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Original article

Polypharmacy in chronic liver disease patients: Implications for disease severity, drug-drug interaction, and quality of life

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ABSTRACT

Multiple prescriptions for different medications may be needed for chronic conditions, increasing the risk of polypharmacy. The WHO defined polypharmacy as "the administration of many drugs at the same time or the administration of an excessive number of drugs". The primary goal of this study was to evaluate polypharmacy in patients with chronic liver disease and to identify potential drug-drug interactions associated with it. A cross-sectional study was conducted at a tertiary care hospital in Mangalore, Karnataka, for six months, from November 2020 to April 2021. The study involved 118 patients with chronic liver disease from various age groups. Data was gathered by analyzing patients' medical records kept on the ward and interviewing them individually. In admission and discharge prescriptions, polypharmacy was examined. Online interaction checkers from Drugs.com and Medscape were used to interpret potential drug-drug interactions. The SF-36 and Chronic Liver Disease Questionnaire were used to measure the quality of life. The data obtained were analyzed statistically to determine the significant correlation. The number of prescribed drugs was significantly correlated ($P = 0.018$) with the severity of liver disease in Child-Pugh categories B and C. Additionally, moderate polypharmacy reduced quality of life ($P < 0.05$), and the physical health category was significantly associated with disease severity ($P < 0.05$). Drug-drug interactions were found in 108 out of the 118 examined prescriptions, totaling 586 interactions in the admission list and 405 interactions in the discharge list. If the potentially serious main drug interaction identified in this study is not well monitored, it could lead to a serious, potentially fatal health condition. Despite being advised, safety is not always guaranteed by liver enzyme monitoring. Therefore, healthcare providers must take additional precautions to avoid inappropriate prescribing, minimize side effects, and ensure drug safety.

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1. Introduction

Chronic liver diseases (CLD) occur globally irrespective of age, sex, locality, or lineage and are the world's 11th leading cause of death (Asrani et al., 2019). As per the latest data published by World Health Organization (WHO) in 2018, liver disease accounts for 3% of the total deaths in India (https://www.worldlifeexpectancy.com/india-liver-disease, Accessed on 09/02/2021). Chronic diseases may require a prescription with multiple medications, often steering to a higher risk of polypharmacy. WHO described polypharmacy as the ''administration of many drugs at the same time or as the administration of an excessive number of drugs"(https://apps.who.int/iris/handle/10665/68896. Accessed on 10/02/2021). It is mostly defined as the simultaneous administration of more than 5 drugs (Stuhec, 2021). Polypharmacy, in turn, has the drawback of increasing the possibility of drug interactions and adverse effects (Varghese et al., 2020). Approximately 50% of older adults over 65) receive at least one unnecessary medication, and research has conclusively shown a substantial correlation between polypharmacy and unfavorable clinical outcomes such as low medication adherence (Maher et al., 2014). WHO has recognized non-adherence as an international primacy in preventing patient harm and optimizing limited health resources (Sabaté, 2003). Due to the growing prevalence of multi-morbidity and polypharmacy, patients with chronic liver disease (CLD) face serious problems. Medications are frequently required to control underlying liver disease, cirrhosis complications, portal hypertension, and comorbidities (Hayward and Weersink, 2020). This adversely impacts medication adherence, leading to increased hospitalization (Hayward et al., 2017).

The Child–Pugh score determines the prognosis of patients with chronic liver disease, primarily cirrhosis. They are categorized as A class (good hepatic function), B class (moderately impaired hepatic function), and C class (advanced hepatic dysfunction) (Tsoris et al., 2021). Patients with chronic liver illness have a lower health-related quality of life (HRQOL), as measured by the generic Short Form 36 (SF-36) or disease-specific questionnaires like the Chronic Liver Disease Questionnaire (Chang et al., 2014; Lam et al., 2009b; Gao et al., 2013; Lam et al., 2009a).

Alteration in pharmacokinetic and pharmacodynamic parameters makes it difficult to manage liver disorders (Palatini and De, 2016). Reduced albumin synthesis substantially increases the blood levels of protein-bound drugs, resulting in drug toxicity (Cheema et al., 2019). Furthermore, metabolism, clearance, distribution, and biliary excretion alter and may lead to drug accumulation or failure to activate the prodrug (Palatini and De, 2016). Polypharmacy in such patients can increase the chance of drug interactions, exacerbating the existing situation. It is challenging to manage such interactions due to wider inter-individual variability (Obach et al., 2005). Since liver disease affects reversible and irreversible enzyme inhibitions, managing inhibitory drug interactions in patients with severe liver dysfunction depends on the mechanism of inhibition. As the inhibitory effect of a reversible inhibitor becomes negligible in advanced hepatic insufficiency, dose adjustment is unnecessary for co-administration. But the extent of irreversible inhibition is partially reduced based on the decreased expression of the inhibited enzyme, which is difficult to measure clinically (Palatini and De, 2016). Wider inter-individual variability makes it challenging to manage. Currently, there are no guidelines for managing drug interactions due to enzyme induction in decompensated cirrhosis. Animal studies have suggested that inducibility depends on the nuclear receptor type and the enzyme isoform. Hence individual dose adjustment based on therapeutic drug monitoring (TDM) is the ideal option to be followed when such interactions are unavoidable (Elzouki et al., 2020).

Polypharmacy is a complex issue that requires careful evaluation and consideration. While there are instances where using multiple medications is necessary and appropriate to treat certain diseases, inappropriate polypharmacy can occur when medications are prescribed without sufficient clinical justification or when healthcare providers lack coordination and monitoring. Therefore, assessing each patient's unique circumstances is important to determine the appropriateness of polypharmacy and to strive for optimal medication management. This study sought to assess polypharmacy in patients with chronic liver disease and its effect on the quality of life in a South Indian hospital setting.

2. Materials and methods

2.1. Sampling

A cross-sectional study was conducted at a tertiary care hospital in Mangalore, Karnataka, for 6 months (November 2020- April 2021). The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Ethics Committee of Shree Devi College of Pharmacy, Mangalore, India (Reference no: YEC-1/310/2018). Patients above 18 years of age diagnosed with chronic liver disease of any etiology were included in the study after obtaining their written informed consent. Patients with mental disorders, obstetrics patients, and those unwilling to participate were excluded. At a 95% level of confidence, a prevalence of 56.3%, and a ± 9% margin of error, the sample size was determined to be 117. Based on the sample size calculation, the data from 118 patients were collected for the study.

2.2. Data collection

Considering the inclusion and exclusion criteria, subjects were recruited in the study after obtaining a signature on written informed consent. Data was acquired using a data collection form by checking patients' medical records kept in the ward and personally interviewing them to assess their quality of life using questionnaires. Before enrollment, the participants were told about the purpose of conducting research and the confidentiality of their information. Once enrolled, we collected subject data in a structured patient proforma. The socio-demographic details including participants' age (18–24, 25–44, 45–64, and greater than 64 years), gender, smoking, and alcoholism history, underlying hepatic disease, medication history (including over-the-counter), pharmacological categories using Anatomical Therapeutic Chemical (ATC) classification (including 14 subcategories) as in Table 1 (https://www.who.int/tools/atc-ddd-toolkit/atc-classification. Accessed on 12/05/2022) were documented in the data collection form. Further, bilirubin (total), Albumin, INR, ascites, and Encephalopathy were noted to calculate Child-Pugh Score to assess the severity of liver disease (Child et al., 1964). Patients' prescriptions were analyzed from patients' medical records before and after discharge to assess the presence of polypharmacy. Based on the information about the number of medications being used by patients, polypharmacy status was determined and categorized

Table 1
Anatomical therapeutic chemical (ATC) pharmacological classification.

Code	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatological
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infective for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculoskeletal system
N	Nervous system
P	Antiparasitic products, insecticides, and repellents
R	Respiratory system
S	Sensory organs
V	Various

as mild (2–4 drugs), moderate (5–9 drugs), and severe (greater than9 drugs)]. Drug-drug interactions were assessed using Drugs.com (https://www.drugs.com/drug_interactions.html, Accessed on 12/05/2022) and Medscape interaction checkers (https://reference.medscape.com/drug-interactionchecker, Accessed on 12/05/202222). Drug duplication occurs because of prescribing more than one medication for the same indication. In this study, patients' prescription was analyzed for drug duplication.

The Chronic Liver Disease Questionnaire (CLDQ) is a valid and reliable tool to assess health-related quality of life (HRQL) in patients with chronic liver disease (Younossi et al., 1999). Consisting of 29 questions testing 6 different psychological and physical domains, including abdominal symptoms (Items 1, 5, 17), Fatigue (Items 2, 4, 8, 11, 13), systemic symptoms (Items 3, 6, 21, 23, 27), activity (Items 7, 9, 14), emotional function (Items 10, 12, 15, 16, 19, 20, 24, 26), worry (Items 18, 22, 25, 28, 29). A 7-point Likert scale was used in all items ranging from 1 (most impairment) to 7 (less impairment). Questionnaire scoring was calculated by dividing the domain score by the number of questions in each domain. In contrast, the total score was calculated by the sum of all domain scores divided by 29.

36-item Short Form Health Survey (SF-36 Questionnaire) (Burholt and Nash, 2011) consists of 36 questions measuring 8 different domains, including general health (2 items), physical functioning (10 items), physical role limitations (4 items), emotional health problems (3 items), social functioning (1 item), bodily pain (2 items), energy and emotions (9 items), social activities (1 item), energy/vitality (4 items). Item scoring varied from dichotomous (yes/no) to six-point Likert scale ranging from "none" to "very severe". Each domain score transformed from 0 (poor health) to 100 (excellent health).

2.3. Statistical analysis

Study population characteristics are reported in descriptive statistics. Mean and the standard deviation is used for continuous data. Frequency and percentage are used for categorical data. Association between groups was evaluated by using the chi-square test (χ^2) and Fisher's exact test (two-tailed, wherever applicable). A statistical package, SPSS version 25, was used to perform the analysis. $P < 0.05$ was deemed to be significant.

3. Results

3.1. Demographic characteristics of patients

The average age of the 118 patients included in the study was 47.99 ± 11.39; 95% were male, and 5% were female. Of the 118 subjects, 14 were categorized as belonging to the A class, 54 to the B class, and 50 to the C class, according to the Child-Pugh score, whereas 78% were alcoholics and 66% were smokers (Table 2).

3.2. Polypharmacy and sociodemographic variables

It was identified that most of the prescriptions had moderate polypharmacy, and it was higher during admission than discharge ($P < 0.001$), as shown in Table 3. A significant association was found between the severity of liver disease and polypharmacy; categories B and C of Child-Pugh showed many prescribed medications (P value; 0.018). A significantly high percentage of alcoholic patients exhibited a severe form of polypharmacy. At the same time, no significant association was noticed between the age, gender, and smoking status of the patient with their polypharmacy condition (Table 4).

3.3. Medications prescribed to chronic liver disease patients according to ATC classification

Of the 171 types of drugs prescribed, most of the drugs were under the category of Alimentary tract and metabolism (A class). The highest number of drugs prescribed in the 'A' category was Lactulose, Pantoprazole, Thiamine, Ranitidine, and Rifaximin in both admitted and discharged lists. Vitamin K and B12 were utilized more in the B class, and in 'C' class, Furosemide, Spironolactone, and Propranolol were highly prescribed. The highest number of anti-infectives (J class) given were Ceftriaxone and Cefotaxime. In the category 'N', Tramadol, Paracetamol, and Lorazepam were prescribed.

3.4. Drug duplication

27 patients were identified with drug duplications, and the most common duplication was with cardiovascular agents, with a maximum of 4 drugs prescribed in both admission and discharge.

3.5. Health-related quality of life

From the CLDQ questionnaire, quality of life was assessed and compared with the severity of disease and polypharmacy. It was observed that quality of life was compromised more with moderate polypharmacy ($p < 0.05$), as shown in Table 5. When assessed with the SF-36 questionnaire, it was observed that limitation due to the physical health domain is closely associated with the disease severity ($p < 0.05$). Other domains showed no statistically significant result.

Table 2
Demographic characteristics of patients.

Characteristics	Number = 118
Gender, n (%)	
-Male	112(95)
-Female	6(5)
Age, mean ± SD, year	47.99 ± 11.39
Social status, n (%)	
-Smoker	40 (33.9)
-Alcoholic	92 (78)
Child-Pugh grading, n (%)	
-Class A	15(12.7)
-Class B	54(45.7)
-Class C	49(41.5)

Table 3
Severity of polypharmacy.

Polypharmacy	On admission n (%)	On discharge n (%)
Mild	6(5.08)	32(27.8)
Moderate	68(57.6)	77(67)
Severe	44(37.2)	6(5.2)
Total	118(100)	115(100)

3.6. Drug interactions

On analyzing 118 prescriptions, drug-drug interactions (DDI) were found in 108, with 586 interactions in the admission list and 405 in the discharge list. Most interactions were of moderate severity (i.e., 77.6% of the total interactions in admission and 87.6% in discharge), followed by minor interactions (15.7% in admission & 9.4% in discharge). 6.7% of the total interaction in admission and 3% in discharge were found to be major. Spironolactone was the highly interacting drug in admission and discharge, followed by Tramadol, Propranolol, Ondansetron, Potassium chloride, and Furosemide in admission. Not more than 3 significant interactions were found per prescription. Among subjects, 8 patients during admission and 1 patient on discharge had more than two significant interactions. The most common major interaction was between Potassium chloride and Spironolactone, followed by Ondansetron with Tramadol. The most common mechanism for significant and moderate interactions was an addition (55.5%), and for minor interactions was hepatotoxicity (15.3%).

3.7. Relation between significant DDI, polypharmacy, and ATC drug classes

A statistically significant association was found between all major drug interactions and the following: polypharmacy, being on alimentary tract and metabolism drugs, being on blood and blood-forming organ drugs, and cardiovascular drugs. Polypharmacy was significantly correlated with alimentary tract and metabolism drugs, as shown in Table 6.

Table 5
Relation of Polypharmacy with Quality of life.

Polypharmacy	Mean CLDQ score	
	Admission	**Discharge**
Mild	1.02	0.929
Moderate	0.842	0.853
Severe	0.906	0.804
P value	**0.0178***	0.068

*$P < 0.05$; CLDQ: Chronic Liver Disease Questionnaire.

4. Discussion

This study analyzed polypharmacy in chronic liver disease patients of all age groups, excluding children during admission and discharge. Age is often associated with various health outcomes. In this study, we categorized age into 4 groups to explore and compare the characteristics and outcomes within each group. In our study, most of the polypharmacy was either moderate or severe in the age group starting from 45 years, necessitating close monitoring of the patients. Further, polypharmacy was significantly linked to alimentary tract and metabolism (Class A) drugs. It also adversely affected the quality of life of the subjects.

In this study, remarkable numbers of potential drug-drug interactions were observed. The drug-drug interactions were observed more in prescriptions with a more significant number of drugs. Most common potential drug interactions belonged to the moderate class (77.6% on the admission drug list and 87.6% on the discharge drug list), and potentially severe drug interactions constituted 6.7% of total drug-drug interactions. A study by Salwe KJ et al (2016) showed similar findings. The liver is a metabolic hub of the human body; it is essential to assess the drug interaction mechanism and how it gets altered in liver disorders

Table 4
Sociodemographic features and polypharmacy.

Characteristics	Variables	Polypharmacy			Total	*P* Value*
		Mild	**Moderate**	**Severe**		
Age	18–24	0(0)	3(100)	0(0)	3(3)	0.013
	25–44	1(2.4)	16(38.1)	25(59.5)	42(36)	
	45–64	5(7.7)	43(66.2)	17(26.2)	65(55)	
	>=65	0(0)	6(75)	2(25)	8(7)	
	Total	6(5.1)	68(57.6)	44(37.3)	118(100)	
Gender	Female	0(0)	5(83.3)	1(16.7)	6(5.1)	0.413
	Male	6(5.4)	63(56.3)	43(38.4)	112(94.9)	
	Total	6(5.1)	68(57.6)	44(37.3)	118(100)	
Smoking status	Yes	3(7.5)	21(52.5)	16(40)	40(33.9)	0.580
	No	3(3.8)	47(60.3)	28(35.9)	78(66.1)	
	Total	6(5.1)	68(57.6)	44(37.3)	118(100)	
Alcoholism status	Yes	4(4.3)	48(52.2)	40(43.5)	92(78)	0.032
	No	2(7.7)	20(76.9)	4(15.4)	26(22)	
	Total	6(5.1)	68(57.6)	44(37.3)	118(100)	
Underlying Hepatic Disease	Decompensated Cirrhosis	2(4.5)	25(56.8)	17(38.6)	44(37.3)	0.996
	Compensated Cirrhosis	4(6.8)	34(57.6)	21(35.6)	59(50)	
	Hepatitis B	0(0)	3(50)	3(50)	6(5.1)	
	Hepatitis C	0(0)	3(75)	1(25)	4(3.4)	
	Hepatocellular Carcinoma (HCC)	0(0)	1(50)	1(50)	2(1.7)	
	Alcoholic Hepatitis	0(0)	2(66.7)	1(33.3)	3(2.5)	
	Total	6(5.1)	68(57.6)	44(37.3)	118(100)	
Child-Pugh score	A (5–6)	3(21.4)	8(57.1)	3(21.4)	14(11.9)	0.018
	B (7–9)	3(5.6)	28(51.9)	23(42.6)	54(45.8)	
	C (10–15)	0(0)	32(64)	18(36)	50(42.4)	
	Total	6(5.1)	68(57.6)	44(37.3)	118(100)	

*Pearson Chi-Square and Fisher's exact test (two-tailed, wherever applicable).

Table 6
Relation between major DDI, polypharmacy and ATC drug classes.

SL NO	ATC CLASS	SEVERE POLYPHARMACY			MAJOR DDI		
		FREQ	x^2	*P value*	FREQ	x^2	*P value*
1	**A**	183	4.51	**0.034**	25	122	< 0.001
2	**B**	52	0.045	0.832	1	34.5	< 0.001
3	**C**	91	3.16	0.076	35	188	< 0.001
6	**H**	8	0.686	0.408	1	10.9	< 0.001
7	**J**	37	2.15	0.142	10	17.8	< 0.001
10	**N**	47	0.022	0.883	21	31.9	< 0.001
12	**R**	25	2.83	0.093	4	14.7	< 0.001

* $P < 0.05$; DDI: drug-drug interaction; ATC: Anatomical therapeutic chemical: FREQ: Frequency.

(Palatini and De, 2016). Synergism was the most common mechanism by which the drugs exhibited major and moderate interactions. All significant DDI was significantly correlated with polypharmacy, being on alimentary tract and metabolism drugs, blood and blood-forming organ drugs, and cardiovascular drugs. That is, the high prevalence of DDI can be attributed to polypharmacy. Propranolol showed a higher number of interactions in our study. It has a high first-pass metabolism, indicating that the plasma drug level of propranolol will be higher in severe liver disorders. That can even increase due to synergistic interaction causing harm to patients. Arthur MJ et al (1985) stated that in patients presenting with severe liver disease (serum albumin<30 g/l), 24 h after a single dose of 20 mg administration of propranolol, it could be detected in plasma with high steady-state concentrations (mean 266.5 ng/ml, range 84–406). The condition would be severe if all the drugs were compared and studied similarly. Hence, it is always better to avoid significant interactions, especially in liver cirrhosis patients. But when such an interaction is unavoidable, the induced drug's effect and plasma concentration should be strictly monitored. The finding that liver cirrhosis alters the magnitude of DDIs significantly has substantial methodological implications.

Polypharmacy is also associated with drug duplications and contraindicated prescribed drug combinations. Duplication was statistically proven higher among the admitted patients than on discharge ($P < 0.01$). In this study, 27 patients on admission and 8 patients on discharge were identified with drug duplications, and the most common duplication was with cardiovascular agents in both admission and discharge.

Most of the drugs administered to patients must be cautiously used in CLD. Following are the drugs prescribed under ATC that require use with caution or are contraindicated in liver disease: furosemide, Spironolactone, Propranalol, Vitamin K, Ceftriaxone, Rifaximin, Tramadol, Paracetamol, Lorazepam, Metronidazole.

Furosemide and spironolactone can induce sudden fluid and electrolyte imbalance in patients with CLD, which may worsen hepatic encephalopathy and can precipitate hepatic coma (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016273s061lbl.pdf. Accessed on 10/09/2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/012151s062lbl.pdf. Accessed on 12/09/2020). A study by Serste T et al (2010) described that subject with cirrhosis and refractory ascites had a higher mortality rate when treated with beta-blockers than the control group. They suggest that the use of propranolol must be contraindicated in those patients (Sistanizad et al., 2013). In patients with cirrhosis and spontaneous bacterial peritonitis, non-selective beta-blockers have been shown to increase the risk of hepatorenal syndrome and death (Mandorfer et al., 2014).

All medications were classified according to the Anatomical Therapeutic Chemical Classification System. The most common ATC class used in our study was from the category of Alimentary tract and metabolism (40%). Most drugs were for vitamin supplements (34.2%) and acid-related disorders (27%). Cardiovascular drugs account for 25.8% of the total drugs; 70.4% were diuretics, and 20.4% were beta blockers. Drugs acting on blood and blood-forming organs were 9.6%, most of which were anti-anemic preparations (86.1%). The ATC system aims to improve the quality of drug use (World Health Organization, 2013). An appropriate observation by clinical pharmacists is required to reduce issues identified with polypharmacy by analyzing prescriptions and suggesting interventions. An earlier study found that including a clinical pharmacist in a collaborative healthcare team reduced polypharmacy, medication errors, drug-related issues, and potential drug interactions and thus improved patients' quality of life. The present study also has shown that polypharmacy compromised patients' quality of life. It was significantly ($p < 0.05$) reduced with moderate polypharmacy and during admission. This study used the chronic liver disease questionnaire (CLDQ) scale score to evaluate patients' quality of life. It was compared with the disease severity assessed using the Child-Pugh score. We found that higher severity of disease (Child-Pugh class-C) was associated with a lower CLDQ score, indicating the worsening of quality of life with increasing disease severity, consistent with the previous study (Stuhec et al., 2019; Sumskiene et al., 2006). SF-36 scores pointed out that the disease severity significantly compromised the physical health domain.

4.1. Limitations of the study

The study was conducted in a single center with a small population for a short period. Hence larger samples and long duration are needed to improve the generalizability of the findings. Moreover, the study focused on potential drug-drug interaction but did not offer any intervention, rendering it impossible to know whether the treating physicians were aware of the interactions. We determined the number of medications consumed based on prescription data. However, they do not convey information on adherence to the prescribed medications or the actual number of pills taken by the patients. Our definition of polypharmacy was based on a cutoff of $\geq$ 5 drugs per prescription, which has been used in previous studies. However, this threshold may not apply to all patients. In addition, most of the people who participated in the research were male (95% of participants were male, while just 5% were female). Several characteristics may render men more likely than women to acquire chronic liver disease; this may be why we could not recruit many female patients for the study. The skewed gender distribution may restrict the generalizability of the study's findings to both genders. Therefore, concluding the effects of polypharmacy on chronic liver disease may not apply to women if they are not adequately represented in the sample.

5. Conclusion

In conclusion, it was observed that most prescriptions had moderate polypharmacy, which indicates that most people administer more than 5 medications simultaneously. Polypharmacy correlates

significantly with ATC drug class A, depicting that most drugs prescribed are from the alimentary tract and metabolism class. This reveals that polypharmacy is a significant issue in liver disease patients where particular precaution is required, that in turn, adversely affects the quality of life of patients. Quality of life decreased with increased disease severity as measured by child-pugh score. An increased number of drugs also increases drug interactions, which may negatively influence health outcomes. The potentially severe major drug interaction identified in this study, if not monitored, may result in serious life-threatening health conditions. Prescribing medicines to patients with liver disease is a difficult task. There are no reliable tests that can identify altered drug metabolism in these patients. Monitoring the liver enzymes, though recommended, cannot always ensure safety. Hence healthcare professionals should take precautions about inappropriate prescribing to evade unwanted drug effects and to ensure drug safety. The medication regimen can be optimized by eliminating drug duplication, reducing the dosing frequency, and regularly reviewing the drug regimen with the help of clinical pharmacy services. Individualizing the treatment based on various factors is the ideal option. Further studies are mandatory to compile more evidence on safe medication practices for liver disease.

6. Ethical approval and consent to participate

The study was approved by the Shree Devi College of Pharmacy's institutional Ethics Committee, Mangalore, India (Reference no: YEC-1/310/2018). The data collector informed participants about the study's goals, methodology, potential risks, the voluntary nature of their participation, and the confidentiality of their responses. They were told they could decline or withdraw without facing any repercussions. All discussions with participants were in the local language to facilitate understanding and comprehension. Those who consented were enrolled in the study after obtaining their signature on an informed consent form.

7. Availability of supporting data

The datasets used and analyzed during the current study are available from the first author upon reasonable request.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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