbidity and mortality globally. Cirrhosis is defined as the development of the nodules surrounded by fibrous bands in response to repetitive chronic liver injuries that ultimately lead to portal hypertension and end-stage liver disease [1, 2]. Cirrhosis is a major factor that disrupts the liver's homeostatic role, leading to immunodeficiency and systematic inflammation [3, 4]. Immune disarray in cirrhosis involves innate and adaptive domains ranging from function cell failure to complete immune anergy [5]. Any invasive procedure, malnutrition, gastrointestinal dysbiosis, multiple hospital admissions, and irrational antibiotic use predispose cirrhosis to opportunistic infections [6]. Candida is a commensal organism in the gastrointestinal tract, disrupting the gastrointestinal barrier and/or change in immunity; it translocates to the systemic circulation [7]. Oesophageal candidiasis is one of the most commonly reported infections among immunodeficiency patients. However, its prevalence among general population varies from 0.3% to 0.4% [8]. Among oesophageal

Corresponding author
Shiran Shetty
E-mail: shiran.shetty@manipal.edu

candida infections, C*andida albicans* is the most commonly reported aetiology [9]. Diabetic mellitus, malignancy, immunosuppressed conditions and use of steroids are the more significant factors contributing to oesophageal candidiasis among non-HIV patients [10]. Data on prevalence, factors, and predictors of oesophageal candidiasis among liver cirrhosis patients is scarce. The present study was conducted to find the prevalence and identify potential predictors for oesophageal candidiasis in patients with liver cirrhosis.

PATIENTS AND METHODS

Study design

This retrospective study was performed among patients with liver cirrhosis who attended the Department of Gastroenterology and Hepatology, Kasturba Medical College, Manipal, Karnataka, India from January 2016 to April 2022. All the patients diagnosed with liver cirrhosis and above the age of 18 years were included in the study. Cirrhosis of the liver was diagnosed based on clinical, biochemical, radiologic, or histopathologic evidence with F4 changes (wherever available). Patient data regarding demographics, etiology of cirrhosis, blood investigational profile, Body Mass Index (BMI), and presence of any decompensating events were recorded in the pre-designed form. The severity of liver disease was assessed with Child-Turcotte-Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) scores. Findings of upper gastrointestinal endoscopy were also recorded. Patients with incomplete data were excluded from the study.

Patient selection and randomization

Patients with liver cirrhosis who were diagnosed as having OC were taken into case. In such patients, OC was confirmed with upper gastrointestinal endoscopy findings of non-washable white plaques/deposits in the oesophagus and/or brush cytology. For the control group, an equal number of patients were selected and matched with case group for age, gender, and etiology.

Statistical analysis

Data were presented as Mean ± SD for quantitative variables and proportion with percentage for qualitative variables. Data cleaning and analysis were performed using Microsoft Excel and Statistical Package for Social Science (SPSS) version 25 (IBM Corp., Armonk, NY, USA), respectively. Chi-square, Fischer test, t-test, Mann Whitney U, re-

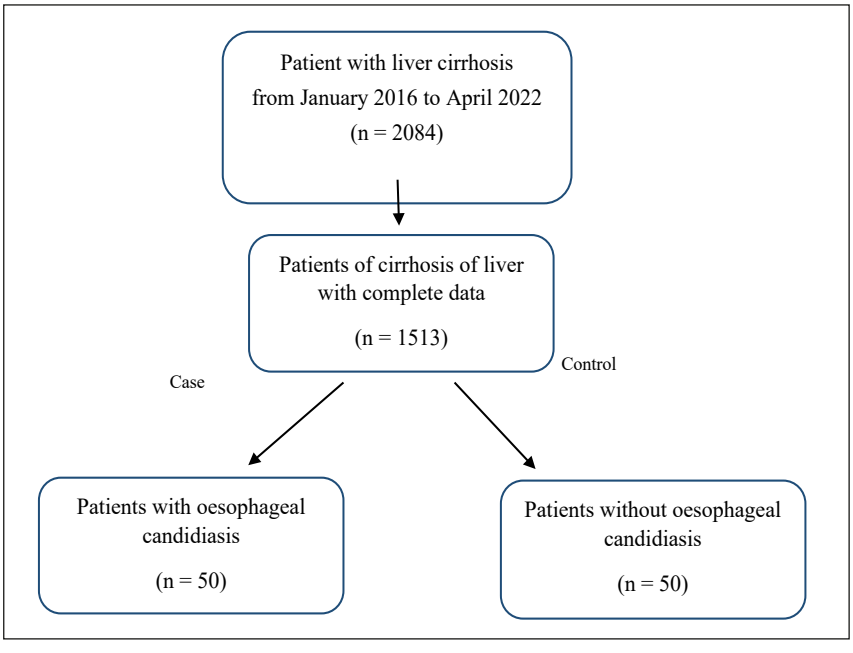

Figure 1 - Patient flow diagram.

gression analysis, and receiver operating characteristics were applied. Statistical significance was determined at a 5% level of significance.

Study approvals
Prior to the study, ethical approval was taken from Institutional Ethical Committee (IEC1-167-2022).

RESULTS

Demographic profile
A total of 2084 patients with liver cirrhosis were identified during the study period. Out of which, 1513 were included in the present study owing to the presence of endoscopic findings. Of these, 50 were diagnosed with OC (prevalence of 3.3%) and were taken into case group (Figure 1). The participant's mean age was 48.60±11.82 years, with most being male patients (94%). Alcohol (76%) followed by cryptogenic/unknown (16%) were the most common reported etiology.

Comparison of cirrhosis-related complications among two groups
Various clinical parameters were compared among both groups. Body Mass Index was significantly lower in case group compared to control group (p-value: 0.045) (Table 1). Comparing both groups, Portal Hypertensive Gastropathy (PHG) was more common in case group compared to control group (p-value: 0.008). Group B had more patients with Acute Kidney Injury (AKI) compared to case group (p-value:0.046). Most of the patients with OC belong to CTP class B and C (44% and 46%, respectively) (Table 1).

Comparison of blood parameters among two groups
Baseline investigations were not significantly different in both groups (Table 1). However, patients

Table 1 - Patients characteristics.

Parameters	*Case (n = 50)*	*Control (n = 50)*	*P value*
Age (mean ± SD)	48.60 ± 11.70	48.60 ± 11.70	1.000
Sex			
Male	47	47	1.000
Female	3	3	
BMI (mean ± SD)	22.51 ± 3.80	23.99 ± 3.41	*0.045**
Etiology n (%)			
Alcohol	38 (76)	38 (76)	
Cryptogenic	8 (16)	8 (16)	1.000
NAFLD	2 (4)	2 (4)	
Hepatitis B	2 (4)	2 (4)	
Co-morbidities n (%)			
DM	11 (22)	17 (34)	0.202
UGIE Findings n (%)			
PHG	26 (52)	13 (26)	*0.008**
EVL	11 (22)	15 (30)	0.362
Peptic Ulcer	5 (10)	12 (24)	0.062
Oesophageal Varices	34 (68)	32 (64)	0.673
Cirrhosis Complication n (%)			
HE	11 (22)	14 (28)	0.488
UGI Bleed	3 (6)	6 (12)	0.487
AKI	2 (4)	8 (16)	*0.046**
HCC	4 (8)	6 (12)	0.505
SBP	7 (14)	8 (16)	1.00
Ascites	37 (74)	37 (74)	1.00
Severity Score			
MELD	17.18 ± 6.92	19.74 ± 8.11	0.141
CTP	8.98 ± 1.82	9.52 ± 2.24	0.269
CTP A/B/C	5/23/22	4/23/23	0.936

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Parameters	*Case (n = 50)*	*Control (n = 50)*	*P value*
Blood Investigations (mean ± SD)			
Complete Blood Count			
Hb (g/dL)	10.44 ± 2.47	9.77 ± 2.40	0.712
HCT (%)	30.80 ± 7.26	28.79 ± 7.57	0.252
Platelet (x10^3/µL)	159.11 ± 135.20	121.82 ± 63.10	0.684
PDW (%)	16.89 ± 1.66	17.56 ± 0.79	*0.008**
TLC (x10^3/µL)	7.96 ± 4.80	8.98 ± 5.18	0.285
ANC (x10^3/µL)	5.59 ± 3.82	6.27 ± 4.45	0.467
AEC (x10^3/µL)	0.25 ± 0.625	0.17 ± 0.12	0.684
ALC (x10^3/µL)	13.4 ± 0.72	1.44 ± 0.85	0.649
MLR	0.72 ± 0.69	0.66 ± 0.34	0.839
NLR	4.97 ± 4.30	4.88 ± 3.49	0.942
Liver Functioning Test			
Total Bilirubin (mg/dL)	5.18 ± 5.88	6.57 ± 6.91	0.296
Direct Bilirubin (mg/dL)	3.90 ± 4.66	4.84 ± 5.53	0.414
Total Protein (g/dL)	6.70 ± 0.84	6.6 ± 0.90	0.727
ALP (U/L)	187.020 ± 114.83	160 ± 84.78	0.617
ALT (IU/L)	53.86 ± 62.33	37.18 ± 17.95	0.234
AST (IU/L)	91.80 ± 59.57	96.90 ± 70.65	0.674
Globulin (g/dL)	3.93 ± 0.82	3.99 ± 0.98	0.716
Albumin (g/dL)	2.77 ± 0.60	2.60 ± 0.62	0.233
Renal Function Test			
Potassium (mmol/L)	4.53 ± 1.12	4.20 ± 0.73	0.126
Sodium (mmol/L)	130.8 ± 6.97	133.6 ± 5.18	0.059
Creatinine (mg/dL)	0.813 ± 0.281	1.20 ± 0.62	*<0.001**
Urea (mg/dL)	24.90 ± 12.86	33.90 ± 22.71	0.117
Coagulation Test			
INR	1.41 ± 0.41	1.75 ± 0.98	0.078

**Statistically significant.*
Abbreviations: AEC: Absolute Eosinophil Count; AKI: Acute Kidney Injury; ALC: Absolute Lymphocyte Count; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; ANC: Absolute Neutrophil Count; AST: Aspartate Aminotransferase; CTP: Child-Turcotte-Pugh; DM: Diabetes Mellitus; EVL: Endoscopic Variceal Ligation; Hb: Haemoglobin; HCC: Hepatocellular Carcinoma; HE: Hepatic Encephalopathy; INR: International Normalized Ratio; MELD: Model for End-stage Liver Disease; MLR: Monocyte-Lymphocyte Ratio; NAFLD: Non-Alcoholic Fatty Liver Disease; NLR: Neutrophil-Lymphocyte Ratio; PDW: Platelet Distribution Width; PHG: Portal Hypertensive Gastropathy; PLT: Platelet; SBP: Spontaneous Bacterial Peritonitis; TLC: Total Leukocyte Count; UGI: Upper Gastro-Intestinal.

in case group showed significant decrease in serum creatinine (0.81 mg/dL in case group vs 1.2 mg/dL in control group; p<0.001) and PDW (16.898% in case group vs 17.566% in control group; p-value: 0.008) (Table 1). Upon bivariate logistic regression, serum creatinine was the independent predictor for OC (Table 2).

Analysis by receiver operating characteristic curve

Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal serum creatinine and PDW concentration predicting OC.

Table 2 - Predictors for oesophageal candidiasis in patients with liver cirrhosis.

Variable	*Odd Ratio*	*95% Confidence Interval*		*p-value*
		Lower Limit	*Upper Limit*	
Serum Creatinine	7.65	2.012	29.088	0.003
PDW	0.833	0.647	1.073	0.142

Abbreviation: PDW: Platelet Distribution Width.

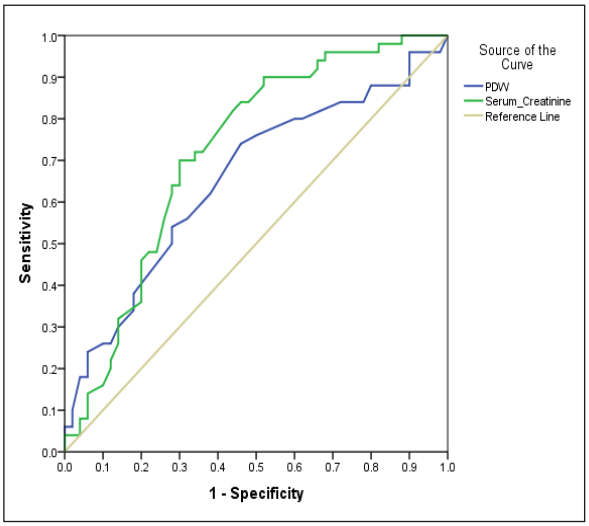

Figure 2 - ROC curve showing the level of serum creatinine and PDW for detecting oesophageal candidiasis.

Serum creatinine

An area under the ROC curve (AUC) of 0.722 with a sensitivity of 0.70 and a specificity of 0.70 were found to predict the OC among liver cirrhosis patients. The optimum critical concentration of serum creatinine in patients who developed OC was <0.86 mg/dL (Figure 2).

Platelet distribution width (PDW)

An area under the ROC curve (AUC) of 0.655 with a sensitivity of 0.620 and specificity of 0.620 were found to predict the OC among liver cirrhosis patients. The optimum critical concentration of PDW in patients who developed OC was <17.45% (Figure 2).

DISCUSSION

In this retrospective study, we aimed to assess the potential predictors for OC in liver cirrhosis patients. Cirrhotic being immunocompromised individuals are predisposed to various bacterial and fungal infections. They are predisposed to different infections due to the reduced opsonization in blood and ascites, decreased antibody production, increased immunosuppressive cytokines, disturbances in complement, and reduced leukocyte function [11]. Many studies have analysed infections like SBP, UTI, and sepsis. This is among the few studies investigating fungal infection in cirrhosis. The present study showed that the prevalence of OC was 3.3% among patients with liver cirrhosis. This is similar to the prevalence of 3.6% reported by another study from North India by Verma et al. (2020) [12]. However, the present study reported a lower prevalence of OC compared to Takahashi et al. (2015) (4.1%) and Peter et al. (2000) (19.4%) [13, 14].

The present study reported a higher prevalence of PHG among patients with OC than those without ($p<0.008$); this is similar to the findings of Verma et al. (2020) [12].

Interestingly, the present study reported a significantly lower PDW count in case group compared to control group. These findings correlate with the study by Zhao et al. (2015) [15]. The study reported a significantly lower PDW count in the invasive fungal infection group compared to the control group. Given the current findings, a ROC curve was performed, which showed an AUC of 0.655 with a sensitivity of 0.620 and specificity of 0.620, similar to results reported by Zhao et al. (2015) [15]. Author reported an AUC of 0.694 with a sensitivity and specificity of 0.65 and 0.84 respectively. In response to the higher demand for platelets, PDW is the release of large platelet from bone marrow. PDW count is increased in the presence of platelet anisocytosis [16]. One possible explanation behind low PDW is that megakaryocytes had not yet been stimulated to release large platelets in the bone marrow. Therefore, PDW seems to be lower in case group compared to control group.

Our study reported non-significant lower MELD (p-value: 0.141) and CTP (p-value: 0.269) scores in case group compared to control group. This is in contrast to few studies that reported higher MELD scores among the OC group compared to those without. One of the possible explanations behind the non-significant lower MELD score is the relationship between sarcopenia and MELD score. Kang et al. (2015), performed a prospective study to evaluate the role of sarcopenia on the prognostic value of cirrhosis [17]. The study reported a significantly lower baseline MELD score (p-value: 0.034) among the sarcopenia group compared to the non-sarcopenia group. Similarly, Tandon et al. (2016), reported a significant relationship between low MELD scores and mortality among sarcopenia patients [18].

Our study showed lower serum creatinine values

among case group than in control group. This is in contrast with study by Verma et al. (2020), reporting a significant increase in serum creatinine among the case group (Oesophageal candidiasis) [12]. Given the findings from the current study, bivariate logistic regression was performed, which showed serum creatinine as the independent predictor for OC among patients with liver cirrhosis. ROC (Receiver Operating Characteristic) curve analysis showed an AUC of 0.722 with a sensitivity of 0.700 and specificity of 0.700. The optimum critical serum creatinine concentration among patients who developed OC was <0.86 mg/dL.

A possible explanation behind the findings is that liver cirrhosis is a catabolic disease, a state in which muscle protein breakdown exceeds synthesis, resulting in significant muscle wasting and lower muscle mass with a decrease in the production of serum creatinine levels. The present study reported significant lower BMI among participants in case group compared to control group. Similarly, Thongprayoon et al. (2016), and Udy et al. (2016), reported the association of lower serum creatinine with low muscle mass and adverse outcomes [19, 20]. Krell et al. (2013) performed a prospective study to evaluate the role of sarcopenia on mortality and complications associated after liver transplant [21]. Concerning infection, the author reported that patients in the lowest tertile of the total psoas area have fourfold higher odds of developing severe infections when compared to patients in the highest tertile. Overall, our patients with OC had low BMI with lower serum creatinine and MELD scores than those without OC. This was probably due to the above explanation, predisposing patients with sarcopenia to OC.

Among the limitations of the present study we must remark that the study is a single-centric retrospective study with inherent design limitations and the number of patients with OC is not large enough to draw a firm conclusion hence cannot be generalized to all patient populations.

The present study recommends a large-scale case-control prospective study from multiple centres to evaluate the role of serum creatinine in OC among patients with liver cirrhosis.

Also, the study strongly suggests using BMI and sarcopenia gradings to assess the relationship between sarcopenia and oesophageal candidiasis.

Conflicts of interest

One part of the study was presented as an abstract (poster presentation) at Indian National Association for Study of the Liver (INASL) 2022.

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