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Original Research

Impacts of pharmacists-managed outpatient clinic in patients with hepatitis c virus infection: A retrospective study in China

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Abstract

Objective: Pharmacists are health care professionals who are actively involved in identifying and solving drug-related problems (DRPs) in patients with hepatitis C virus (HCV) infection. However, the effectiveness of pharmaceutical services at outpatient clinic for patients with HCV infection have not been reported in China. This study aims to describe and investigate the impacts of pharmacists-managed outpatient clinic in patients with HCV infection. **Methods:** We conducted a descriptive and retrospective study between May 2020 and April 2022. In order to give full play to the efficacy of direct-acting antivirals (DAAs), we established a referral process for HCV patients with DAAs. Doctors prescribed DAAs for HCV-infected outpatients, and then transferred them to the outpatient clinic managed by pharmacists. Pharmacists cooperated to complete the pharmaceutical monitoring of DAAs treatment for patients. The pharmacist conducted a comprehensive evaluation of the patient's medication and developed planned intervention measures based on identified DRPs. **Results:** A total of 473 eligible patients participated in 851 pharmaceutical care. A total of 518 DRPs were identified (an average of 1.1 per patient). Treatment effectiveness (48.8%) was the most common DRP. The most commonly recommended intervention was changing the drug (18.3%). There were 97.1% patients accepting the interventions and 93.05% patients completely implemented. The overall sustained virologic response at week 12 posttreatment (SVR12) rate was 98.5% (466/473). The most cost-effective treatment was selected in 98.7% of patients. **Conclusions:** We confirmed that pharmacists had a valuable role to perform pharmacy services for HCV-infected outpatients. The intervention of pharmacists is effective in solving the DRPs and saving drug costs.

Keywords: Pharmacists, Pharmaceutical Clinic, Drug-related problems, Hepatitis C virus infection, Direct-acting antivirals, China, Retrospective study

Background

Hepatitis C is a global epidemic, and people of different genders, ages and ethnicities are susceptible to HCV. According to WHO estimates, in 2019, there were 58 million cases of chronic HCV infection worldwide, 290,000 deaths from cirrhosis or HCC caused by HCV infection, and about 1.5 million new infections worldwide in 2019.[1] According to data published by Polaris Observatory HCV Collaborators, there were an estimated 9.487 million HCV infected people in China in 2020.[2] All HCV RNA-positive patients, regardless of cirrhosis, chronic kidney disease, or extrahepatic manifestations, should receive antiviral therapy.[3]

The treatment of hepatitis C has gone through two stages of development: the first phase with interferon as the representative drug and the second phase with DAAs as the representative drug. From interferon to DAAs, the administration mode has changed from injection to oral administration, and the therapeutic effect has been improved, the treatment cycle has been shortened, and the incidence of adverse reactions has been reduced.[4] DAAs has significant efficacy but is expensive, and the affordability of patients is poor. In 2019, the Chinese Medical Insurance Bureau conducted drug negotiations on DAAs for the first time, and finally included three drugs, Elbasvir/grazoprevir, Ledipasvir/sofosbuvir and Sofosbuvir/velpatasvir. The price of the included drugs dropped by more than 85% on average. At the same time, the National Medical Insurance Bureau limited the medical insurance reimbursement for three types of DAAs: Ledipasvir/sofosbuvir and Elbasvir/grazoprevir for patients with gene type 1b, and Sofosbuvir/velpatasvir for patients other than gene type 1b for patients.[5]

Despite being more acceptable to patients, current DAAs therapies still require careful selection based on patient-specific factors such as viral genotype, presence of cirrhosis, treatment history, and comorbidities.[6] What's more, patients taking DAAs are at risk for adverse drug events, drug interactions, compliance, and other DRPs.[7-10] Therefore, it is important to conduct pharmaceutical care to review drug therapy for HCV patients. Relevant studies have shown that pharmacists have the ability to intervene in the treatment of

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DAAs in HCV patients,[11-13] because pharmacists have sufficient expertise and can play a key role in identifying DDI, monitoring ADR, improving medication compliance, and preventing HCV reinfection.

In 2020, the first hepatitis C clinic managed by pharmacists in a tertiary teaching hospital in Beijing was established. In addition to the diagnosis and treatment of HCV patients in our hospital, there are pharmacists to provide professional pharmaceutical services. There have been no reports in China of pharmacists providing pharmaceutical care to outpatients with HCV to assist or facilitate drug therapy. The main objective of this study was to describe those DRPs that pharmacists identify and manage, and to assess the impact of pharmacist intervention on outpatients with hepatitis C.

METHODS

Study design and setting

The single-center, retrospective, descriptive study was conducted at Beijing Youan Hospital, Capital Medical University. Beijing Youan Hospital affiliated to Capital Medical University is a tertiary comprehensive teaching hospital with 750 beds. This hospital is a reference centre for the management of liver diseases (including hepatocellular carcinoma and liver transplantation) and HIV/AIDS care.

Participants are eligible for inclusion if they are HCV-infected outpatients who visited our pharmaceutical clinic between May 2020 and April 2022. If they are younger than 18 years of age or their course of treatment is unknown, they will be excluded. We retrospectively reviewed patient records to assess the pharmacists' provision of pharmaceutical care to these patients in the pharmaceutical clinic and its impact on drug use.

Development and implementation of the pharmaceutical clinic

Three DAAs used in our hospital, namely Elbasvir/grazoprevir, Ledipasvir/sofosbuvir and Sofosbuvir/velpatasvir, were set as active early warning drugs in the hospital information system (HIS). When a doctor prescribes a DAAs, HIS will automatically pop up a warning box for the corresponding drug, reminding the doctor that the drug is prone to DRPs in the course of the patient's use. The doctor can comprehensively consider the patient's situation and refer the patient to the pharmaceutical clinic, where the pharmacist will provide professional guidance to the patient.

The pharmaceutical clinic provides advanced patient-centered services (a series of specialized pharmaceutical services such as drug evaluation, drug consultation, drug education, and drug regimen adjustment suggestions for patients). The service process includes 6 steps: information collection, drug evaluation, drug recommendation, drug education, follow-up, and document management. The pharmaceutical service flow of HCV patients in our hospital is shown in Figure 1.

Outcome measures

Detection of DRPs

The pharmacists evaluate the indications, effectiveness, safety, economy, compliance and other aspects of drug therapy, and conduct a comprehensive analysis based on evidence-based evidence and patients' specific conditions. Focus on the treatment needs of patients and address patient individualized medication and other DRPs. The DRPs classification is conducted independently by 2 pharmacists and the validity and reliability of these assessments is confirmed by a senior pharmacist. The DRPs and recommendations were evaluated using The Pharmaceutical Care Network Europe (PCNE) Classification for DRPs V9.1 regarding problem, causes, planned interventions and intervention acceptance.[14]

Health outcomes

The study also evaluates the patient's medication effect, main curative effect for sustained virologic response (SVR), It means that after regular antiviral treatment, the viral load in the body falls below the detection level, and the HCV RNA is still negative after 12 weeks of drug withdrawal, then the SVR is virological cure.

Cost-effectiveness outcomes

Check whether doctor-prescribed DAAs treatment is the most cost-effective according to China's Hepatitis C prevention and treatment guidelines and China's medical insurance reimbursement policy, and calculate the percentage of patients using the most cost-effective DAA treatment and the direct savings achieved through pharmacist intervention.

Satisfaction with the pharmaceutical clinic

The satisfaction of HCV infected patients participating in pharmaceutical clinic was investigated, and the questionnaire was designed according to the actual situation of pharmacy outpatient department. The questionnaire included five questions: outpatient environment, service attitude, pharmacist professional level, Whether it helped after the visit, and the overall treatment experience. Likert scale was used for evaluation,[15] Each item is scored on a scale of 1 to 5. 5 points for very satisfied, 4 points for medium satisfied, 3 points for neutral, 2 points for medium dissatisfied and 1 point for very dissatisfied.

Data collection and Analysis

The clinical data of all patients were collected from the electronic medical record of hospital information system based on pharmacist record. The following information was documented: patients' demographic factors (age, sex), disease factors (active or currently under treatment), therapeutic regimens (dosing, frequency and treatment duration) of each medication. All DRPs and interventions made by the pharmacists were also documented. Additionally, laboratory findings and cost of medicines were collected.

All data analyses were performed using Microsoft Excel 2016 and IBM SPSS version 23.0 software. A descriptive analysis was

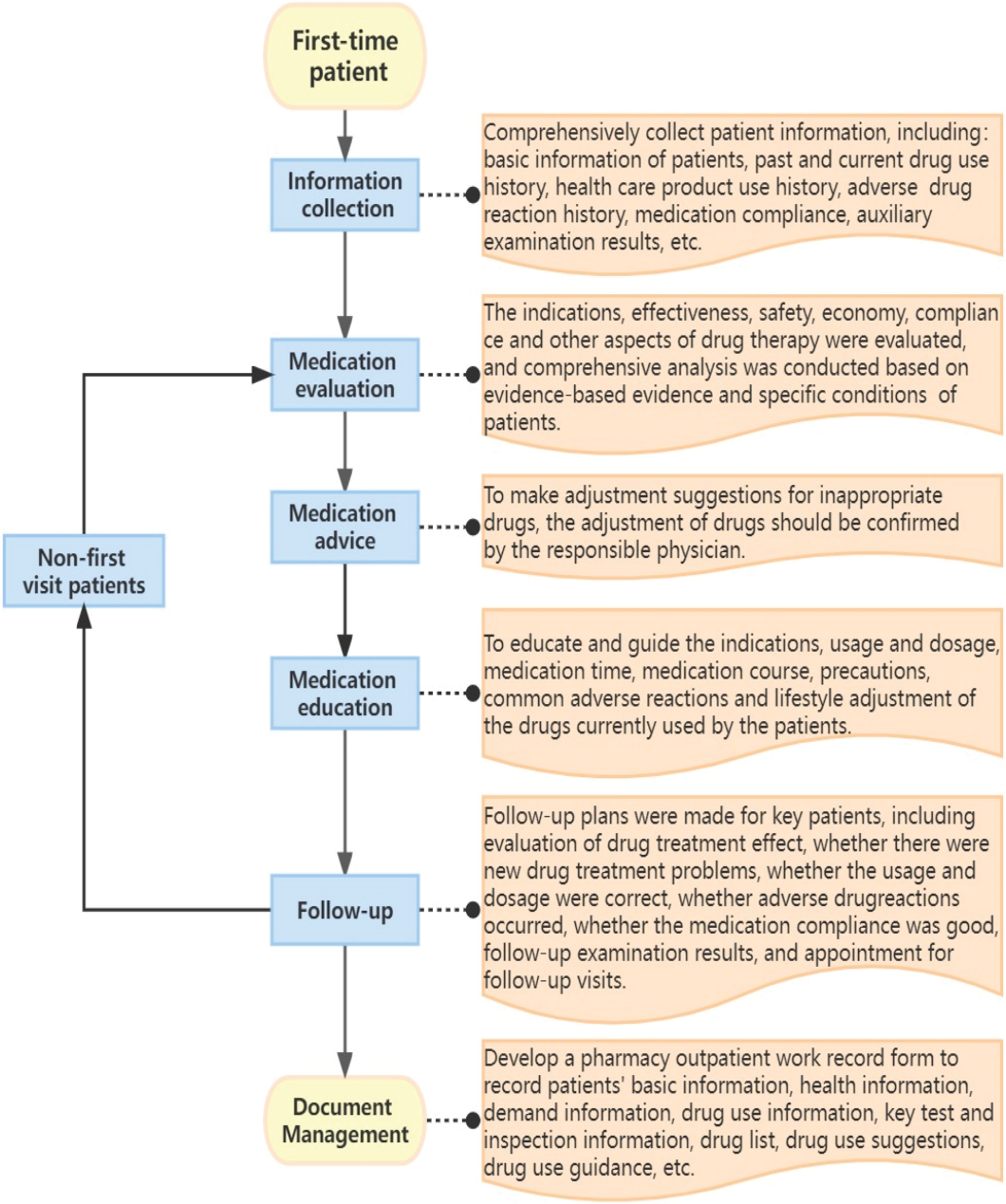

Figure 1. Pharmaceutical care process for HCV sspatients

conducted on patients' demographics, disease characteristics, types of DRPs and types of drug interactions. Continuous data were expressed as mean with standard deviation. Categorical variables were expressed as the number and percentages. Groups were compared by Student t test for continuous variables, A *P*-value of <.05 was considered to be statistically significant.

Ethical aspects

This study was approved by the institutional review boards of Beijing Youan Hospital affiliated to Capital Medical University, Retrospective studies and case reviews may be conducted and the Board waived the need for patients' informed consent.

RESULTS

Characteristics of Study Population

A total of 473 eligible patients were invited to participate in the study during their outpatient visits, The patients' characteristics are shown in Table 1. The majority of patients were male (59.20%), had not been treated for hepatitis C (71.04%), and genotype 1b (54.99%). The most commonly used DAA was Sofosbuvir/velpatasvir (47.78%). At baseline, the mean number of concurrent medications (SD) per patient was 3.85(2.79), and the most common comorbidities were hypertension (24.95%), hyperlipidemia (21.99%), and diabetes (19.03%).

Detection of DRPs

A total of 473 eligible patients with 851 visits have been recorded and managed by the pharmacist over 2 years and the average number of clinic visits per patient was 1.8 times. As shown in Table 2, a total of 518 DRPs were identified during the study period. An average of 1.1 DRPs were detected per patient. Treatment effectiveness (44.98%) was the most common DRPs, followed by treatment safety (38.22%). The main causes of DRPs were inappropriate drug combinations (50.77%) and patients intentionally taking less than prescribed drugs or not taking them at all for some reason (13.13%). The most commonly recommended intervention was medication regimen modification (43.82%), followed by drug discontinuation (18.34%). 97.10% of the patients received the intervention, and 93.05% of the patients fully implemented it.

Table 1. The demographic and clinical characteristics of 473 patients

Characteristics	Total (n=473)
Age (y), mean ± SD	51.2(13.52)
Age≥65(y),n(%)	89(18.82%)
Male,n(%)	280(59.20%)
Prior HCV treatment,n(%)	
Treatment-naive	336(71.04%)
Prior treatment with peginterferon plus ribavirin	137(28.96%)
HCV genotype,n(%)	
1b	260(54.99%)
2a	85(17.97%)
3a	32(6.77%)
3b	38(8.03%)
6a	9(1.90%)
Unknown genotype	49(10.36%)
HCV RNA,log IU/mL,mean±SD	3.91(2.44)
ALT,IU/L,mean±SD	72.38(66.58)
AST,IU/L,mean±SD	62.87(46.77)
TBIL,umol/L,mean±SD	23.25(26.81)
DBIL,umol/L,mean±SD	9.57(19.85)
eGFR,ml/min,mean±SD	106.35(18.97)
Treatment agents,n(%)	
Elbasvir/grazoprevir	102(21.56%)
Ledipasvir/sofosbuvir	145(30.66%)
Sofosbuvir/velpatasvir	226(47.78%)
Comorbidities,n(%)	
Hypertension	118(24.95%)
Hyperlipidemia	104(21.99%)
Diabetes	90(19.03%)
Liver cirrhosis	65(13.74%)
Peptic ulcer	61(12.90%)
Chronic gastritis	52(10.99%)
Acute coronary disease	43(9.09%)）
Fatty liver	30(6.34%)
Cerebral apoplexy	22(4.65%)
Gout	19(4.02%)
Osteoporosis	14(2.96%)
HIV coinfection	10(2.11%)
Other diseases	39(8.25%)

Abbreviations: HCV, hepatitis c virus; RNA, ribonucleic acid; ALT, alanine aminotransferase;
AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

Table 2. Classification of DRPs identified according to PCNE V9.1 (n=518)

Code	Detailed classification	n(%)
Problems		
P1	**Treatment effectiveness**	**233(44.98%)**
P1.1	No effect of drug treatment despite correct use	25(4.83%)
P1.2	Effect of drug treatment not optimal	146(28.19%)
P1.3	Untreated symptoms or indication	62(11.97%)
P2	**Treatment safety**	**198(38.22%)**
P2.1	Adverse drug event (possibly) occurring	198(38.22%)
P3	**Other**	**87(16.80%)**
P3.1	Unnecessary drug-treatment	25(4.83%)
P3.3	Problem with cost-effectiveness of the treatment	62(11.97%)
Causes		
C1	**Drug selection**	**346(66.80%)**
C1.1	Inappropriate drug according to guidelines/ formulary	38(7.34%)
C1.2	No indication for drug	25(4.83%)
C1.3	Inappropriate combination of drugs,or drugs and herbal medications, or drugs and dietary supplements	263(50.77%)
C1.6	Too many different drugs/active ingredients prescribed for indication	20(3.86%)
C3	**Dose selection**	**50(9.65%)**
C3.1	Drug dose too low	17(3.28%)
C3.3	Dosage regimen not frequent enough	22(4.25%)
C3.4	Dosage regimen too frequent	11(2.12%)
C4	**Treatment duration**	**18(3.47%)**
C4.1	Duration of treatment too short	11(2.12%)
C4.2	Duration of treatment too long	7(1.35%)
C7	**Patient related**	**104(20.08%)**
C7.1	Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	68(13.13%)
C7.2	Patient uses/takes more drug than prescribed	11(2.12%)
C7.3	Patient abuses drug (unregulated overuse)	8(1.54%)
C7.7	Inappropriate timing or dosing intervals	17(3.28%)
Planned interventions		
I1	**At prescriber level**	**226(43.63%)**

I1.2	Prescriber asked for information	37(7.14%)
I1.4	Intervention discussed with prescriber	189(36.49%)
I2	**At patient level**	**292(56.37%)**
I2.1	Patient (drug) counselling	120(23.17%)
I2.2	Written information provided (only)	96(18.53%)
I2.3	Patient referred to prescriber	76(14.67%)
I3	**At drug level**	**518(100.00%)**
I3.1	Drug changed to …	227(43.82%)
I3.2	Dosage changed to …	45(8.69%)
I3.4	Instructions for use changed to …	65(12.55%)
I3.5	Drug paused or stopped	95(18.34%)
I3.6	Drug started	86(16.60%)
I4	**Other intervention or activity**	**35(6.76%)**
I4.2	Side effect reported to authorities	35(6.76%)
Intervention acceptance		
A1	**Intervention accepted**	**503(97.10%)**
A1.1	Intervention accepted and fully implemented	482(93.05%)
A1.2	Intervention accepted, partially implemented	21(4.05%)
A2	**Intervention not accepted**	**15(2.90%)**
A2.2	Intervention not accepted: no agreement	9(1.74%)
A2.3	Intervention not accepted: other reason (specify)	6(1.16%)

The main cause of DRPs occurrence was inappropriate drug combinations (50.77%), 263 drug interactions identified by pharmacists in 473 patients, and the type and number of DDI are shown in Table 3. The highest risk of interaction with DAAs was found in proprietary Chinese patent medicine or herbal (41.83%), followed by Acid-suppressing agents (18.25%) and Antihypertensive agent (11.03%). In addition, the number of DDI occurrence of the three DAAs was calculated, and the number of DDI occurrence was the highest in Sofosbuvir/velpatasvir, followed by Ledipasvir/sofosbuvir, and Elbasvir/grazoprevir.

Health outcomes

The overall cure rate in the study (SVR12) was 98.94% (468/473), and in the 5 patients (1.06%) who did not achieve SVR12, 3 (0.63%) experienced virologic failure during treatment and 2 (0.42%) experienced virologic relapse after the end of treatment. None of the patients experienced a serious adverse drug event, and none stopped taking their medication due to an adverse drug event.

Cost-effectiveness outcomes

Through pharmacists' intervention, the most cost-effective treatment option was selected in 98.73% of patients. The total cost of DAAs treatment for 473 patients was 4,583,907 renminbi (9677.3 renminbi per patient). Treatment modifications suggested by pharmacists to a more cost-effective DAA regimen led to cost savings of 303,960 renminbi. As shown in Table 4, the cost of other drugs also decreased significantly (476.97±285.81 VS 418.55±252.75 renminbi, P=0.018).

Table 3. Type and count of interacting agents(case/%)

Type of interacting	Total No.(%)	Interacting agents	Total No.(%)
Potential Interaction	144(54.75%)	Acid-suppressing agents	48(8.25%)
		Antihypertensive agents	29(11.03%)
		Lipid Lowering agents	21(7.98%)
		hypoglycemic	14(5.32%)
		Antiarrhythmic	9(3.42%)
		Antituberculosis	7(2.66%)
		Antiretroviral	7(2.66%)
		Sedative hypnotic	5(1.90%)
		diuretic	2(0.76%)
		immunosuppressant	2(0.76%)
contraindications	9(3.42%)	antiepileptic	3(1.14%)
		antiasthmatic	3(1.14%)
		Antiarrhythmic	3(1.14%)
No relevant data or Risk ambiguity	110(41.83%)	Chinese patent medicine or Herbal	110(41.83%)

Satisfaction with the Pharmaceutical Clinic

The level of patient satisfaction is shown in Table 5, and the score of "overall treatment satisfaction" is 4.81. The satisfaction score of each project was above 4 points, and the satisfaction level was between "very satisfied" and "medium satisfied", among which "pharmacist service attitude" scored the highest and "outpatient environment" scored the lowest.

DISCUSSION

The establishment and practice of hepatitis C clinic managed by pharmacists not only provide a new practice environment for pharmacists, but also meet the needs of patients. Most published studies on outpatient pharmaceutical care have generally focused on chronic conditions such as hypertension, diabetes, asthma, and hyperlipidemia.[16-20] However, it should be recognized that HCV patients would also benefit greatly from pharmaceutical care by assisting with HCV treatment

Table 4. Average cost of medications per patient for every month

	Preintervention	Postintervention	*P*
Average drug cost per patient for every month(RMB) (Not including DAA)	476.97±285.81	418.55±252.75	0.018
Cost of Direct-acting Antiviral Agents (RMB)	3225.77±1087.98	2994.9±1269.42	0.069

Table 5. Patient satisfaction with pharmaceutical care

Categories	Satisfaction score	Satisfaction level	Ranking
service attitude	4.91±0.29	satisfied	1
Whether it helped after the visit	4.87±0.34	satisfied	2
Overall satisfaction with the pharmacy service	4.81±0.39	satisfied	3
Pharmacist professional level	4.75±0.43	satisfied	4
Outpatient environment	4.62±0.48	satisfied	5

selection, providing patient counseling, monitoring response to treatment, assessing adverse events, assessing drug interactions, and improving access to and adherence to treatment, all to improve patient outcomes.

To our knowledge, this study was the first to evaluate the outcomes of pharmaceutical care in outpatients with hepatitis C in mainland China. Our study showed that an average of 1.1 DRPs per patient was found among our HCV outpatient. The most common DRPs are drug interactions, untreated indications, noncompliance, and adverse drug reactions. Of the planned interventions (n=518), 97.10% were accepted by the patient or physician. In China, the time of doctors is relatively tight. In order to achieve comprehensive pharmaceutical care for patients, the participation of pharmacists in the management and follow-up of patients' drug therapy has become a good supplement. This study shows that pharmacist-led outpatient services play an important role in solving patients' DRPs.

Drug interactions are one of the main issues in DAAs treatment and a key area of patient management. Pharmacists conduct systematic patient profile reviews and ensure that patients are provided with a complete list of all up-to-date medications to ensure the appropriateness and safety of the regimen. Data from this study showed that 42.77% of HCV patients had DDI, and pharmacists conducted 263 interventions for actual or potential DDI, among which the most interventions were for the use of Chinese patent medicine or herbal recommendations. Chinese patent medicine, or herbs, are popular in China and are widely believed to be safer than other medicines. However, most Chinese patent medicine and herbs still lack DDI research data with DAAs.[21] Unless very special circumstances, pharmacists will advise patients to stop taking DAAs before, and to resume taking Chinese medicine after completing DAAs treatment for 14 days. Secondly, DDI occurs more frequently in gastrointestinal drugs, because Ledipasvir is an NS5A inhibitor, which is better absorbed in acidic environment, and any drug that affects gastric acid level will reduce the absorption of this drug.[22] Therefore, every patient with a prescription containing Ledipasvir is explicitly asked if they are taking any medications for gastric ulcers or gastroesophageal reflux disease, including antacids, PPI, and H2RA. If taking these drugs, patients are advised to take them separately or reduce the dosage of omeprazole according to the instructions. In this study, 9 patients with drug contraindications, mainly with antiarrhythmic drugs (amiodarone) and central nervous system drugs (phenytoin and oxcarbazepine). Due to the risk of bradycardia, amiodarone and sofosbuvir containing DAAs are contraindicated, and although the mechanism of this effect is unknown, the use of both drugs together should still be avoided.[23] Induction of CYP3A4 and P-glycoprotein by phenytoin and oxcarbazepine may significantly reduce serum concentrations of Elbasvir/grazoprevir and lead to loss of efficacy and potential treatment failure.[24,25] Therefore, pharmacists recommend suspending the use of drugs with contraindications.

Some previous reports have suggested that SVR 12 rates are 90-98% in real-world Settings.[26-29] In this study, the SVR12 rate was 98.94%, which is relatively higher than in previous studies, and our results confirm the high efficiency of DAAs. Compliance with DAAs treatment in this study was very high, with 99.8% of patients having a compliance rate of ≥95%. Several factors may influence this outcome, such as the shorter duration of the DAAs regimen, the patient's desire to be treated and therefore actively involved in disease management, and the close monitoring of patients by pharmacists. For patients who are at risk of poor compliance detected at baseline visits, pharmacists will alert them over the phone. These results suggest that pharmaceutical care provided by pharmacists contributes to the improvement of patient compliance and helps achieve favorable SVR rates.

Regarding the economic effect, post-intervention data showed that patients' monthly DAAs drug costs and other drug costs decreased. This reduction in drug costs is similar to what has been reported in other pharmaceutical clinic studies.[30-32] We developed recommendations on the most cost-effective options for each population based on HCV genotype, fibrosis stage and other clinical data. The findings showed that pharmacists' interventions in monitoring compliance with guidelines and Medicare reimbursement policies facilitated most patients' choice of the most cost-effective treatment.

There are some limitations to our study. First, this is a single-center study, and our findings may not apply to patient populations at other institutions. However, we surmise that the patient population at our institution is representative of Chinese patients. Second, this was a retrospective study and the number of patients in this study was small. This can lead to unremarkable results. Finally, no control group with which to compare the impact of the Pharmaceutical care. We evaluate the usefulness of our pharmaceutical care by comparing it to previous reports. In terms of economic effect, the self-comparison study of patients pre and postintervention data were conducted.

CONCLUSION

We demonstrate that pharmacists play an important role in outpatient HCV patient care. Pharmacists are able to identify and resolve DRPs in these patients. Close monitoring of patients by pharmacists contributes to the successful completion of treatment and has high SVR12 and satisfaction in most populations. Pharmacists promote the choice of the most cost-effective treatment for patients in most cases.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the institutional review boards of Beijing Youan Hospital affiliated to Capital Medical University, Retrospective studies and case reviews may be conducted and the Board waived the need for patients' informed consent. All methods were performed in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

Can Huang, Wei Liu conceived and designed this study. Can Huang, Aiping Gao, Cuixia Guo, Jinmei Jia, Yonghong Zheng collected and analyzed data. Yonghong Zheng, Wei Liu supervised the conduct of this study. Can Huang, Aiping Gao drafted the manuscript, and all authors contributed substantially to its revision. All authors read and approved the final manuscript.

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