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Research Article

Patients with Liver Cirrhosis

Treatment Approach Analysis of Hospitalized Patients with Liver Cirrhosis; A Prospective Observational Study

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Abstract: The analysis of medications prescribed for managing patients with liver cirrhosis provide essential insight into appropriate therapeutic regimens and prevents inappropriate therapeutic outcomes. This study aimed to analyze the treatment approach of hospitalized patients with liver cirrhosis and identify drug-drug interactions (DDIs) and hepatic dose adjustment associated with treatment. A prospective observational study was conducted for 12 months in the Medicine Department of Bharati Hospital and Research Center, located in Pune, India. Medication charts of 113 patients who were diagnosed with cirrhosis were reviewed. Pharmaceutical care-related standard tools were applied to identify DDIs and medications requiring hepatic dose adjustment. Investigating the number of complications showed that ascites (40.7%) were the most common complication associated with liver cirrhosis. The treatment approach analysis revealed that antibiotics (23.6%), diuretics (22.5%), and analgesics (13.8%) were the most frequently prescribed pharmacological class of medications. The most commonly identified DDIs was an interaction between Mefenamic Acid-Furosemide (46.3%). In addition, approximately half of prescribed Paracetamol (48.1%) required its dose to be adjusted according to the patient's liver function test. Therefore, periodic analysis of prescribed medications needs to be performed since the inappropriate selection of medications can further lead to drug-related problems like DDIs or hepatic dose adjustment. Our findings provide feedback to prescribers to improve the appropriate selection of medications and enhance patient safety.

Keywords: *Treatment approach analysis, Liver cirrhosis, Drug-drug interaction, and Hepatic dose adjustment*

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1. INTRODUCTION

Liver cirrhosis is considered one of the complications of chronic liver diseases, which results from various mechanisms induced by liver injury that can lead to necro-inflammation and fibrogenesis. Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. [1] Liver cirrhosis is a growing cause of human morbidity and mortality in more industrialized countries. Also, it is the 14th most common reason for adult mortality worldwide, leading to 1.03 million deaths annually. [2] The World Health Organization (WHO) reported that liver diseases, including liver cirrhosis, cause approximately 2.5% of annual deaths.[3] The significant goals of managing patients with cirrhosis include slowing or reversing the progression of liver disease, preventing superimposed insults to the liver, and identifying medications that require dose adjustments or should be avoided entirely. Chronic liver disease, especially liver cirrhosis, may modulate several features determining the behavior of medications in the body. Hemodynamic changes and complications (e.g., edema and ascites) caused by liver cirrhosis can modify drug pharmacokinetics parameters. Alteration of these pharmacokinetic-related parameters is variable depending on the patient's characteristics, like the severity of liver cirrhosis and the specific medication. However, these changes commonly can consequence in a higher level of medications and possibly lead to unwanted drug-related harm and toxicity in patients with liver cirrhosis.[4] Patients with liver cirrhosis are at increased risk of adverse events with many medications because of impaired hepatic metabolism or renal excretion. Therefore, many medications require dose adjustments or should be avoided entirely. In addition, several pharmacological medication classes have been associated with liver injury and require hepatic dose adjustment.[5] An inappropriately prescribed medication in patients with liver cirrhosis can sometimes be harmful., and may worsen liver cirrhosis or cause faster deterioration of liver function. Thus medications should be prescribed with caution or the dose should be adjusted carefully in patients with liver cirrhosis.[6] There are several institutions and guidelines like the WHO, European Association for the Study of Liver (EASL), and American Association for Study of Liver Disease (AASLD) that recommend evidence-based practice guidelines for the management and treatment of the etiology and complications of liver cirrhosis. There is no specific drug therapy for cirrhosis. Liver transplantation is the only definitive treatment. Available drug therapy for complications of cirrhosis only minimally improves long-term survival. However, analysis of the treatment approach and prescribed medications in patients with liver cirrhosis helps us to determine the most prescribed medications. Also, it enables us to identify the appropriateness of prescribed medications regimen among these patients. Overall, the study of prescribing pattern analysis seeks to monitor, evaluate and recommend modifications to physicians to improve rational drug use and patient safety.[7] The aims of the study were, therefore, to analyze the treatment approach of hospitalized patients with liver cirrhosis and to identify drug-drug interactions (DDIs) and hepatic dose adjustment associated with treatment.

2. MATERIALS AND METHODS

2.1 Study Design and Site

A prospective observational study on treatment approach analysis of patients with liver cirrhosis was conducted in the Medicine Department of Bharati Hospital and Research Center, located in Pune, India. The Bharati Hospital and Research Center is a tertiary care academic and referral hospital providing outpatient and inpatient healthcare-related services to Pune and surrounding areas. Also, it is an institution for the training of healthcare professionals. The study was performed over 12 months, from February 2019 to February 2020.

2.2 Study Inclusion Criteria

Patients 18 years and older admitted to the Medicine Department and diagnosed with liver cirrhosis were included in the study, and their prescribed medication charts were analyzed. Based on laboratory results and definite diagnostic imaging findings, liver cirrhosis was diagnosed by in-charged physicians. In addition, patients with decompensated cirrhosis also were included in this study. Decompensated cirrhosis was defined as a patient with liver cirrhosis who presented with one or more life-threatening cirrhosis complications like variceal hemorrhage, ascites, and Spontaneous Bacterial. Peritonitis (SBP), Hepatorenal Syndrome, Hepatic Encephalopathy, and Hepatopulmonary Syndrome. [1] We calculated the severity of liver disease by using the Child-Pugh score. [8] Written informed consent was obtained from study patients or the patient's caregiver when patients could not communicate.

2.3 Study Exclusion Criteria

The patients who were admitted to the Medicine Department for less than 24 hours and patients who were discharged against medical advice were excluded from this study.

2.4 Ethical Approval

The Institutional Human Ethics Committee of Bharati Hospital and Research Center approved the current study in Pune, India (Reference number: BHRC/IHEC/2019-31).

2.5 Data Collection

We comprehensively analyzed patients` medication charts to identify the most commonly prescribed medications for managing liver cirrhosis and associated drug-related problems (DRPs) like DDIs and hepatic dose adjustment. Moreover, patients` medical records, demographic, and clinical-related data were collected using a specially designed form. Lexicomp® drug interaction was used for identifying DDIs. According to Lexicomp®, DDIs are classified into five risk rating categories; "A" (no known interaction), which means still no data have revealed an interaction between the specified drugs; "B" in which no action is required to manage such an interaction; "C" where drug interaction required close monitoring to identify potential adverse outcome; "D" indicates interaction is associated with a high risk for occurrence of adverse outcome and "X" where drug combination is contraindicated, and it must be avoided. We only considered DDIs with risk rating categories of C and D as clinically significant since these interactions required specific management to avoid patient harm. Lexicomp® clinical drug information was approached to assess the appropriateness of the prescribed drug dose per patient's hepatic function. [9]

3. STATISTICAL ANALYSIS

Mean, standard deviation, frequencies, and percentages of patients' demographic/clinical characteristics, prescribed

medications, DDIs, and hepatic dose adjustment were calculated by using descriptive statistics. The Statistical Package for Social Sciences for Windows, version 22.0, was used to analyze study data.

4. RESULTS

4.1 Clinical Characteristics of Study Patients

Patients' demographic and clinical characteristics were documented in suitably designed data collection forms during the study procedure (Table 1). One hundred thirteen patients met the study criteria and were included in the study. Most patients were males (96, 85.0%) with a mean age of 51.7 ± 11.4 years, and the average length of hospital stay was 13.2 ± 6.4 days. Child-Pugh liver severity analysis showed that most of the patients (68, 60.2%) admitted to the hospital belonged to Class C (severe liver impairment) severity score. Analyzing the number of complications showed that the ascites (46, 40.7%) were the most common complication associated with liver cirrhosis, followed by hepatic encephalopathy (24, 21.2%), hepatorenal syndrome (14, 12.4%), variceal hemorrhage (6, 5.3%), spontaneous bacterial peritonitis (2, 1.8%), and hepatopulmonary syndrome (2, 1.8%). Anemia (58, 51.1%), electrolyte imbalance (39, 34.5%), diabetes mellitus (27, 23.9%), hypertension (19, 16.8%), ischemic heart disease (17, 15.0%), chronic kidney disease (14, 12.4%), and respiratory illnesses (4, 3.5%) were identified comorbidities among study patients.

Table 1. Clinical characteristics of patients in the study

Total number of study patients	N = 113
Age (years)	
Mean ± SD	51.7 ± 11.4
Sex n (%)	
Male	96 (85.0)
Female	17 (15.0)
length (days) of hospital stay	
Mean ± SD	13.2 ± 6.4
Number of prescribed medications	
Mean ± SD	16.7 ± 5.6
Alcoholic n (%)	89 (78.8)
Smoker n (%)	53 (47.0)
Child-Pugh liver severity score n (%)	
B	45 (39.8)
C	68 (60.2)
Liver cirrhosis complications n (%)	
Ascites	46 (40.7)
Hepatic encephalopathy	24 (21.2)
Hepatorenal syndrome	14 (12.4)
Variceal hemorrhage	6 (5.3)
Spontaneous bacterial peritonitis	2 (1.8)
Hepatopulmonary syndrome	2 (1.8)
Liver cirrhosis comorbidities n (%)	
Anemia	58 (51.1)
Electrolyte imbalance	39 (34.5)
Diabetes mellitus	27 (23.9)
Hypertension	19 (16.8)
Ischemic heart disease	17 (15.0)
Chronic kidney disease	14 (12.4)
Respiratory illnesses	4 (3.5)

SD; standard deviation.

4.2 *Treatment Approach Analysis*

Overall, 1326 medications were documented through treatment approach analysis of study patients. Antibiotics (313, 23.6%), diuretics (298, 22.5%), analgesics (183, 13.8%), vitamin/mineral supplements (121, 9.2%), and proton pump inhibitors (114, 8.6%) were the most commonly prescribed pharmacological class of medications. Details of treatment approach analysis of patients with liver cirrhosis are presented in Table 2.

Table 2. Treatment approach analysis of patients with liver cirrhosis (n = 1326)

Most commonly prescribed therapeutic classes of medications	N (%)
Antibacterial agents	**313 (23.6)**
Piperacillin-Sulbactam	112 (35.8)
Ceftriaxone	82 (26.2)
Rifaximin	47 (15.0)
Cefoperazone-Sulbactam	24 (7.7)

Cefotaxime	22 (7.0)
Metronidazole	19 (6.1)
Cefuroxime	7 (2.2)
Diuretics	**298 (22.5)**
Furosemide	113 (37.9)
Spironolactone	93 (31.2)
Mannitol	58 (19.5)
Metolazone	34 (11.4)
Analgesics	**183 (13.8)**
Paracetamol	81 (44.3)
Mefenamic acid	62 (33.9)
Diclofenac	22 (12.0)
Aceclofenac	9 (4.9)
Tramadol	9 (4.9)
Vitamin/mineral supplements	**121 (9.2)**
Calcium	56 (46.3)
Potassium chloride	37 (30.6)
Vitamin k	19 (15.7)
Thiamine	9 (7.4)
Proton pump inhibitors	**114 (8.6)**
Pantoprazole	74 (64.9)
Omeprazole	27 (23.7)
Esomeprazole	13 (11.4)
Laxatives	**104 (7.5)**
Lactulose	104 (100.0)
Beta-blockers	**75 (5.7)**
Propranolol	75 (100.0)
Blood products	**43 (3.3)**
Albumin	24 (55.8)
Whole blood	11 (25.6)
Fresh frozen plasma	8 (18.6)
Alpha/Beta agonist	**39 (3.0)**
Noradrenaline	39 (100.0)
Anti-Fibrinolytic agents	**36 (2.8)**
Tranexamic acid	36 (100.0)

4.3 Identifying Drug-Drug Interactions

Lexicomp® drug interaction was applied for identifying DDIs. Overall, 41 DDIs were identified. These were DDIs with risk rating categories of D, C, and X, which indicate that management of DDIs requires either close therapy monitoring (Category C), considering safer alternatives (category D), and avoiding such interactions (category X) to mitigate the occurrence of related patient harm. Interaction between Furosemide-Mefenamic acid (19, 46.3%) was the most commonly identified DDIs with moderate risk rating category of D, which required close monitoring of the therapeutic approach (Table 3).

Table 3. Identified drug-drug interactions according to LEXICOMP (N = 41)

Drug-drug interaction	N (%)	Potential clinical outcome	Risk and severity rating*
Furosemide-Mefenamic acid	19 (46.3)	Mefenamic acid may diminish the diuretic effect of furosemide. Furosemide may enhance the nephrotoxic effect of mefenamic acid.	D, Moderate
Furosemide-Diclofenac	11 (26.9)	Diclofenac may diminish the diuretic effect of furosemide. Furosemide may enhance the nephrotoxic effect of diclofenac.	D, Moderate
Spironolactone-Mefenamic acid	8 (19.5)	Mefenamic acid may diminish the antihypertensive effect of spironolactone and enhance the hyperkalemic effect of spironolactone.	C, Major
Pantoprazole-Cefuroxime	3 (7.3)	Pantoprazole may decrease the absorption of Cefuroxime.	X, Moderate

Risk rating category C (monitor therapy), D (consider therapy modification), X (avoid combination).

4.4 Hepatic Dose Adjustment

Drugs requiring hepatic dose adjustment were identified using Lexicomp clinical drug information. Paracetamol (26, 48.1%), Metronidazole (19, 35.2%), and Tramadol (9, 16.7%) were prescribed medications that required their dose to be adjusted according to the patient's liver function test (Table 4).

Table 4. Medications required hepatic dose adjustment (N= 54)

Medications	N (%)	Hepatic dose adjustment based on liver cirrhosis severity*
Paracetamol	26 (48.1)	Mild to moderate impairment: Low dose (≤ 2 to 3 g/day). Severe impairment: Use is contraindicated.
Metronidazole	19 (35.2)	Severe impairment: Reduce dose by 50%.
Tramadol	9 (16.7)	Immediate release, severe impairment: 50 mg every 12 hours. Extended-release, severe impairment: Avoid use.

Mild to moderate impairment; Child-Pugh class A and B. Severe impairment; Child-Pugh class C.

5. DISCUSSION

The treatment approach of hospitalized patients with liver cirrhosis was analyzed, DDIs, and hepatic dose adjustment associated with treatment were identified. The majority of our study patients were male. Generally, men are two times more likely to develop and die from chronic liver disease, including liver cirrhosis, than women. [10] Demographic analysis of patients showed that most were alcoholics. Alcohol is a well-known risk factor for the occurrence of liver cirrhosis.[11] Liver cirrhosis is associated with several complications like ascites, hepatic encephalopathy, hepatorenal syndrome, variceal hemorrhage, SBP, and hepato-pulmonary syndrome. Once these complications develop, patients are considered to have decompensated liver cirrhosis, and consequently, these patients should be considered for liver transplantation. Ascites, an accumulation of fluid within the peritoneal cavity, is the most common complication of cirrhosis and a leading cause of developing SBP, which is an infection of preexisting ascitic fluid. [12] We also found ascites as the most common identified complication of cirrhosis. Treatment approach analysis of prescribed therapeutic regimens revealed that antibacterial agents and diuretics were among the most frequently prescribed therapeutic class of drugs for the management of complications associated with liver cirrhosis. This finding was consistent with the results reported by other studies. [13,14] Ascites and related SBP is typically treated with diuretics and antibacterial agents. Most of the study patients with ascites were treated with a diuretic regimen, including Furosemide and Spironolactone. A randomized controlled trial of three diuretic regimens concluded that the most successful therapeutic regimen for managing cirrhotic ascites is the combination of oral Furosemide and Spironolactone. [15] Patients suspected of SBP received empiric antibacterial therapy, including Piperacillin-Sulbactam and Ceftriaxone. Antibacterial therapy should be initiated as soon as SBP is suspected of maximizing the patient's chance of survival. Previously, third-generation cephalosporins such as ceftriaxone were recommended for managing SBP, with approximately a 90% resolution rate. Intravenous Cefotaxime (2 g every 12 hours) is recommended as the first-line anti-biotics when multidrug resistances are not prevalent. [16] One randomized trial that examined Cefotaxime in patients with liver cirrhosis and severe SBP revealed several benefits encompassing a higher rate of resolution of the infection, no nephrotoxicity, and no superinfection associated with therapy. [17] Therefore using Cefotaxime as a very effective antibacterial agent needs to be considered in managing SBP associated with liver cirrhosis. Complications associated with cirrhosis may develop a variable degree of acute or chronic pain. Management of pain in patients with liver cirrhosis is challenging since selecting appropriate analgesic agents requires a comprehensive understanding of medications' pharmacokinetic and side effect profiles. [18] In the current analysis, Paracetamol was the first and most commonly prescribed analgesic for pain management. Paracetamol is an effective and safe analgesic for patients with chronic liver disease, considering patients should not actively drink alcoholic beverages. The dose of Paracetamol should be limited to 2 grams per day to avoid harmful effects that may be caused due to accumulation of toxic metabolites. However, Paracetamol entirely should be avoided in patients with alcoholic hepatitis or acute liver injury. Mefenamic acid was the second most common analgesic used to manage pain among study patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of variceal hemorrhage, impaired renal function, and the development of diuretic-resistant ascites. Thus, NSAIDs like Mefenamic acid, Diclofenac, and Aceclofenac are inappropriate drugs of choice for managing pain in cirrhotic patients and should generally be avoided among these patients. [19] For patients who received enteral medications, proton pump inhibitors (PPI) were prescribed to decrease the risk of stress ulceration; ulceration of the upper gastrointestinal tract due to hospitalization. A study showed that PPIs use is associated with an increased risk of SBP, so PPIs should be avoided or only to be given to patients who have clear indications for their use. [20] Overall, we identified 1326 medications prescribed for managing study patients. A patient with liver cirrhosis who suffers from several comorbidities receives more drugs, and polypharmacy is a well-known risk factor that potentiates the occurrence of (DRPs) among patients with liver cirrhosis and patients with other chronic diseases. [21] Moreover, a study showed that patients with more severe liver cirrhosis had a significantly higher proportion of DRPs like DDIs and hepatic dose adjustment. More severe disease requires more complicated pharmacotherapeutic management and hence more medication exposure. [22] Fourthly-one DDIs were detected, of which interaction between Furosemide and NSAIDs such as Mefenamic acid and Diclofenac was the most frequently occurring DDIs. An inappropriate selection of NSAIDs as analgesics may have contributed to the occurrence of such interaction. NSAIDs inhibit renal production of prostaglandins, in turn reducing the excretion of urinary sodium in patients with cirrhosis and can precipitate acute renal failure, azotemia, and worsened ascites. [23] In addition, the interaction between Furosemide and NSAIDs increases the nephrotoxic effect of NSAIDs. Perhaps selecting a safer analgesic such as acetaminophen with a relatively lower than usual dose can improve medication utilization and safety. [24] Through the process of treatment approach analysis, 54 medications that required hepatic dose adjustment were identified. Numerous medications' hepatic metabolism and metabolites are impaired in patients with hepatic impairment. This further leads to accumulation of both the parent drug and its metabolites in the body. All patients with hepatic impairment require strict dose adjustment to avoid toxicity, ineffective therapy, and patient injuries. [25-26] Paracetamol was the most commonly

prescribed medication that required its dose to be adjusted carefully to avoid further hepatic damage and increased hepatic enzymes. [9]

6. CONCLUSION

The present study analyzed the treatment approach of hospitalized patients with liver cirrhosis. Antibacterial agents and diuretics were the most commonly prescribed medications for managing liver cirrhosis complications like SBP and ascites. NSAIDs were the most common analgesics for managing pain among patients, and an inappropriate selection of NSAIDs contributed to the occurrence of the most common identified DDIs. It was observed that several medications required hepatic dose adjustment to avoid patients` exposure to the risk of drug/metabolite accumulation and potential adverse drug effects. A periodic analysis of prescribed medications should be performed as an inappropriate selection of medications can induce DRPs like DDIs or hepatic dose adjustment. Further research focusing on approaches to improve the consistency of healthcare practitioners with recommendations provided by evidence-based medicine practice guidelines and approaches to minimize the occurrence of DRPs among these patients is warranted.

7. AUTHORS CONTRIBUTION STATEMENT

Azardokht Karimi Miri, Atmaram P. Pawar, and Bijoy Kumar Panda developed the study concept, objectives, and design. Azardokht Karimi Miri performed a significant contribution to the acquisition of patient-related data and data analysis. Atmaram P. Pawar and Bijoy Kumar Panda supervised the study process. All authors discussed the results and contributed to the writing of the manuscript.

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9. CONFLICT OF INTEREST

Conflict of interest declared none.

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