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The Role of Clinical Pharmacist in Reducing Drug Related Problems in Decompensated Liver Cirrhosis Patients

Ameer A. Khazal[*,1] and Mohammed Y. Jamal [2]

[1] Ministry of Health and Environment, Al-Karkh Health Directorate, Baghdad, Iraq

[2]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Abstract

Patients with decompensated cirrhosis have typically prescribed a combination of therapeutic and prophylactic medications. Polypharmacy increases the probability of medication errors and drug related problems. Clinical pharmacists are highly effective at identifying, resolving, and preventing clinically important drug-related problems in their patients' care. The objectives of the study were the identification and classification of drug-related problems, as well as the discussion of these problems with health care providers (physicians, pharmacists, and nurses) and patients. Reduce their incidence as effectively as possible and educate all research participants on the significance of following their prescribed drug regimen. Prospective, interventional, clinical study for 80 hospitalized decompensated liver cirrhosis patients was conducted at Baghdad Teaching Hospital and lasted for four months from the first of December 2021, until the 31st of March 2022. The study involved two phases, the first one was an observational to identify drug related problems and classify them according to the Pharmaceutical Care Network Europe classification version 9.1, and the second phase was interventional to increase the awareness of patients and health care providers about those problems and to propose a proper solution for each one. The majority of drug-related problems were attributable to the effect of drug treatment not optimal in 41.5%, Adverse drug events (possibly) were detected in 41.5 %, and untreated symptoms or indications in 17%. Causes were Drug overdose in 30.2%, patients unintentionally using the drug in the wrong way in 22.6%, and unavailability of the prescribed drug in 13.2%. Omeprazole and lactulose were the most common medications causing problems. Acceptance and full implementation were high and observed in 71.7% of pharmacist interventions while 15.1% of the intervention that the pharmacist recommended to the health care providers and patients have no agreement. Significant numbers of Iraqi patients with decompensated liver cirrhosis have drug-related problems, and the use of proton pump inhibitors in too high dose was accountable for a large number of problems. Physicians and clinical pharmacists collaborated exceptionally well.

Keyword: Drug related problems, Decompensated liver cirrhosis, Clinical pharmacist, Iraq

دور الصيدلاني السريري في تقليل المشاكل المتعلقة بالأدوية لدى مرضى تليف الكبد اللا تعويضي

امير علي خزعل*[،١] و محمد ياوز جمال[٢]

[١]وزارة الصحة والبيئة ، دائرة صحة بغداد، الكرخ ، بغداد ، العراق.

[٢]فرع الصيدلة السريرية، كلية الصيدلة، جامعة بغداد ، بغداد ، العراق.

الخلاصه

عادة ما يصف المرضى الذين يعانون من تليف الكبد اللا تعويضي مجموعة من الأدوية العلاجية والوقائية. يزيد تعدد الأدوية من احتمالية الأخطاء الدوائية والمشكلات المتعلقة بالأدوية. يتمتع الصيادلة السريريون بفاعلية عالية في تحديد وحل ومنع المشكلات ذات الصلة بالأدوية المهمة سريريًا في رعاية مرضاهم. كانت أهداف الدراسة تحديد وتصنيف المشاكل المتعلقة بالدواء ، وكذلك مناقشة هذه المشاكل مع مقدمي الرعاية الصحية (الأطباء والصيادلة والممرضين) والمرضى. تقليل حدوثها بأكبر قدر ممكن من الفعالية والقيام بتثقيف جميع المشاركين في البحث حول أهمية اتباع نظام الأدوية الموصوف لهم. أجريت دراسة سريرية مستقبلية وتدخلية لـ ٨٠ مريضاً من مرضى تليف الكبد اللاتعويضي في مستشفى بغداد التعليمي واستمرت لمدة أربعة أشهر من الأول من كانون الأول (ديسمبر) ٢٠٢١حتى ٣١ آذار (مارس) ٢٠٢٢، وتضمنت الدراسة مرحلتين ، الأولى كانت مرحلة ملاحظة لتحديد المشكلات المتعلقة بالأدوية وتصنيفها وفقًا لتصنيف شبكة الرعاية الصيدلانية الأوروبية الإصدار ٩.١ ، وكانت المرحلة الثانية تدخلية لزيادة وعي المرضى ومقدمي الرعاية الصحية بهذه المشكلات واقتراح حل مناسب لكل منها.تُعزى غالبية المشكلات المتعلقة بالادوية إلى تأثير العلاج الدوائي غير الأمثل في ٤١.٥٪، والحدث الدوائي الضار (ربما) الذي يحدث في ٤١.٥٪، والأعراض أو المؤشرات غير المعالجة في ١٧٪. كانت الأسباب هي زيادة جرعة الدواء في ٣٠.٢٪، واستخدام المريض للدواء بشكل خاطئ عن غير قصد في ٢٢.٦٪ ، والدواء الموصوف غير متوفر في ١٣.٢٪.كان أوميبرازول واللاكتولوز أكثر الأدوية التي تسبب المشاكل شيوعًا. كان القبول والتنفيذ الكامل مرتفعًا ولوحظ في ٧١.٧٪من التدخلات الصيدلانية. بينما ١٥.١٪من التدخلات التي اوصى بيها الصيدلي لمقدمي الرعاية والمرضى لم تلاقي القبول. يعاني عدد كبير من المرضى العراقيين المصابين بتليف الكبد اللا تعويضي من مشاكل متعلقة بالأدوية ، وكان استخدام مثبطات مضخة البروتون بجرعات عالية جدًا مسؤولاً عن عدد كبير من المشاكل. تعاون الأطباء والصيادلة السريريون بشكل جيد للغاية.

الكلمات المفتاحية: المشاكل المتعلقة بالادوية، تليف الكبد اللاتعويضي ، الصيدلي السريري ،العراق.

[1]Corresponding author E-mail: ameer.92alobeidi@gmail.com
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Introduction

Cirrhosis naturally develops through an asymptomatic compensated phase followed by a decompensated phase characterized by the development of overt clinical manifestations, the most common of which are ascites, bleeding, encephalopathy, and jaundice. Following the start of any of these symptoms, the disease often progresses more rapidly toward death or liver transplantation [(1)]. Cirrhosis and other chronic liver diseases contribute significantly to worldwide morbidity and mortality. Cirrhosis accounted for 2.4% of global deaths in 2017, up from 1.9% in 1990. In 2017, there were also 106 million cases of decompensated cirrhosis and 112 million cases of compensated cirrhosis globally[(2)]. Cirrhosis becomes a systemic illness if decompensation occurs, resulting in multi-organ/system dysfunction[(3)]. Decompensation marks a prognosis tipping point, as the median survival time for compensated cirrhosis reduces from more than 12 years to less than two years for decompensated cirrhosis [(4)]. Rebleeding, acute kidney injury, with or without the characteristics of hepatorenal syndrome, hepato-pulmonary syndrome, Porto pulmonary hypertension, cirrhotic cardiomyopathy, and bacterial infections may further accelerate the course of the decompensated condition[(5)]. Drug-Related Problems (DRPs) are drug-related events or circumstances that interfere with or have the potential to interfere with desirable health outcomes. Pharmaceutical Care Network Europe (PCNE) created a classification scheme for DRPs in 1999, and it has been regularly updated since then. The most recent version (9.1) was published in February 2020, and it includes problems, causes, and interventions [(6)]. DRPs were identified to be common in patients with liver cirrhosis. DRPs were reported at a frequency of 14 to 23.4 %. Drug interactions, improper dosage, and the use of contraindicated medicines were the most common causes of DRPs[(7)]. Patients who have decompensated cirrhosis are more likely to have DRPs. Nearly 60% of drug-related problems were recognized and resolved as a direct result of the pharmacist intervention [(8)]. The study aimed to identify and categorize any drug-related problems among decompensated liver cirrhosis patients, as well as to eliminate these problems by providing appropriate advice in partnership with healthcare practitioners.

Patients and Methods

A prospective, interventional, clinical study was conducted at Baghdad Teaching Hospital. The study involved two phases: observational and interventional (behavioral). The major objective of the first phase (observation) was to assess the prevalence of DRP in individuals with decompensated liver cirrhosis.

During the observation phase, the researcher identified and classified any drug-related problems using PCNE Classification for Drug-Related Problems version 9.1[(6)]. In the second phase, the researcher pharmacist conducted interventions with patients their caregivers about the problems related to the improper use of their medication regimen, and also interventions were conducted with hospital gastroenterologists about the DRPs that related to physician's errors e.g. (improper drug dose, incorrect dosage frequency, contraindication). Data collection lasted for four months from the first of December 2021, until the 31st of March 2022. Eighty patients with decompensated liver cirrhosis were enrolled in the study.

Inclusion criteria

1. Hospitalized patients with decompensated liver cirrhosis
2. Patients older than 18 years old.
3. Patients who provide their agreement to participate in the study.

Exclusion criteria

Patients who refuse to participate in the study were excluded from the study

Data collection/ observational phase

The research team designed a special sheet to collect data according to the study's objectives. Patient's demographic data, comorbidities, laboratory investigations, numbers, and related drugs were collected from their case sheets and by participating in daily morning tours with the physicians and clinical pharmacists. All information was verified with patients, caregivers , orphysicians. The researcher was interested in identifying and classifying all types of DRPs according to the PCNE classification scheme [(6)].

Interventional phase

This interventional phase was conducted concurrently with the observational phase and included delivering appropriate clinical pharmacological interventions on both the patient and physician levels, then determining the level of agreement over these interventions. At the patient level, the majority of patients were extremely ill and unable to communicate, so the researcher interviewed members of the patients' families or caregivers. The majority of drug-related problems at the patient level were due to the improper use of their medication regimen or using their medication in low doses that did not match their prescribed dose which led to the nonoptimal effect of their treatment.

The interventions at the patient level included speaking to the patients or their caregivers and providing them with verbal and in-writing information regarding the proper use of their medication regimen. At the physician's level, the researcher proposed a proper clinical intervention according to the American Association for the study of liver diseases (AASLD) Guidelines [9]. The intervention focused on that the physicians are prescribing the drugs that the decompensated liver cirrhosis patients need in their therapeutic and prophylaxes regimen at the proper dose, at the right frequency, and that their choice of medication complies with the guideline. These interventions for the physicians were accompanied by information from the references (ASSLD Guidelines) to convince the physicians to make the necessary modification that was proposed by the researcher. Also, all the all-prescribed drugs were screened for potential drug interactions by using Medscape.

Ethical consideration

A research proposal was approved by the Scientific Committee of the College of the Pharmacy/ University of Baghdad before it was submitted and officially approved. In addition, the study was approved by the hospitals, and a verbal agreement was gained from the patients. regarding critically ill patients' agreement was gained from their family members.

Statistical analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS) software version 25. Descriptive statistics (means, standard deviation, frequencies, and percentages) were conducted for all study items. A P-value of less than 0.05 was considered statistically significant.

Results

In this study, the mean age of the decompensated liver cirrhosis patients was 52.46 ± 16.43. The mean Body Mass Index (BMI) was 28.04 ± 4.12. More than two-thirds of the patients in the study sample were Male 58 (72.5 %), about work 70 % of the patients were self-employed, and illiterate patients made up the majority of the study population 70 (87.5 %). Alcoholic liver cirrhosis was the most common etiology in study group 35(43.8%). Diabetes Mellites (DM) was the most frequent comorbidities in decompensated liver cirrhosis patients 23(28.7%). regarding complication of liver cirrhosis ascites was found in 41(51.2%) of the patients, also 11 of the study sample presented to the hospital with two complications, whereas the rest presented with a single complication, as shown in Table (1).

Table 1. Demographic data and clinical characteristics of the study sample. Parameter

Variable	N	Min	Max.	Mean	Std. Dev.
Age (years)	80	18	75	52.46	16.43
Weight (kg)	80	51	128	82.78	14.71
Height (m)	80	1.39	1.87	1.72	0.09
BMI	80	19.59	41.21	28.04	4.12
Character		**subcategories**		**N**	**%**
Gender		Male		58	72.5
		Female		22	27.5
Work		Self employed		56	70.0
		Employed		3	3.8
		Housewife		19	23.8
		Student		2	2.5
Education		Uneducated		70	87.5
		Secondary school		9	11.3
		College degree		1	1.3
Etiology		Cryptogenic		20	25
		Alcoholic		35	43.8
		HBV		9	11.3
		HCV		8	10.0
		AIH		6	7.5
		Wilson disease		1	1.3
		NAFLD		1	1.3
Comorbidities of patients		hypertension		13	16.3
		DM		23	28.7
		Acute myeloid leukemia		1	1.3
		Parkinson disease		1	1.3
		Osteoarthritis		1	1.3
		chronic kidney disease		1	1.3
		Benign prostate hypertrophy		1	1.3
Number of complications of liver cirrhosis for each patient		One complication		69	86.3
		Two complications		11	13.7
Complication of decompensated cirrhosis		Ascites		41	51.2
		Bleeding		22	27.5
		Hepatic encephalopathy		18	22.5
		Jaundice		10	12.5
Total				80	100

HBV; Hepatitis B Virus, HCV; Hepatitis C virus, AIH; Auto-Immune Hepatitis, NAFLD; Non-Alcoholic Fatty Liver Disease.

The main DRPs were related to the effect of drug treatment is not optimal in 41.5%, adverse drug events(possibly) occurring in 41.5%, and the least for untreated symptoms or indications at 17% as shown in Table (2).

Table 2. Main DRPs.

Main DRPs	N	%
Effect of drug treatment not optimal	22	41.5
Adverse Drug Events (possibly) occurring	22	41.5
Untreated symptoms or indication	9	17.0
Total	53	100.0

There were 16 causes (30.2%) of DRPs related to the Drug dose of a single active ingredient being too high, while the Patient unintentionally administering/using the drug in a wrong way was responsible for 12 causes (22.6%) of DRPs. Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements, Duration of treatment too short, Patient uses/taking more drugs than prescribed had the least causes one for each (1.9%) as shown in Table (3).

Omeprazole was the most drug encountered that caused DRPs, with the Drug dose of 40mg or greater per day were considered too high and intervention was proposed to physicians to convince them to use it in a reduced dose, followed by lactulose in which the Patient unintentionally administers/uses the drug in a wrong way that not match their prescribed dose which led to non-optimal effects of the treatment. Norfloxacin, Metronidazole, Octreotide, Gaviscon, Prednisolone, and Simal had the least frequent DRPs as Shawon in the Table (4).

Table 3. Causes of DRPs.

Causes of drug-related problems	N	%
Drug dose of single active ingredient too high	16	30.2
Patient unintentionally administers/uses the drug in a wrong way	12	22.6
Prescribed drug not available	7	13.2
Drug dose too low	6	11.3
Dosage Regimen is not frequent enough	3	5.7
Inappropriate drug according to guidelines/formulary	2	3.8
No or incomplete drug treatment in spite of existing indication	2	3.8
Necessary information not provided or incorrect advice provided	2	3.8
Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	1	1.9
Duration of treatment too short	1	1.9
Patient uses/takes more drug than prescribed	1	1.9
Total	53	100.0

Table 4. Distribution of medication according to the cause of DRPs expressed as a number(percentage).

drugs	C1.1	C1.3	C1.5	C3.1	C3.2	C3.3	C4.1	C5.1	C5.2	C7.2	C7.8	Total (%)
Omeprazole	0(0)	1 (100)	0(0)	0(0)	15(93.8)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	16(30.2)
Lactulose	0(0)	0(0)	2(100)	1(16.6)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	6(50)	9(16.9)
Rifaximin	0(0)	0(0)	0(0)	0(0)	0(0)	2(66.7)	0(0)	1(14.3)	0(0)	0(0)	1(8.3)	4(7.7)
Ciprofloxacin	0(0)	0(0)	0(0)	2(33.4)	0(0)	0(0)	1(33.3)	0(0)	0(0)	0(0)	0(0)	3(5.6)
Cefotaxime	0(0)	0(0)	0(0)	2(33.4)	0(0)	0(0)	0(0)	1(14.3)	0(0)	0(0)	0(0)	3(5.6)
Lasix	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(100)	0(0)	1(8.3)	3(5.6)
Albumin	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	3(42.8)	0(0)	0(0)	0(0)	3(5.6)
spironolactone	0(0)	0(0)	0(0)	1(16.6)	0(0)	0(0)	0(0)	1(14.3)	0(0)	0(0)	0(0)	2(3.8)
Urso	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(16.8)	2(3.8)
Paracetamol	1(50)	0(0)	0(0)	0(0)	1(6.2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(3.8)
Norfloxacin	0(0)	0(0)	0(0)	0(0)	0(0)	1(33.3)	0(0)	0(0)	0(0)	0(0)	0(0)	1(1.9)
Metronidazole	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(8.3)	1(1.9)
Octreotide	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(14.3)	0(0)	0(0)	0(0)	1(1.9)
Gaviscon	1(50)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(1.9)
Prednisolone	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	1(1.9)
Simal	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(8.3)	1(1.9)
Total	2(100)	1(100)	2(100)	6(100)	16(100)	3(100)	1(100)	7(100)	2(100)	1(100)	12(100)	53(100)

C1.1; Inappropriate drug according to guidelines/formulary, C1.3; Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements, C1.5; No or incomplete drug treatment in spite of existing indication, C3.1; Drug dose too low, C3.2; Drug dose of a single active ingredient too high, C3.3; Dosage regimen not frequent enough, C4.;1 Duration of treatment too short, C5.1; Prescribed drug not available, C5.2; Necessary information not provided or incorrect advice provided, C7.2; Patient uses/takes more drug than prescribed, C7.8; Patient unintentionally administers/uses the drug in a wrong way

The most common frequent pharmacist intervention was the intervention proposed to the prescriber in 29(54.7%) followed by speaking to a family member/caregiver 20(37.7%) as Shawon in the Table (5).

Table 5. Types of pharmacist interventions

The pharmacist intervention	N	%
Prescriber informed only	2	3.8
Intervention proposed to prescriber	29	54.7
Spoken to family member/caregiver	20	37.7
Instructions for use changed to	2	3.8
Total	53	100.0

Acceptance and full implementation were observed in 71.1% of the intervention while no agreement on intervention was seen in 15.1% as shown in table (6).

Table 6. Distribution of the patients according to acceptance per planned intervention

Acceptance	N	%
Intervention accepted and fully implemented	38	71.7
Intervention accepted but not implemented	3	5.7
Intervention not accepted: not feasible	4	7.5
Intervention not accepted: no agreement	8	15.1
Total	53	100

Discussion

Drug related problems were frequently related to medications provided to individuals with decompensated liver cirrhosis. These DRPs caused unnecessary harm ranging from treatment failure, morbidities, and patient death, which supports the engagement of clinical pharmacists in the assessment of the pharmacotherapeutic regimen for critically sick patients with decompensated liver cirrhosis(Aghili and Kasturirangan) [(10)]. In the current study, the main of DRPs were related to the effect of drug treatment is not optimal, adverse drug events(possibly) occurring, and the least untreated symptoms or indication. In Australia, Hayward et al., (2019) [(8)] studied medication-related problems in 57 outpatients with decompensated liver cirrhosis without using PCNE classification and identified 375 problems in which Nonadherence (31.5%) and indication problems (29.1%) were the most prevalent DRPs types. In another study in Basal/Switzerland by Franz et al., (2012) [(11)] which studied potential drug-drug interactions and adverse drug reactions in 400 cirrhotic patients, in about 28% of the study patients 200, adverse drug reactions were identified. It is clear that the DRPs were different in each of the studies that were discussed earlier; this could be a consequence of the complexity involved in the pharmacotherapy of patients with decompensated liver cirrhosis, who often suffer from a variety of serious complications that necessitate the use of multiple drugs for either therapeutic or prophylactic purposes[(12)]. The increasing loads of patients and treating physicians necessitate the clinical pharmacist's involvement in formulating, enabling, and actively participating in the arrangement of the medications and leading the treating physician towards safer treatment options. In the current study, the most frequent causes of drug related problems were the drug dose of a single active ingredient too high followed by the patient unintentionally administering/using the drug in a wrong way, and the unavailability of the prescribed drug. These findings were comparable to the results of the study done by Franz et al., (2013) [(13)] in Switzerland who enrolled 400 patients in his study and found of all 1653 drugs prescribed, (20 %) of the drugs were improperly dosed in 184 cirrhotic patients. Mohammed and Aidoo (2020) in Ghana who enrolled 152 liver cirrhosis patients in their study found that About 32% of the 572 noncompliant prescriptions were related to pharmacotherapy, while 68% were due to safety guideline recommendations [(14)]. these results were in partial concordance with the result of Aghili and Kasturirangan (2019) in India who studied DRPs in 78 critically ill decompensated liver cirrhosis patients using PCNE classification and reported that the most prevalent drug-related problems were drug-drug interactions (48.7%), followed by nonconformity to guidelines (15.5%), improper drug form (11.9%), and contraindication (9.6 %)[(10)].

According to the findings from earlier research, the proportion of liver cirrhosis patients whose drug prescriptions are in high doses that are not in compliance with guidelines is high. This could be due to the fact that there is a lack of formal consultation between clinical pharmacists and physicians during the patient care process. Regarding certain drug related problems in this study in which omeprazole was used at too high dose, the result of the current study is comparable to the result of Mohammed and Aidoo (2020) who reported that omeprazole was used at a high dose in about 65% of the liver cirrhosis patients [(14)]. The use of proton pump inhibitors in cirrhotic patients has been linked to infections and hepatic encephalopathy and should be carefully considered. The maximum dose of omeprazole should be decreased for child Pugh score A and B patients [(15)]. Hayward et al., (2019) reported in their study that nearly two-thirds of intervention patients, who were prescribed lactulose throughout the study period did not take it as directed [(8)]. This is

comparable to our results in which lactulose syrup was the second most encountered drug that causes DRPs through the patients unintentionally administering/using the drug in a wrong way. A significant number of patients with decompensated cirrhosis do not adhere to prescribed treatment regimens. Given the possible clinical importance, it is necessary to investigate further the relationship between "Low" medication adherence and patients' serious concerns or doubts about the necessity of their drugs. In addition to patient-specific education regarding the disease and medication management, interventions that promote positive reinforcement of the value and necessity of drugs may enhance adherence[16].

The interventions in this study were accepted and fully implemented in 71.7%. of DRPs. This higher acceptance level is also reported by Párraga et al., (2018) who reported that nearly 70% of the pharmacist intervention on one-third of the prescription for hepatic insufficiency patients that are a candidate for pharmacist intervention was accepted[17]. Also, Aghili and Kasturirangan (2019) reported in their study that 73.3% of the pharmacist intervention was accepted and fully implemented [10]. As a result, it is safe to claim that the proactive participation of clinical pharmacists as a credible source of pharmacological information in the pharmacotherapeutic management of decompensated cirrhotic patients is crucial in terms of identifying DRPs and preventing injury. Clinical interventions were implemented with the intention of assisting in the improvement of patients' outcomes by actively participating in the identification of DRPs and providing appropriate clinical interventions to the treating physician or the nurse in certain circumstances, or directly to patients.

Limitation

The most important limitation was patients were extremely exhausted and lacked the incentive to share information, necessitating the use of family members to acquire information, while some patients were left alone in hospitals, which made the mission more challenging. In addition, the sample size was small and the study was conducted in one center

Conclusion

1. There was a significant number of DRPs among decompensated liver cirrhosis patients.
2. The majority of drug-related problems were attributable to the effect of drug treatment not being optimal and Adverse drug events (possibly) occurring. The most frequent cause was the Drug dose of single active ingredients too high followed by the patient unintentionally using the drug in the wrong way. And the main drugs responsible for DRPs were omeprazole and lactulose.
3. Physicians and clinical pharmacists collaborated exceptionally well, and a high percentage of proposed interventions were accepted and fully implemented

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Conflicts of Interest

The authors declare that there is no conflict of interest

Ethics statements

The study was approved by ethics committee of the College of the Pharmacy/ University of Baghdad (acceptance number 513 on 24/1/2022).

Author Contributions

Ameer A.K. and Mohammed Y.J. conceived and designed the study. Ameer A.K. performed the data collection. Ameer A.K. and Mohammed Y.J. performed data analysis and interpretation of the results. Ameer A.K. wrote the initial draft of the manuscript, Ameer A.K. and Mohammed Y.J. wrote and revised the full paper. All authors have read and agreed to the published version of the manuscript.

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