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Comorbidities and the use of comedications among patients with chronic hepatitis C in Korea: a nationwide cross-sectional study

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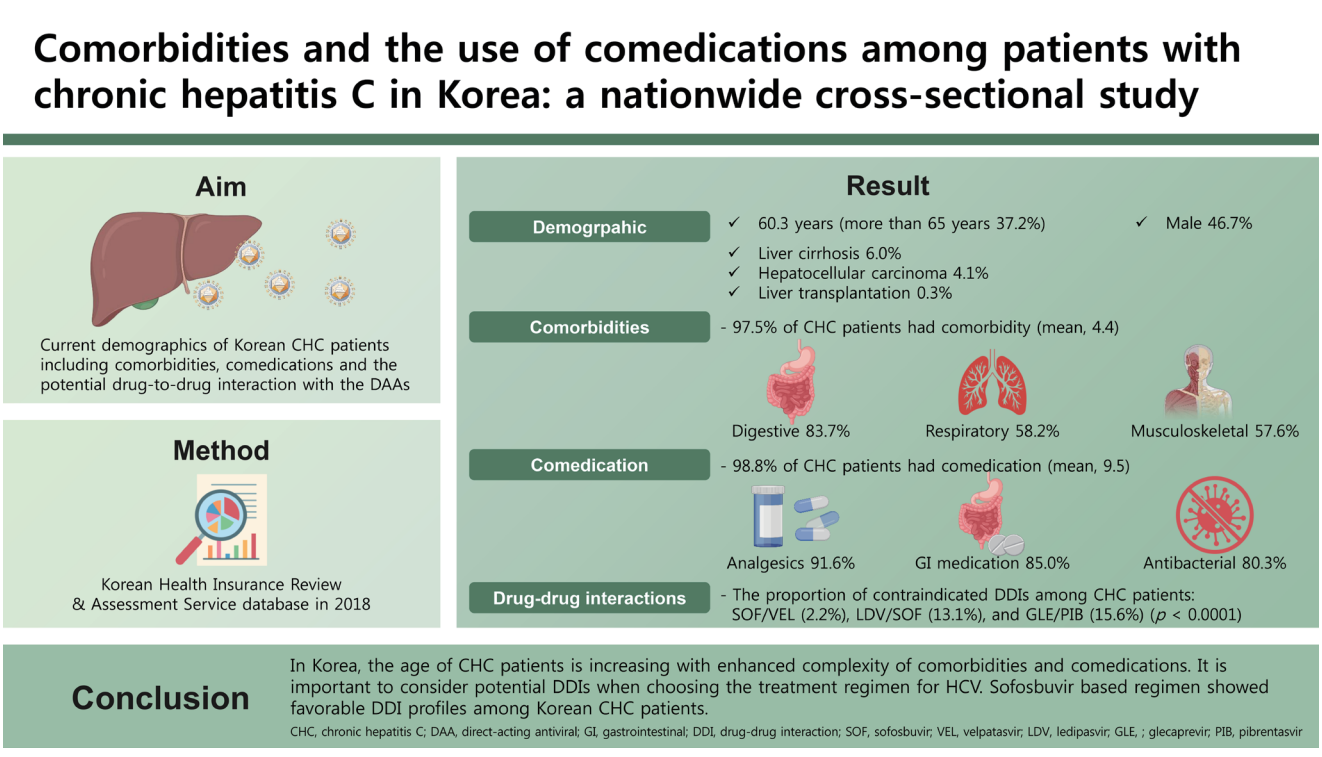

Background/Aims: Chronic hepatitis C (CHC) is the second leading cause of liver-related mortality and is more prevalent in the elderly population in Korea. Decisions to initiate treatment and selection of proper antiviral agents may be challenging among elderly patients due to relevant comorbidities, comedications, and drug-drug interaction (DDI). It may be helpful to understand the current demographic status and comorbidities of CHC patients in the country.

Methods: Patients aged ≥ 18 years and diagnosed with CHC (KCD-7 code B18.2) were extracted from the Korean Health Insurance Review & Assessment Service database in 2018. Data on comorbidities and comedications were assessed and potential DDIs were analyzed.

Results: A total of 50,476 patients with CHC, with a mean age of 60.3 years and 46.7% male patients were identified. The proportion of patients with cirrhosis, hepatocellular carcinoma, and liver transplantation was 6.0%, 4.1%, and 0.3%, respec-

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tively and 37.2% of patients were more than 65 years of age. The three most common comorbidities were diseases of the digestive system (83.7%), respiratory system (58.2%), and musculoskeletal system and connective tissue (57.6%). The three most common comedications were analgesics (91.6%), gastrointestinal agents (85%), and antibacterials (80.3%). Lipid-lowering agents and anticonvulsants were prescribed in 28.5% and 14.8% of patients. Rate of potential DDI for contraindication was 2.2%, 13.1%, and 15.6% with sofosbuvir/velpatasvir, ledipasvir/sofosbuvir, and glecaprevir/pibrentasvir.

Conclusions: With the increasing age of patients with CHC, comorbidity, comedication, and potential DDI should be considered when choosing antivirals in Korea. Sofosbuvir-based regimens showed favorable DDI profiles among Korean patients.

Keywords: Hepatitis C; Drug interactions; Polypharmacy; Antiviral agents/therapeutic use; Comorbidity

INTRODUCTION

Hepatitis C virus (HCV) infection still remains a global public health issue with 170 million patients developing chronic hepatitis C (CHC), among whom 32.2 million reside in Asia [1]. Hepatocellular carcinoma (HCC) is the sixth most common cancer with 10% of cases originating from HCV infection in Korea [2]. The rising disease burden of HCV infection also reinforces the goal of the World Health Organization to eradicate HCV infection by 2030 [3] and thereby warrants the need to implement the universal national HCV screening for early diagnosis and implementation of optimal HCV infection treatment [4].

The introduction of oral direct-acting antivirals (DAAs) has resulted in an unprecedented shift in providing more efficacious and expansive treatment options for individuals with CHC with fewer adverse events as compared with the previous peg-interferon based treatments [5]. While comparing with the western countries where most of the patients are young intravenous drug users [3], the prevalence of CHC increases with age in Korea with procedures-based transmission such as acupuncture, tattooing, and piercing as the major root of transmission [6,7]. One study using the Korean National Health Insurance (NHI) claims database of 2013 has shown that 84.8% of patients with CHC had at least one comorbidity and 96.8% of the patients took at least one prescribed medication [8]. With such patient demographics, a thorough review of comorbidity and comedication is required before HCV treatment to prevent any drug-drug interactions (DDIs) [8]. This is further reinforced by the International guidelines including the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Asian Pacific Association for the Study of the Liver recommended thorough review of medications in all HCV patients to consider DDI risk prior to starting DAA therapy or other medications during treatment in all patients undergoing DAAs intervention [9-11]. It is thus paramount for physicians to understand the comorbidities and comedication profiles of patients with CHC to optimally manage chronic HCV infection along with their comorbidities [12]. With the growing importance of DDI evaluation and the updated availability of pangenotypic DAA regimens, there is a strong need to explore the comorbidities and potential DDI profiles of patients with CHC in Korea. Therefore, this study was conducted to identify the comedications, and comorbidities of Korean patients with CHC and the potential DDI of ledipasvir/sofosbuvir (LDV/SOF), SOF/velpatasvir (SOF/VEL), and glecaprevir/pibrentasvir (GLE/PIB), which are available pangenotypic DAA regimens in Korea.

METHODS

Study design

This retrospective, cross-sectional study used data extracted from Health Insurance Review & Assessment Service (HIRA) database from January 1st to December 31st, 2018. The HIRA database is the national claims database of Korea which covers 90% of the total population and carries compiled data from healthcare providers for patients' actual medical service utilization across the country [13]. This study was approved by the Institutional Review Board at the Korea National Institute for Bioethics Policy (2020-1854-001) and informed consent was waived due to the study nature of retrospective data analysis.

Patient selection and data retrieval

Patients aged ≥ 18 years and have been diagnosed with

Korean Standard Classification of Diseases (KCD)-7 code "B18.2 (chronic hepatitis C [CHC])", the Korean version of the International Classification of Disease-10 codes [14] or any of its subcategories as primary diagnosis in 2018 were selected for analysis. The demographic characteristics, patients' comorbidity profiles, and prescribed medications throughout 2018 were identified and retrieved for each de-identified patient. The patients were categorized into four subgroups by liver disease status: liver transplant (LT), HCC, liver cirrhosis (LC) as diagnosis of exclusion, and CHC patients not included in LT, HCC, or LC groups. Any patients with LT-related code of Z94.4 (LT status), or T86 (LT failure and rejection) were classified as LT group. Excluding patients with LT-related diagnosis, patients with HCC-related code of HCC (C22 [malignant neoplasm of liver and intrahepatic bile ducts], C22.0 [liver cell carcinoma], and C22.9 [malignant neoplasm of liver, not specified as primary or secondary]) were categorized as HCC group. The LC patient category was defined as all patients with LC diagnosis except for those who had LT or HCC.

Analyses of comorbidities and comedication profiles by the patients' cirrhosis status and DAA exposure status were also conducted. The cirrhosis status is defined as whether a patient had been diagnosed with cirrhosis with the following codes, irrespective of whether the patient was categorized in the four disease subgroups: CHC (B18.2), liver cirrhosis (LC; K74 [fibrosis and cirrhosis of liver], K74.0 [hepatic fibrosis], K74.1 [hepatic sclerosis], or K74.2 [hepatic fibrosis and hepatic sclerosis]).

DAA exposure status group was identified if the selected patient was prescribed with any of the following DAA regimens at least once between 2015 and 2018: ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/ritonavir + DSV), daclatasvir + asunaprevir (DCV/ASV), elbasvir/grazoprevir, GLE/PIB, or any regimen using SOF including SOF, SOF/VEL, LDV/SOF, DCV + SOF, ASV + DCV + SOF, and SOF/VEL/voxilaprevir (SOF/VEL/VOX).

Assessment of comorbidities

Comorbidities were captured according to the main and sub-disease KCD-7 codes and classified into disease categories. Diagnostic codes captured for ≥ 1 inpatient or ≥ 2 outpatient experiences for patients with diagnostic codes of CHC were included in comorbidity analyses. The number of comorbidities was counted by disease categories and individual disease codes. The number of patients with each disease code was counted and compared by age group, gender, cirrhosis status, and DAA exposure status.

Detailed information on KCD-7 codes and disease categories is included in Supplementary Table 1.

Assessment of prescribed comedications

The prescribed medications taken by patients with CHC were identified by main substance, ingredients, and drug classes. Classification of drugs was based on main substance information provided by Liverpool University (https://www.hep-druginteractions.org, accessed June 2020), and if the information was not available, the information provided by Peking University (http://newywxhzy.ashermed.com) was referred. The category of cytotoxic drugs includes both cytotoxic and HCC therapies, and the human immunodeficiency virus (HIV) drug category includes HIV Nucleoside Reverse Transcriptase Inhibitors, HIV entry integrase inhibitors, and HIV protease inhibitors.

The proportion of patients with each prescribed medication and the mean number of prescribed medications used per patient was calculated by drug classes. The mean number of prescribed medications per patient and the proportion of patients taking ≥ 1 medication was analyzed, and subgroup analyses were conducted stratified by age, gender, and underlying liver disease group. When a patient had been prescribed two or more medications of the same composition with different brand names, or medications with different dosages, the number of prescribed medications was counted as one based on its identical active ingredient even though the drug codes were different.

Assessment of potential DDIs between prescribed comedications and various DAA regimens against HCV

All prescribed medications to patients with CHC throughout 2018 were collected and analyzed for potential DDIs with three different DAA regimens, LDV/SOF, SOF/VEL, and GLE/PIB. The analysis was conducted under the assumption that the patients were treated by these DAA regimens with the current medical conditions and comedications. DDIs were categorized into four categories based on the information derived from Liverpool University and Pecking University: "Contraindication", "Dose-reduction/additional monitoring required" (possible interaction; defined as the plausible need for additional monitoring and/or dose adjustments for safe administration of comedications and patient safety

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[15]), "No clinically significant interaction expected" (no interaction), and "No available information". If a patient was prescribed with multiple medications in different DDI categories, a patient was included into the worse DDI category. The detailed information on prescribed medications for this analysis is included in Supplementary Table 2.

Statistical analysis

Demographic characteristics, comorbidities and comedication profiles were reported cross-sectionally in 2018. The descriptive analysis of patient characteristics and health outcomes was summarized using means and standard deviation (SD) for continuous variables and using counts and percentages for ordinal and nominal variables. The chi-square test was used to compare between groups and each DDI across the three DAA regimens. All data analyses were performed using SAS® Enterprise Guide software version 6.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was assessed at $p < 0.05$.

RESULTS

Demographics and clinical characteristics of the study population

A total of 50,476 patients were identified as CHC in 2018. The mean age (± SD) was 60.3 ± 12.7 years and 37.2% of the patients were more than 65 years old. When the patients were divided into four subgroups, those with CHC, LC, HCC, and LT were 89.7%, 6.0%, 4.1%, and 0.3%, respectively. The mean ages of each subgroup showed significant differences from each other. The mean ages of CHC, LC, and HCC group was 59.7, 64.5, and 66.7 years, respectively ($p < 0.0001$) (Table 1).

Table 1. Demographics, comorbidities, and comedications of study population

	Total	CHC	LC	HCC	LT	*p* value
Patients	50,476	45,275 (89.7)	3,012 (6.0)	2,050 (4.1)	139 (0.3)	< 0.0001
Age, yr	60.3 ± 12.7	59.7 ± 12.7	64.5 ± 11.4	66.7 ± 11.4	60.6 ± 7.9	< 0.0001
Age, yr	60 (52–70)	60 (51–69)	64 (56–74)	68 (59–76)	60 (56–66)	< 0.0001
Age group						< 0.0001
18–34 years	1,405 (2.8)	1,385 (3.1)	6 (0.2)	14 (0.7)	0	
35–44 years	3,474 (6.9)	3,348 (7.4)	78 (2.6)	46 (2.2)	2 (1.4)	
45–54 years	11,312 (22.4)	10,494 (23.2)	537 (17.8)	252 (12.3)	29 (20.9)	
55–64 years	15,536 (30.8)	14,024 (31.0)	917 (30.4)	529 (25.8)	66 (47.5)	
65–74 years	11,402 (22.6)	9,947 (22.0)	801 (26.6)	618 (30.1)	36 (25.9)	
≥ 75 years	7,347 (14.6)	6,077 (13.4)	673 (22.3)	591 (28.8)	6 (4.3)	
Gender						< 0.0001
Male	23,592 (46.7)	20,763 (45.9)	1,470 (48.8)	1,268 (61.9)	91 (65.5)	
Female	26,884 (53.3)	24,512 (54.1)	1,542 (51.2)	782 (38.1)	48 (34.5)	
Comorbidities						< 0.0001
≥ 1 comorbidity	49,235 (97.5)	44,076 (97.4)	2,996 (99.5)	2,025 (98.8)	138 (99.3)	
Comedication						< 0.0001
≥ 1 comedication	49,846 (98.8)	44,666 (98.7)	2,998 (99.5)	2,043 (99.7)	139 (100.0)	
DAA exposure						< 0.0001
DAA exposed	23,244 (46.0)	20,554 (45.4)	1,677 (55.7)	962 (46.9)	51 (36.7)	

Values are presented as mean ± standard deviation, median (Q1–Q3), or number (%).
LT (Z944 or T864) was defined as patients who have diagnosis codes related to LT and were excluded from other groups; HCC (C22, C220, C229) was defined as patients who have HCC after excluding patients with LT; excluding for LT or HCC patients, LC was defined as diagnosis of exclusion among the remaining patients (K74, K740, K741, K742); CHC was defined as patients not included in LT, HCC, or LC groups.
CHC, chronic hepatitis C; LC, liver cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant.

When investigating the status of comorbidities, almost all patients (97.5%) had one or more co-morbidities. The proportion of patients with one or more comorbidities was 97.4% in CHC group, 98.8% in HCC group, and 99.3% in LT group ($p < 0.0001$) (Table 1).

When investigating the status of comedications, almost all patients (98.8%) had one or more comedications. The proportion of patients with one or more comedications was 98.7% in CHC group, 99.7% in HCC group, and 100.0% in LT group ($p < 0.0001$) (Table 1).

Of the total patients, 46.0% had DAA exposure, with the LC group having the highest proportion of patients with DAA exposure (55.7%) compared to other subgroups, followed by HCC (46.9%), CHC (45.4%), and LT (36.7%) ($p < 0.0001$) (Table 1).

Comparison between DAA-exposed and DAA-unexposed group

The mean age of DAA-exposed patients and DAA-unexposed patients was 60.23 ± 11.83 years and 60.35 ± 13.31 years ($p = 0.28$), respectively. The proportion of DAA-exposed patients was higher in the age groups of 45–54 years (23.9% vs. 21.1%), 55–64 years (31.8% vs. 29.9%), and 65–74 years (22.9% vs. 22.4%) ($p < 0.0001$) (Table 2). There were more male patients in the DAA-unexposed group (47.7%) than in the DAA-exposed group (45.6%) ($p < 0.0001$). The proportions of patients with comorbidities (97.9% vs. 97.2%) ($p < 0.0001$) and comedications (98.9% vs. 98.6%) ($p = 0.004$) were higher in the DAA-exposed group as compared with DAA-unexposed group (Table 2).

Comorbidity profiles of the study population

The mean number of comorbidities by disease categories was 4.4 (Fig. 1, Supplementary Table 3). The proportion of patients with comorbidities increased with age and the patients aged ≥ 75 years had the highest number of co-morbidities. The mean number of comorbidities by disease category was higher in females (4.7) than males (4.2), and in patients with cirrhosis (4.8 vs. without cirrhosis: 4.4) (Supplementary Table 3).

The top three most prevalent disease categories include diseases of the digestive system (83.7%), the respiratory system (58.2%), and the musculoskeletal system and connective tissue (57.6%) (Supplementary Table 3). Diseases of

Table 2. Demographic characteristics and health conditions of study population by DAA exposure status

	DAA exposure status		*p* value
	Unexposed (n = 27,232)	Exposed (n = 23,244)	
Age, yr	60.35 ± 13.31	60.23 ± 11.83	0.28
Age, yr	61 (52–70)	60 (52–69)	–
Age group			< 0.0001
18–34 years	974 (3.6)	431 (1.9)	
35–44 years	1,975 (7.3)	1,499 (6.4)	
45–54 years	5,759 (21.1)	5,553 (23.9)	
55–64 years	8,150 (29.9)	7,386 (31.8)	
65–74 years	6,089 (22.4)	5,313 (22.9)	
≥ 75 years	4,285 (15.7)	3,062 (13.2)	
Gender			< 0.0001
Male	12,996 (47.7)	10,596 (45.6)	
Female	14,236 (52.3)	12,648 (54.4)	
Comorbidities			< 0.0001
≥ 1 comorbidity	26,473 (97.2)	22,762 (97.9)	
Comedication			0.004
≥ 1 comedication	26,856 (98.6)	22,990 (98.9)	

Values are presented as mean ± standard deviation, median (Q1–Q3), or number (%).
DAA, direct-acting antiviral.

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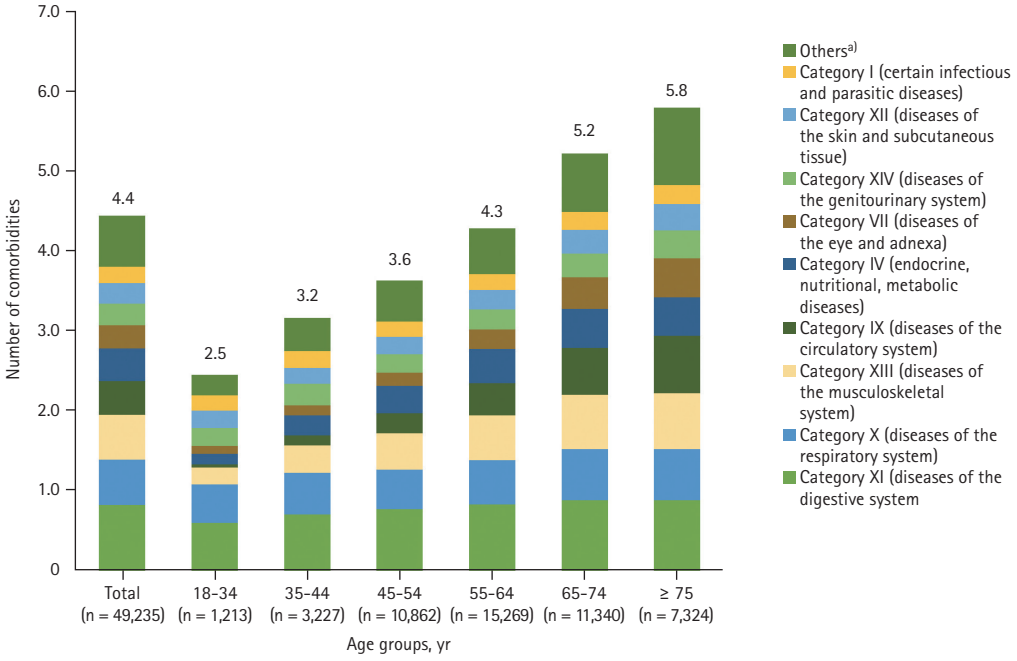

Figure 1. Distribution of chronic hepatitis C patients in Korea with ≥ 1 comorbidities based on age and disease categories. [a)]Include the following disease categories: category V (mental and behavioral disorders); category VI (diseases of the nervous system); category II (neoplasms); category VIII (diseases of the ear and mastoid processes); and category III (diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism).

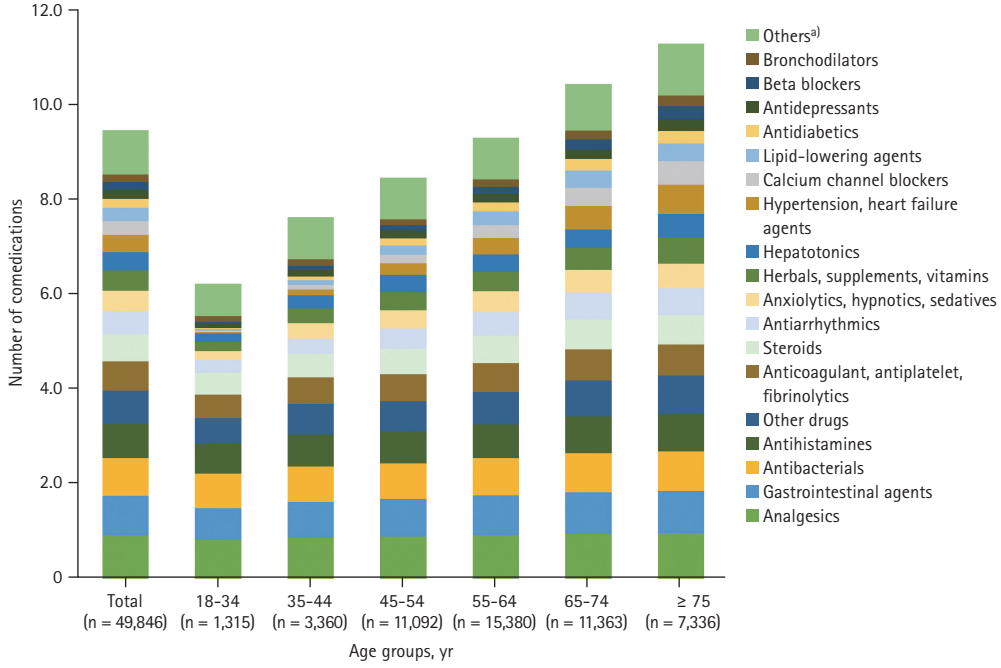

Figure 2. Distribution of chronic hepatitis C patients in Korea with ≥ 1 comedications based on age and comedication categories. [a)]Include comedications of anaesthetics, muscle relaxants; antifungals; anticonvulsants; bisphosphonates; hepatitis drugs; parkinsonism agents; antipsychotics, neuroleptics; antivirals; antiprotozoals; cytotoxics; contraceptives and hormonal replacements; immunosuppressants; antimigraine agents; oxytocics; human immunodeficiency virus drugs; and anthelmintics.

the respiratory system (category X), diseases of the musculoskeletal system (category XIII), and diseases of the circulatory system (category IX) were observed to have greater increase with age, albeit not significant ($p > 0.05$) (Fig. 1, Supplementary Table 3). When looking into the KCD-7 disease diagnostic codes, hypertension (34.1%), dyslipidemia (21.5%), diabetes mellitus (19.9%), peptic ulcer or gastrointestinal ulcer (7.9%), and ischemic heart diseases (6.2%) were the most prevalent diseases in patients with CHC (Supplementary Table 4).

The prevalence of hypertension, diabetes mellitus, and peptic ulcer or gastrointestinal ulcer was significantly high-

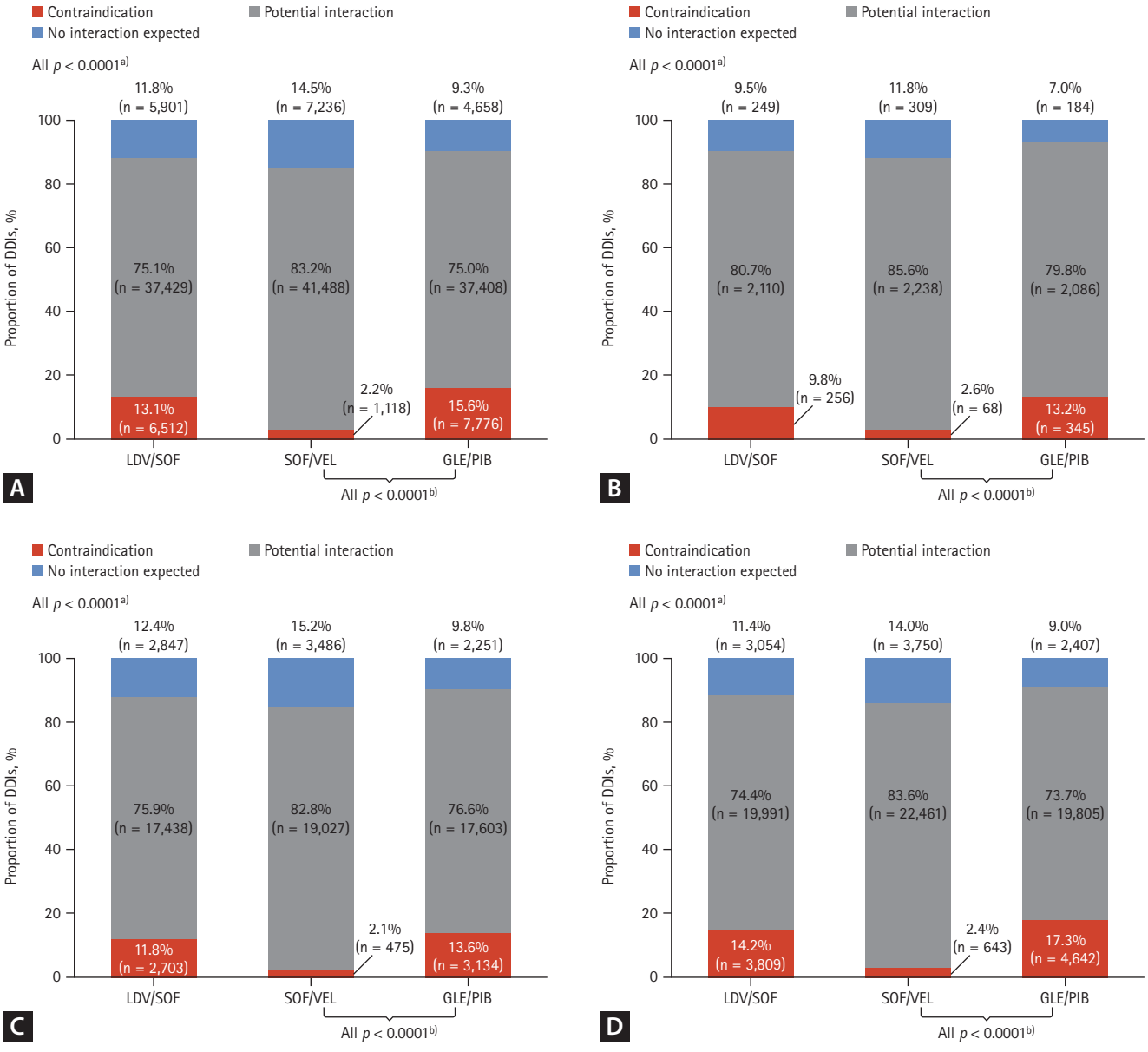

Figure 3. The proportion of potential drug-drug interaction (DDI) types with direct-acting antiviral (DAA) regimen by health conditions in hepatitis C virus (HCV) infected patients. (A) Proportion of DDIs reported among all HCV diagnosed patients. (B) Proportion of DDIs reported among HCV diagnosed patients with cirrhosis. (C) Proportion of DDIs reported among all HCV diagnosed patients in the DAA exposed group. (D) Proportion of DDIs reported among all HCV diagnosed patients in the DAA unexposed group. DDI were categorized as 'Contraindication' from reference of Liverpool University and Pecking University. LDV, ledipasvir; SOF, sofosbuvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir. [a]*p* values indicated for each potential DDIs (contraindication; potential interaction; no interaction expected) across each DAA regimen (LDV/SOF vs. SOF/VEL vs. GLE/PIB). [b]*p* values indicated for potential DDIs (contraindication; potential interaction; no interaction expected) across each DAA regimen (SOF/VEL vs. GLE/PIB).

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er in the DAA-exposed groups than in the DAA-unexposed group ($p < 0.0001$). However, dyslipidemia, ischemic heart diseases were more prevalent in the DAA-unexposed group ($p < 0.0001$) (Supplementary Table 4).

Prescribed concurrent medication profiles/ patterns of CHC patients

The mean number of comedications in overall patients was 9.5 and the number of comedications increased with age, from 6.2 in younger age group (18–34 years) to 11.3 in older age group (≥ 75 years) (Fig. 2). Female patients (9.7 vs. males: 9.2) and patients with cirrhosis (10.9 vs. without cirrhosis: 9.4) had a higher number of prescribed comedications (Supplementary Table 5).

The commonly prescribed medications (> 50%) were analgesics (91.6%), gastrointestinal agents (85.0%), anti-

Table 3. Contraindicated DDIs with DAA regimens in HCV infected patients

Class	Molecule	No. of patients	LDV/SOF	SOF/VEL	GLE/PIB
Lipid-lowering agents	Atorvastatin	6,334 (12.7)			X
Lipid-lowering agents	Rosuvastatin	5,546 (11.1)	X		
Lipid-lowering agents	Simvastatin	701 (1.4)			X
Anticonvulsants	Carbamazepine	366 (0.7)	X	X	X
Antibacterials	Rifampicin	264 (0.5)	X	X	X
Antiarrhythmics	Amiodarone	215 (0.4)	X	X	
Herbals/supplements/vitamins	St John's wort	170 (0.3)	X	X	X
Anticoagulant, anti-platelet and fibrinolytic	Dabigatran	73 (0.1)			X
Anticonvulsants	Oxcarbazepine	47 (0.1)	X	X	X
Cytotoxics	Vincristine	30 (0.1)			X
Anticonvulsants	Phenobarbital	25 (0.1)	X	X	X
Antiarrhythmics	Dronedarone	22 (0.0)	X	X	
Anticonvulsants	Phenytoin	20 (0.0)	X	X	X
Anticonvulsants	Primidone	9 (0.0)	X	X	X
HIV drugs	Ritonavir	8 (0.0)			X
Lipid-lowering agents	Lovastatin	8 (0.0)			X
Antipsychotics/neuroleptics	Pimozide	6 (0.0)	X		X
HIV drugs	Lopinavir	6 (0.0)			X
HIV drugs	Darunavir/cobicistat	5 (0.0)			X
Antibacterials	Rifabutin	–[a]	X	X	X
Other drugs	Modafinil	–[a]		X	
HIV drugs	Atazanavir alone	–[a]			X
HIV drugs	Atazanavir/cobicistat	–[a]			X
HIV drugs	Darunavir + ritonavir	–[a]			X
HIV drugs	Efavirenz	–[a]		X	X
Hypertension/heart failure agents	Bosentan	–[a]		X	X
Cytotoxics	Vinblastine	–[a]			X
HIV drugs	Etravirine	–[a]		X	X

Table marked with X is for drugs that are categorized as 'Contraindicated' from reference of Liverpool University and Pecking University.

DDI, drug-drug interaction; DAA, direct-acting antiviral; HCV, hepatitis C virus; LDV, ledipasvir; SOF, sofosbuvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; HIV, human immunodeficiency virus.

[a]As per Health Insurance Review & Assessment Service, counts/values ≤ 3 are masked.

bacterials (80.3%), antihistamines (73.5%), anticoagulant, antiplatelet, and fibrinolytics (62.2%), and steroids (58.5%) (Supplementary Table 5).

Potential DDIs associated with DAA regimens

The proportion of contraindicated DDIs among CHC patients across the three DAA regimens was lowest in SOF/VEL (2.2%), followed by LDV/SOF (13.1%), and GLE/PIB (15.6%) ($p < 0.0001$) (Fig. 3A). SOF-containing regimens (SOF/VEL, LDV/SOF) had lower contraindicated DDI risk compared to GLE/PIB, respectively (Fig. 3A).

The proportion of no interaction expected was lowest in GLE/PIB (9.3%), followed by LDV/SOF (11.8%), and SOF/VEL (14.5%) ($p < 0.0001$) (Fig. 3A). Similar trends were observed in patients with cirrhosis and in the DAA-exposed group as well as when compared in age groups ($p < 0.0001$) (Fig. 3B-D, Supplementary Table 6).

Of all contraindications when classified by drug classes, the HIV drug class with GLE/PIB had the greatest number of prescribed comedications with contraindications, followed by anticonvulsants with all three DAA regimens (Supplementary Fig. 1). The three most common comedications which were classified as "contraindication" were atorvastatin with GLE/PIB (12.7%), rosuvastatin with LDV/SOF (11.1%), and simvastatin with GLE/PIB (1.4%) (Table 3).

DISCUSSION

This study aimed to investigate the demographics, comorbidities, and comedication profiles of patients with CHC in Korea using the nationwide claims database of 2018, and to identify any potential DDIs with the latest DAA regimens. Herein, our study found that the mean age of Korean patients with CHC was 60 years in 2018 with 37.2% of patients over the age of 65. This demonstrates the high disease burden in the elderly population with CHC in Korea, enforcing the importance of treating HCV infection at the earliest to prevent complications [16]. In a previous study including nationwide Korean CHC patients, the mean age was around 57. This suggests an aging trend in Korean patients with HCV wherein, risk factors associated with aging should be taken into consideration when treating CHC patients of older age [17].

In this study, nearly all identified CHC patients had comorbidities (97.5%) and comedications (97.5%). The previous study of CHC patients from another national data base of 2013 showed that 84.8% of CHC patients had comorbidities and 96.8% of patients with comedications [8]. Since this study implemented the similar inclusion and exclusion criteria for patient selection from the previous study [8], as well as methods of counting comorbidity and comedications, one can assume that the proportions of CHC patients with comorbidities and comedications have relatively increased. This could be associated with the high proportion of elderly patients aged ≥ 55 years recorded in this study (n = 34,285), wherein the elderly patients would have higher underlying comorbidities than younger patients [18].

When looking into comorbidities by disease code, hypertension, dyslipidemia, and diabetes are the most prevalent among CHC patients regardless of age group. As these are chronic metabolic diseases that require continued monitoring and treatment, this finding also highlighted the importance of considering comorbidities and comedications when initiating DAA treatment in patients with CHC.

It is interesting to see that SOF-containing regimens (SOF/VEL, LDV/SOF) had lower contraindicated DDI risk compared to GLE/PIB, respectively. This is aligned with another previous study [10,19], where a real-world observational Italian study reported that contraindications due to DDIs remained higher in GLE/PIB cohorts both before (9.3%) and during DAA treatment (3.2%), while patients with contraindicated co-treatments decreased from 3.2% to 0.4% after SOF/VEL initiation [10]. Similar observations were highlighted in the Taiwanese study. In this study, a total of 86.3% of hepatitis C patients had ≥ 1 comorbidity and 75.7% of patients received ≥ 1 concomitant medication [19]. The study demonstrated a high prevalence of comorbidities and widespread use of concomitant medications [19]. Among patients without cirrhosis or with compensated cirrhosis, contraindications were more prevalent with PTV/ritonavir/OBV plus DSV (13.3%), DCV/ASV (6.0%) and GLE/PIB (5.4%) compared with SOF-based regimens (0.8–2.1%). SOF-based regimens had no contraindications in patients with decompensated cirrhosis [19].

There are a few limitations to the study. The study had investigated potential DDIs by collecting all the comedications for the patients with CHC diagnosis but not actual DDIs linked to individual patients. Furthermore, the study was conducted based on the national claims database, which is more focused on prescribed medications. There can be additional medications such as over-the-counter medications

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that the patients are taking without prescriptions. Due to the nature of administrative data, errors or omissions of diagnostic codes could exist. Considering the nature of the claims data and the National health care system in Korea, this HIRA data represents characteristics of the HCV patients diagnosed in Korea. Since the previous research from Chung et al. [8], utilized the 2013 NHIS (National Health Insurance System) data and the HIRA data was used to identify patients recorded in 2018, we could not have a direct comparison between the two data sets. Although we were not able to make a direct comparison of the 2013 NHIS data to the 2018 HIRA data, the HIRA data well represents the prescription pattern nationwide as we investigated the changing trends of CHC patients in Korea. Therefore, this study holds value in providing an aging trend of patients with HCV as well as an increase in the comorbidity and comedication patterns in such patients. This study also reports the latest potential DDI in patients with HCV which can be taken into consideration by physicians when initiating treatment with DAAs in patients with chronic HCV infection.

Overall, the study findings highlighted that there was a trend toward increasing mean age, comorbidity, and comedication of Korean patients with CHC in 2018. This study also provided an update in DDI analyses wherein, newer pangenotypic DAA regimens available since 2013 were included, which can be referenced for practical clinical use.

While DAAs regimens objectively treat HCV infection, consideration of comorbidities and prescribed comedication is essential to minimize the risks of DDIs especially since there is a growing proportion of elderly HCV-diagnosed patients. In this setting, evaluation of comorbidities and comedication is essential to minimize the potential risk of DDIs and choose the safe options with favorable DDI features ahead of treating CHC patients, to improve patient outcomes and optimize patient management.

KEY MESSAGE

1. With the increasing age of chronic hepatitis C patients in Korea, number of comorbidity and comedication is increasing.
2. Drug-drug interaction (DDI) should be considered and consulted prior to hepatitis C virus treatment.
3. In general, sofosbuvir-based regimen has lower DDI in Korean patients.

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Conflict of interest
Kyung Min Kwon is an employee of Gilead Sciences. Jae-Jun Shim is an employee of the Department of Internal Medicine, Kyung Hee University College of Medicine, Seoul, Korea, and Cheorwon Hospital, Gangwon-do, Korea. Gi-Ae Kim is an employee of the Department of Internal Medicine, Kyung Hee University College of Medicine, Seoul, Korea. Bo Ok Kim, Helin Han, and Hyun Jung Ahn are employees of Cerner Enviza.

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Supplementary Table 1. List of comorbidities

Category	Category name	Disease
Category I	Certain infectious and parasitic diseases	Arthropod-borne viral fevers and viral hemorrhagic fevers
		Bacterial, viral and other infectious agents
		Certain zoonotic bacterial diseases
		Chronic hepatitis B
		Helminthiases
		Human immunodeficiency virus (HIV) disease
		Infections with a predominantly sexual mode of transmission
		Intestinal infectious diseases
		Mycoses
		Other bacterial diseases
		Other diseases caused by chlamydia
		Other infectious diseases
		Other spirochetal diseases
		Other viral diseases
		Pediculosis, acariasis and other infestations
		Protozoal diseases
		Rickettsioses
		Sequelae of infectious and parasitic diseases
		Tuberculosis
		Viral hepatitis
		Viral infections characterized by skin and mucous membrane lesions
		Viral infections of the central nervous system
Category II	Neoplasms	Benign neoplasms
		In situ neoplasms
		Malignant neoplasm of breast
		Malignant neoplasms of bone and articular cartilage
		Malignant neoplasms of digestive organs
		Malignant neoplasms of eye, brain and other parts of central nervous system
		Malignant neoplasms of female genital organs
		Malignant neoplasms of ill-defined, secondary and unspecified sites
		Malignant neoplasms of independent (primary) multiple sites
		Malignant neoplasms of lip, oral cavity and pharynx
		Malignant neoplasms of male genital organs
		Malignant neoplasms of mesothelial and soft tissue
		Malignant neoplasms of respiratory and intrathoracic organs
		Malignant neoplasms of thyroid and other endocrine glands
		Malignant neoplasms of urinary tract
		Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
		Melanoma and other malignant neoplasms of skin
		Neoplasms of uncertain or unknown behavior

Supplementary Table 1. Continued

Category	Category name	Disease
Category III	Disease of the blood and blood-forming organs and certain disorders involving the immune mechanism	Aplastic and other anemias
		Certain disorders involving the immune mechanism
		Coagulation defects, purpura and other hemorrhagic conditions
		Hemolytic anemias
		Nutritional anemias
		Other diseases of blood and blood-forming organs
Category IV	Endocrine, nutritional and metabolic disease	Diabetes mellitus
		Disorders of other endocrine glands
		Disorders of thyroid gland
		Dyslipidemia
		Malnutrition
		Metabolic disorders
		Obesity and other hyperalimentation
		Other disorders of glucose regulation and pancreatic internal secretion
		Other nutritional deficiencies
Category V	Mental and behavioral disorders	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence
		Behavioral syndromes associated with physiological disturbances and physical factors
		Disorders of adult personality and behavior
		Disorders of psychological development
		Mental and behavioral disorders due to psychoactive substance use
		Mental retardation
		Mood (affective) disorders
		Neurotic, stress-related and somatoform disorders
		Organic, including symptomatic, mental disorders
		Schizophrenia, schizotypal and delusional disorders
		Unspecified mental disorder
Category VI	Diseases of the nervous system	Cerebral palsy and other paralytic syndromes
		Demyelinating diseases of the central nervous system
		Diseases of myoneural junction and muscle
		Episodic and paroxysmal disorders
		Extrapyramidal and movement disorders
		Inflammatory diseases of the central nervous system
		Nerve, nerve root and plexus disorders
		Other degenerative diseases of the nervous system
		Other disorders of the nervous system
		Polyneuropathies and other disorders of the peripheral nervous system
		Systemic atrophies primarily affecting the central nervous system
Category VII	Diseases of the eye and adnexa	Disorders of choroid and retina
		Disorders of conjunctiva
		Disorders of eyelid, lacrimal system and orbit

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Supplementary Table 1. Continued

Category	Category name	Disease
		Disorders of lens
		Disorders of ocular muscles, binocular movement, accommodation and refraction
		Disorders of optic nerve and visual pathways
		Disorders of sclera, cornea, iris and ciliary body
		Disorders of vitreous body and globe
		Glaucoma
		Other disorders of eye and adnexa
		Visual disturbances and blindness
Category VIII	Diseases of the ear and mastoid process	Diseases of external ear
		Diseases of inner ear
		Diseases of middle ear and mastoid
		Other disorders of ear
Category IX	Diseases of the circulatory system	Acute rheumatic fever
		Cerebrovascular diseases
		Chronic rheumatic heart diseases
		Diseases of arteries, arterioles and capillaries
		Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
		Hypertension
		Hypertensive diseases
		Ischemic heart diseases
		Other and unspecified disorders of the circulatory system
		Other forms of heart disease
		Pulmonary heart disease and diseases of pulmonary circulation
Category X	Diseases of the respiratory system	Acute upper respiratory infections
		Chronic lower respiratory diseases
		Influenza and pneumonia
		Lung diseases due to external agents
		Other acute lower respiratory infections
		Other diseases of pleura
		Other diseases of the respiratory system
		Other respiratory diseases principally affecting the interstitial
		Suppurative and necrotic conditions of lower respiratory tract
Category XI	Diseases of the digestive system	Alcoholic liver disease
		Diseases of appendix
		Diseases of liver
		Diseases of esophagus, stomach and duodenum
		Diseases of oral cavity, salivary glands and jaws
		Diseases of peritoneum
		Disorders of gallbladder, biliary tract and pancreas
		Esophagitis or gastroesophageal

Supplementary Table 1. Continued

Category	Category name	Disease
		Hernia
		Noninfective enteritis and colitis
		Other diseases of intestines
		Other diseases of the digestive system
		Peptic ulcer or gastrointestinal ulcer
Category XII	Diseases of the skin and subcutaneous tissue	Bullous disorders
		Dermatitis and eczema
		Disorders of skin appendages
		Infections of the skin and subcutaneous tissue
		Other disorders of the skin and subcutaneous tissue
		Papulosquamous disorders
		Radiation-related disorders of the skin and subcutaneous tissue
		Urticaria and erythema
Category XIII	Diseases of the musculoskeletal system and connective tissue	Arthrosis
		Chondropathies
		Deforming dorsopathies
		Disorders of bone density and structure
		Disorders of muscles
		Disorders of synovium and tendon
		Infectious arthropathies
		Inflammatory polyarthropathies
		Other disorders of the musculoskeletal system and connective tissue
		Other dorsopathies
		Other joint disorders
		Other osteopathies
		Other soft tissue disorders
		Spondylopathies
		Systemic connective tissue disorders
Category XIV	Diseases of the genitourinary system	Chronic renal disease
		Diseases of male genital organs
		Disorders of breast
		Glomerular diseases
		Inflammatory diseases of female pelvic organs
		Noninflammatory disorders of female genital tract
		Other diseases of urinary system
		Other disorders of kidney and ureter
		Other disorders of the genitourinary system
		Renal failure
		Renal tubulo-interstitial diseases
		Urolithiasis

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Supplementary Table 2. List of comedication and drug-drug interaction with DAAs

	LDV/SOF	SOF/VEL	GLE/PIB
Anesthetics and muscle relaxants			
Bupivacaine	○	○	○
Cisatracurium	○	○	○
Isoflurane	○	○	○
Ketamine	○	○	○
Nitrous oxide	○	○	○
Propofol	○	○	○
Thiopental	○	○	○
Tizanidine	○	○	○
Analgesics			
Aceclofenac	○	○	○
Alfentanil	○	○	△
Aspirin	○	○	○
Buprenorphine	○	○	○
Celecoxib	○	○	○
Codeine	○	○	○
Dexketoprofen	○	○	○
Dextropropoxyphene	○	○	○
Diamorphine	○	○	○
Diclofenac	○	○	○
Diflunisal	○	○	○
Dihydrocodeine	○	○	○
Etoricoxib	○	○	○
Fentanyl	○	○	△
Flurbiprofen	○	○	○
Hydrocodone	○	○	△
Hydromorphone	○	○	○
Ibuprofen	○	○	○
Indomethacin	○	○	○
Ketoprofen	○	○	○
Mefenamic acid	○	○	○
Meloxicam	○	○	○
Methadone	○	○	○
Morphine	○	○	○
Naproxen	○	○	○
Oxycodone	○	○	△
Paracetamol (acetaminophen)	○	○	○
Pethidine (meperidine)	○	○	○
Piroxicam	○	○	○
Tapentadol	○	○	○
Tramadol	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Anthelmintics			
Albendazole	○	○	○
Ivermectin	○	○	○
Oxamniquine	○	○	○
Praziquantel	○	○	○
Pyrantel	○	○	○
Antiarrhythmics			
Amiodarone	X	X	△
Bepridil	○	○	○
Digoxin	△	△	△
Disopyramide	○	○	○
Dofetilide	○	○	○
Dronedarone	X	X	△
Flecainide	○	○	○
Lidocaine (lignocaine)	○	○	○
Mexiletine	○	○	○
Propafenone	○	○	○
Quinidine	△	△	△
Vernakalant	○	○	○
Antibacterials			
Amikacin	○	○	○
Amoxicillin	○	○	○
Ampicillin	○	○	○
Azithromycin	○	○	○
Aztreonam	○	○	○
Benzylpenicillin	○	○	○
Capreomycin	○	○	○
Cefaclor	○	○	○
Cefadroxil	○	○	○
Cefalexin	○	○	○
Cefazolin	○	○	○
Cefixime	○	○	○
Cefotaxime	○	○	○
Cefradine	○	○	○
Ceftaroline	○	○	○
Ceftazidime	○	○	○
Ceftriaxone	○	○	○
Cefuroxime	○	○	○
Chloramphenicol	○	○	○
Ciprofloxacin	○	○	○
Clarithromycin	○	○	△
Clavulanic acid	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Clindamycin	○	○	○
Cloxacillin	○	○	○
Dapsone	○	○	○
Ertapenem	○	○	○
Erythromycin	○	○	△
Ethambutol	○	○	○
Flucloxacillin	○	○	○
Fusidic acid			
Gentamicin	○	○	○
Imipenem	○	○	○
Isoniazid	△	△	△
Levofloxacin	○	○	○
Linezolid	○	○	○
Lymecycline	○	○	○
Meropenem	○	○	○
Methenamine	○	○	○
Metronidazole	○	○	○
Moxifloxacin	○	○	○
Nafcillin			
Nitrofurantoin	○	○	○
Norfloxacin	○	○	○
Ofloxacin	○	○	○
Penicillin V	○	○	○
Piperacillin	○	○	○
Pivmecillinam	○	○	○
Pyrazinamide	○	○	○
Rifabutin	X	X	X
Rifampicin	X	X	X
Rifapentine	X	X	X
Rifaximin	○	○	△
Spectinomycin	○	○	○
Streptomycin	○	○	○
Sulfadiazine	○	○	○
Tazobactam	○	○	○
Telithromycin	△	○	△
Temocillin	○	○	○
Tetracyclines	○	○	○
Ticarcillin	○	○	○
Trimethoprim/sulfamethoxazole	○	○	○
Troleandomycin	○	△	X
Vancomycin	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Anticoagulant, anti-platelet and fibrinolytic			
Acenocoumarol	△	○	△
Anagrelide	○	○	○
Apixaban	△	△	△
Clopidogrel	○	○	○
Dabigatran	△	△	X
Dalteparin	○	○	○
Danaparoid	○	○	○
Dipyridamole	○	○	○
Edoxaban	△	△	△
Eltrombopag	○	△	X
Enoxaparin	○	○	○
Fluindione	△	○	△
Fondaparinux	○	○	○
Heparin	○	○	○
Phenprocoumon	△	○	△
Prasugrel	○	○	○
Rivaroxaban	△	△	△
Streptokinase	○	○	○
Ticagrelor	△	△	△
Ticlopidine	○	○	○
Warfarin	△	△	△
Anticonvulsants			
Carbamazepine	X	X	X
Clonazepam	○	○	○
Eslicarbazepine	○	X	X
Ethosuximide	○	○	○
Gabapentin	○	○	○
Lacosamide	○	○	○
Lamotrigine	○	○	○
Levetiracetam	○	○	○
Oxcarbazepine	X	X	X
Perampanel	○	○	○
Phenobarbital	X	X	X
Phenytoin	X	X	X
Pregabalin	○	○	○
Primidone	X	X	X
Retigabine	○	○	○
Rufinamide	△	△	△
Sultiame	○	○	○
Tiagabine	○	○	○

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Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Topiramate	○	○	○
Valproate	○	○	○
Vigabatrin	○	○	○
Zonisamide	○	○	○
Antidepressants			
Agomelatine	○	○	○
Amitriptyline	○	○	○
Bupropion	○	○	○
Citalopram	○	○	○
Clomipramine	○	○	○
Desipramine	○	○	○
Desvenlafaxine	○	○	○
Doxepin	○	○	○
Duloxetine	○	○	○
Escitalopram	○	○	○
Fluoxetine	○	○	○
Fluvoxamine	○	○	○
Imipramine	○	○	○
Lithium	○	○	○
Maprotiline	○	○	○
Milnacipran	○	○	○
Mirtazapine	○	○	○
Moclobemide	○	○	○
Nefazodone	○	○	○
Nortriptyline	○	○	○
Paroxetine	○	○	○
Sertraline	○	○	○
Tianeptine	○	○	○
Trazodone	○	○	○
Trimipramine	○	○	○
Venlafaxine	○	○	○
Vortioxetine	○	○	○
Antidiabetics			
Acarbose	○	○	○
Albiglutide	○	○	○
Alogliptin	○	○	○
Canagliflozin	○	○	○
Dapagliflozin	○	○	○
Dulaglutide	△	△	△
Empagliflozin	○	△	○
Exenatide	△	△	△
Glibenclamide (glyburide)	○	○	△

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Gliclazide	○	○	○
Glimepiride	○	○	○
Glipizide	○	○	○
Insulin	○	○	○
Linagliptin	○	○	○
Liraglutide	△	△	△
Lixisenatide	○	○	○
Metformin	○	○	○
Nateglinide	○	○	○
Pioglitazone	○	○	○
Repaglinide	○	△	△
Rosiglitazone	○	○	○
Saxagliptin	○	○	○
Sitagliptin	○	○	○
Tolbutamide	○	○	○
Vildagliptin	○	○	△
Antifungals			
Amphotericin B	○	○	○
Anidulafungin	○	○	○
Caspofungin	○	○	○
Fluconazole	○	○	○
Flucytosine	○	○	○
Griseofulvin	○	○	○
Itraconazole	○	○	○
Ketoconazole	○	○	△
Miconazole	△	○	○
Nystatin	○	○	○
Posaconazole	○	○	△
Terbinafine	○	○	○
Voriconazole	○	○	○
Antihistamines			
Astemizole	○	○	△
Bilastine	△	△	△
Cetirizine	○	○	○
Chlorphenamine	○	○	○
Desloratadine	○	○	○
Diphenhydramine	○	○	○
Ebastine	○	○	△
Fexofenadine	○	○	△
Hydroxyzine	○	○	○
Levocetirizine	○	○	○
Loratadine	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Promethazine	○	○	○
Terfenadine	○	○	△
Antimigraine agents			
Almotriptan	○	○	○
Eletriptan	○	○	○
Ergotamine	△	○	△
Frovatriptan	○	○	○
Methylergonovine	△	○	△
Naratriptan	○	○	○
Pizotifen	○	○	○
Rizatriptan	○	○	○
Sumatriptan	○	○	○
Zolmitriptan	○	○	○
Antiprotozoals			
Amodiaquine	○	○	○
Artemether	○	○	○
Artemisinin	○	△	○
Artesunate	○	△	○
Atovaquone	○	○	○
Chloroquine	○	○	○
Dihydroartemisinin	○	△	○
Doxycycline	○	○	○
Halofantrine	○	○	○
Hydroxychloroquine	○	○	○
Lumefantrine	○	○	○
Mefloquine	△	○	△
Pentamidine	○	○	○
Primaquine	○	○	○
Proguanil	○	○	○
Pyrimethamine	○	○	○
Quinine	△	○	△
Sodium stibogluconate	○	○	○
Sulfadoxine	○	○	○
Antipsychotics/neuroleptics			
Amisulpride	○	○	○
Aripiprazole	○	○	△
Chlorpromazine	○	○	○
Clozapine	○	○	△
Flupentixol	○	○	○
Fluphenazine	○	○	○
Haloperidol	○	○	○
Iloperidone	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Levomepromazine	○	○	○
Olanzapine	○	○	○
Paliperidone	△	△	△
Perazine	○	○	○
Pericyazine	○	○	○
Perphenazine	○	○	○
Pimozide	X	○	X
Pipotiazine	○	○	○
Prochlorperazine	○	○	○
Quetiapine	○	○	△
Risperidone	△	△	△
Sulpiride	○	○	○
Tiapride	○	○	○
Trifluoperazine	○	○	○
Ziprasidone	○	○	○
Zuclopentixol	○	○	○
Antivirals			
Aciclovir	○	○	○
Amantadine	○	○	○
Brivudine	○	○	○
Cidofovir	○	○	○
Foscarnet	○	○	○
Oseltamivir	○	○	○
Rimantadine	○	○	○
Valaciclovir	○	○	○
Zanamivir	○	○	○
Anxiolytics/hypnotics/sedatives			
Alprazolam	○	○	○
Bromazepam	○	○	○
Bromperidol	○	○	○
Buspirone	○	○	○
Clobazam	○	○	○
Clorazepate	○	○	○
Diazepam	○	○	○
Estazolam	○	○	○
Flurazepam	○	○	○
Lorazepam	○	○	○
Lormetazepam	○	○	○
Midazolam (oral)	○	○	○
Midazolam (parenteral)	○	○	○
Oxazepam	○	○	○
Quazepam	○	○	○

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Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Temazepam	○	○	○
Triazolam	○	○	○
Zaleplon	○	○	○
Zolpidem	○	○	○
Zopiclone	○	○	○
Beta blockers			
Atenolol	○	○	○
Bisoprolol	○	○	○
Carvedilol	△	△	△
Celiprolol	○	○	○
Labetalol	○	○	○
Metoprolol	○	○	○
Nebivolol	○	○	○
Oxprenolol	○	○	○
Pindolol	○	○	○
Propranolol	○	○	○
Sotalol	○	○	○
Timolol	○	○	○
Bisphosphonates			
Alendronic acid	○	○	○
Ibandronic acid	○	○	○
Pamidronate	○	○	○
Risedronate	○	○	○
Bronchodilators			
Formoterol	○	○	○
Indacaterol	○	○	○
Ipratropium bromide	○	○	○
Montelukast	○	○	○
Omalizumab	○	○	○
Salbutamol	○	○	○
Salmeterol	○	○	○
Theophylline	○	○	△
Tiotropium	○	○	○
Calcium channel blockers			
Amlodipine	△	○	○
Diltiazem	△	△	△
Felodipine	△	○	○
Nicardipine	○	○	○
Nifedipine	○	○	○
Nimodipine			
Nisoldipine	○	○	○
Nitrendipine	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Verapamil	○	○	△
Contraceptives and hormone replacement			
Conjugated estrogens (HRT)	○	○	○
Dienogest	○	○	○
Drospirenone (POP)	○	○	○
Dydrogesterone/estradiol (HRT)	○	○	○
Estradiol	○	○	○
Ethinylestradiol	○	○	X
Levonorgestrel (implant)	○	○	○
Medroxyprogesterone (oral)	○	○	○
Medroxyprogesterone/estradiol (HRT)	○	○	○
Norethisterone (norethindrone)/ estradiol (HRT)	○	○	○
Cytotoxics			
Abiraterone	○	○	○
Anastrozole	○	○	○
Bevacizumab	○	○	○
Bortezomib	○	○	○
Capecitabine	○	○	○
Carboplatin	○	○	○
Cetuximab	○	○	○
Chlorambucil	○	○	○
Cisplatin	○	○	○
Cyclophosphamide	○	○	○
Dasatinib	○	○	○
Doxorubicin	○	○	△
Erlotinib	△	△	△
Estramustine	○	○	○
Etoposide	○	○	○
Everolimus	△	△	△
Exemestane	○	○	○
Fludarabine	○	○	○
Gefitinib	○	○	○
Gemcitabine	○	○	○
Idarubicin	○	○	○
Imatinib	○	△	△
Ipilimumab	○	○	○
Irinotecan	△	△	△
Letrozole	○	○	○
Mercaptopurine	○	○	○
Mesna	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Methotrexate	○	△	△
Mitoxantrone	△	△	△
Nilotinib	○	△	△
Nivolumab	○	○	○
Oxaliplatin	○	○	○
Paclitaxel	○	○	△
Rituximab	○	○	○
Sorafenib	○	○	○
Sunitinib	△	△	△
Tamoxifen	○	△	○
Vinblastine	○	△	X
Vincristine	○	△	X
Vinorelbine	△	△	△
Erectile dysfunction agents			
Vardenafil	○	○	○
Gastrointestinal agents			
Aluminum hydroxide	△	△	○
Alverine citrate	○	○	○
Antacids	△	△	○
Aprepitant	○	○	○
Bisacodyl	○	○	○
Cimetidine	△	△	△
Cisapride	△	○	△
Dantron	○	○	○
Domperidone	○	○	△
Droperidol	○	○	△
Esomeprazole	△	△	△
Famotidine	△	△	△
Granisetron	○	○	△
Ispaghula husk	○	○	○
Lactulose	○	○	○
Lansoprazole	△	△	△
Linaclotide	○	○	○
Loperamide	△	○	△
Lubiprostone	○	○	○
Macrogol	○	○	○
Mebeverine	○	○	○
Mesalazine	○	○	○
Methylcellulose	○	○	○
Metoclopramide	○	○	○
Naloxegol	○	○	○
Omeprazole	△	△	△

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Ondansetron	○	○	○
Pantoprazole	△	△	△
Prucalopride	○	○	○
Rabeprazole	△	△	△
Ranitidine	△	△	△
Senna	○	○	○
Simeticone	○	○	○
Trimebutine	○	○	○
HCC therapies			
Pembrolizumab	○	○	○
Hepatitis drugs			
Adefovir	○	○	○
Entecavir	○	○	○
Lamivudine (HBV)	○	○	○
Peginterferon alfa-2a	△	△	△
Peginterferon alfa-2b	△	△	△
Ribavirin	○	○	○
Tenofovir alafenamide	○	○	○
Tenofovir-DF (HBV)	△	△	○
Hepatotonics			
Milk thistle (silymarin)	○	○	○
Ursodeoxycholic acid	○	○	○
Herbals/supplements/vitamins			
Aloe vera	○	○	○
Ascorbic acid (vitamin C)	○	○	○
Colecalciferol (vitamin D)	○	○	○
Cyanocobalamin (vitamin B12)	○	○	○
Diosmin	○	○	○
Echinacea	○	○	○
Ferrous sulfate (iron supplements)	○	○	○
Folic acid	○	○	○
Garlic	○	○	○
Ginkgo biloba	○	○	○
Ginseng	○	○	○
Grapefruit juice	○	○	○
Retinol (vitamin A)	○	○	○
Riboflavin (vitamin B2)	○	○	○
Serenoa repens	○	○	○
St John's wort	X	X	X
Thiamine (vitamin B1)	○	○	○
Valerian	○	○	○

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Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Vitamin E	○	○	○
HIV drugs			
Dolutegravir	○	○	○
Efavirenz	○	X	X
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/c/FTC/TAF)	○	○	○
Elvitegravir/cobicistat/emtricitabine/tenofovir-DF (EVG/c/FTC/TDF)	△	△	○
Etravirine	○	X	X
Maraviroc	○	○	○
Nevirapine	○	X	X
Raltegravir	○	○	○
Rilpivirine	○	○	○
Abacavir	○	○	○
Emtricitabine/tenofovir alafenamide (FTC/TAF)	○	○	○
Emtricitabine/tenofovir-DF (FTC/TDF, PrEP)	△	△	○
Ritonavir	○	○	X
Stavudine	○	○	○
Tipranavir	X	X	X
Zidovudine	○	○	○
Atazanavir alone	○	○	X
Atazanavir/cobicistat	○	○	X
Darunavir+ritonavir	○	○	X
Darunavir/cobicistat	○	○	X
Fosamprenavir	○	○	X
Indinavir	○	○	X
Lopinavir	△	○	X
Nelfinavir			
Hypertension/heart failure agents			
Acebutolol	○	○	○
Ambrisentan	○	○	△
Amiloride	○	○	○
Azilsartan	○	○	○
Benazepril	○	○	○
Bendroflumethiazide	○	○	○
Bosentan	○	X	X
Bumetanide	○	○	○
Candesartan	○	○	△

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Captopril	○	○	○
Chlorothiazide	○	○	○
Chlortalidone	○	○	○
Cilazapril	○	○	○
Clevidipine	○	○	○
Clonidine	○	○	○
Doxazosin	○	○	○
Enalapril	○	○	△
Eplerenone	△	○	△
Eprosartan	○	○	○
Fosinopril	○	○	○
Furosemide	○	○	○
Hydralazine	○	○	○
Hydrochlorothiazide	○	○	○
Iloprost	○	○	○
Indapamide	○	○	○
Irbesartan	△	○	△
Isradipine	△	○	△
Ivabradine	○	○	○
Lacidipine	○	○	○
Lercanidipine	○	○	○
Lisinopril	○	○	○
Losartan	○	○	○
Macitentan	○	○	○
Methyldopa	○	○	○
Metolazone	○	○	○
Moxonidine	○	○	○
Olmesartan	○	○	△
Perindopril	○	○	○
Prazosin	○	△	△
Quinapril	○	○	○
Ramipril	○	○	○
Ranolazine	△	○	△
Rilmenidine	○	○	○
Sildenafil (pulmonary arterial hypertension)	○	○	○
Spironolactone	○	○	○
Telmisartan	○	○	△
Torasemide	○	○	○
Trandolapril	○	○	○
Valsartan	○	○	○
Xipamide	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Zofenopril	○	○	○
Illicit/recreational			
Amphetamine	○	○	○
Cocaine	○	○	○
Mephedrone	○	○	○
Methamphetamine	○	○	○
Immunosuppressants			
Adalimumab	○	○	○
Azathioprine	○	○	○
Basiliximab	○	○	○
Ciclosporin (cyclosporine)	○	○	△
Eculizumab	○	○	○
Etanercept	○	○	○
Fingolimod	○	○	○
Lenalidomide	○	○	○
Mycophenolate	○	○	○
Pirfenidone	○	○	○
Sirolimus	○	○	△
Tacrolimus	○	○	△
Teriflunomide			
Tocilizumab	○	○	○
Lipid lowering agents			
Atorvastatin	△	△	X
Bezafibrate	○	○	○
Ezetimibe	○	○	△
Fenofibrate	○	○	○
Fish oils	○	○	○
Fluvastatin	△	△	△
Gemfibrozil	○	○	△
Lovastatin	△	△	X
Pitavastatin	△	△	△
Pravastatin	△	○	△
Rosuvastatin	X	△	△
Simvastatin	△	△	X
Other drugs			
Acamprosate	○	○	○
Acetazolamide	○	○	○
Acitretin	○	○	○
Alfuzosin	○	○	○
Allopurinol	○	○	○
Atomoxetine	○	○	○
Atropine	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Baclofen	○	○	○
Betahistine	○	○	○
Bimatoprost	○	○	○
Brinzolamide	○	○	○
Bromocriptine	○	○	○
Calcitonin	○	○	○
Calcium resonium	○	○	○
Carbimazole	○	○	○
Carisoprodol	○	○	○
Cilostazol	○	○	○
Clomifene	○	○	○
Colchicine	△	△	△
Colestyramine	△	△	△
Conivaptan	○	○	○
Cyclobenzaprine	○	○	○
Cytisine	○	○	○
Darbepoetin	○	○	○
Denosumab	○	○	○
Desmopressin	○	○	○
Dextromethorphan	○	○	○
Disulfiram	○	○	○
Donepezil	○	○	○
Dorzolamide	○	○	○
Dutasteride	○	○	○
Epoetin alfa	○	○	○
Febuxostat	○	○	○
Filgrastim	○	○	○
Finasteride	○	○	○
Flibanserin	○	○	△
Gadopentetate (gadolinium)	○	○	○
Goserelin	○	○	○
Hyoscine	○	○	○
Isosorbide mononitrate	○	○	○
Isotretinoin	○	○	○
Lanreotide	○	○	○
Levothyroxine	○	○	○
Melatonin	○	○	○
Memantine	○	○	○
Methylphenidate	○	○	○
Minoxidil	○	○	○
Mirabegron	○	○	△
Modafinil	△	X	△

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Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Naftidrofuryl	○	○	○
Naloxone	○	○	○
Naltrexone	○	○	○
Neostigmine	○	○	○
Nicorandil	○	○	○
Orlistat	△	△	△
Penicillamine	○	○	○
Pentoxifylline	○	○	○
Phenylephrine	○	○	○
Pilocarpine	○	○	○
Piracetam	○	○	○
Potassium	○	○	○
Protamine sulphate	○	○	○
Pseudoephedrine	○	○	○
Pyridostigmine	○	○	○
Raloxifene	○	○	○
Sevelamer	△	△	△
Silodosin	△	△	△
Solifenacin	○	○	△
Strontium ranelate	○	○	○
Sulfasalazine	○	△	△
Tamsulosin	○	○	○
Thalidomide	○	○	○
Tolterodine	○	○	○
Tranexamic acid	○	○	○
Varenicline	○	○	○
Oxytocics			
Ergometrine (ergonovine)	△	○	△
Misoprostol	○	○	○
Parkinsonism agents			
Benztropine	○	○	○
Carbidopa	○	○	○
Orphenadrine	○	○	○
Pramipexole	○	○	○
Procyclidine	○	○	○
Rasagiline	○	○	○
Ropinirole	○	○	○
Steroids			
Beclometasone	○	○	○
Betamethasone	○	○	○
Budesonide	○	○	○
Ciclesonide	○	○	○

Supplementary Table 2. Continued

	LDV/SOF	SOF/VEL	GLE/PIB
Clobetasol (topical)	○	○	○
Clobetasone (topical)	○	○	○
Dexamethasone	○	○	△
Fludrocortisone	○	○	○
Flunisolide	○	○	○
Fluticasone	○	○	○
Hydrocortisone (topical)	○	○	○
Methylprednisolone	○	○	○
Mometasone	○	○	○
Prednicarbate	○	○	○
Prednisone	○	○	○
Triamcinolone	○	○	○

DAA, direct-acting antiviral; LDV, ledipasvir; SOF, sofosbuvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; ○, no clinically significant interaction expected; Blank, no available information; X, contraindication; △, dose-reduction/Additional monitoring required; HRT, hormone replacement therapy; POP, progestin-only pill; HBV, hepatitis B virus; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis.

Supplementary Table 3. Comorbidity by disease category, age group, gender, cirrhosis status and DAA exposure status

	Total	Age group of total CHC patients						Gender		Cirrhosis status		DAA exposure		*p* value
		18–34 years	35–44 years	45–54 years	55–64 years	65–74 years	≥ 75 years	Male	Female	without cirrhosis	with cirrhosis	Unexposed	Exposed	
Total hepatitis C infected patients	50,476	1,405 (2.8)	3,474 (6.9)	11,312 (22.4)	15,536 (30.8)	11,402 (22.6)	7,347 (14.6)	23,592 (46.7)	26,884 (53.3)	47,850 (94.8)	2,626 (5.2)	27,232 (54.0)	23,244 (46.0)	–[a]
Mean number of comorbidities by disease code	7.58 (4.87)	3.76 (3.19)	4.96 (3.62)	5.84 (4.02)	7.20 (4.46)	9.33 (5.07)	10.32 (4.97)	7.01 (4.87)	8.08 (4.82)	7.52 (4.86)	8.60 (5.03)	7.58 (4.92)	7.58 (4.82)	–[a]
Mean number of comorbidities by disease category	4.4	2.5	3.2	3.6	4.3	5.2	5.8	4.2	4.7	4.4	4.8	4.4	4.5	–[a]
Patient with ≥ comorbidity	49,235 (97.5)	1,213 (86.3)	3,227 (92.8)	10,862 (96.0)	15,269 (98.2)	1,134 (99.4)	7,324 (99.6)	22,873 (96.9)	26,362 (98.1)	46,619 (97.4)	2,616 (99.6)	26,473 (97.2)	22,762 (97.9)	–[a]
Comorbidity by disease category														
Category XI (diseases of the digestive system)	41,223 (83.7)	837 (69.0)	2,435 (75.5)	8,678 (79.9)	12,830 (84.0)	10,019 (88.4)	6,424 (87.7)	19,100 (83.5)	22,123 (83.9)	38,667 (82.9)	2,556 (97.7)	21,977 (83.0)	19,246 (84.6)	< 0.0001
Category X (diseases of the respiratory system)	28,674 (58.2)	676 (55.7)	1,803 (55.9)	5,564 (51.2)	8,645 (56.6)	7,262 (63.7)	4,724 (64.5)	12,299 (53.8)	16,375 (62.1)	27,259 (58.5)	1,424 (54.4)	15,521 (58.6)	13,153 (57.8)	0.3554
Category XIII (diseases of the musculoskeletal system and connective tissue)	28,347 (57.6)	297 (24.5)	1,207 (37.4)	5,189 (47.8)	8,717 (57.1)	7,763 (68.5)	5,174 (70.6)	11,479 (50.2)	16,868 (64.0)	26,836 (57.6)	1,511 (57.8)	15,295 (57.8)	13,052 (57.3)	0.9758
Category IX (diseases of the circulatory system)	21,559 (43.8)	51 (4.2)	432 (13.4)	2,863 (26.4)	6,243 (40.9)	6,719 (59.3)	5,251 (71.7)	10,152 (44.4)	11,407 (43.3)	20,251 (43.4)	1,308 (49.9)	11,624 (43.9)	9,935 (43.6)	0.8971
Category IV (endocrine, nutritional and metabolic disease)	20,704 (42.1)	187 (15.4)	859 (26.6)	3,862 (35.6)	6,642 (43.5)	5,599 (49.4)	3,555 (48.5)	9,270 (40.5)	11,434 (43.4)	19,583 (42.0)	1,121 (42.9)	11,048 (41.7)	9,656 (42.4)	0.0269
Category VII (diseases of the eye and adnexa)	14,404 (29.3)	143 (11.8)	445 (13.8)	1,838 (16.9)	3,832 (25.1)	4,532 (39.7)	3,614 (49.3)	5,914 (25.9)	8,490 (32.2)	13,586 (29.1)	818 (31.3)	7,822 (29.5)	6,582 (28.9)	0.3134

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Supplementary Table 3. Continued

	Total	Age group of total CHC patients						Gender		Cirrhosis status		DAA exposure		*p* value
		18–34 years	35–44 years	45–54 years	55–64 years	65–74 years	≥ 75 years	Male	Female	without cirrhosis	with cirrhosis	Unexposed	Exposed	
Category XIV (diseases of the genitourinary system)	13,667 (27.8)	315 (26.0)	936 (28.9)	2,640 (24.3)	3,867 (25.3)	3,367 (29.7)	2,542 (34.7)	5,922 (25.9)	7,745 (29.4)	13,022 (27.9)	645 (24.7)	7,584 (28.6)	6,083 (26.7)	< 0.0001
Category XII (diseases of the skin and subcutaneous tissue)	13,084 (26.6)	307 (25.3)	690 (21.4)	2,475 (22.8)	3,795 (24.9)	3,375 (29.8)	2,442 (33.3)	6,136 (26.8)	6,948 (26.4)	12,376 (26.5)	708 (27.1)	7,035 (26.6)	6,049 (26.6)	0.6267
Category I (certain infectious and parasitic diseases)	10,537 (21.4)	267 (22.0)	728 (22.6)	2,146 (19.8)	3,060 (20.0)	2,566 (22.6)	1,770 (24.2)	4,749 (20.8)	5,788 (21.9)	9,939 (21.3)	598 (22.9)	5,697 (21.5)	4,840 (21.3)	0.7879
Category V (mental and behavioural disorders)	9,095 (18.5)	112 (9.2)	465 (14.4)	1,760 (16.2)	2,424 (15.9)	2,163 (19.1)	2,171 (29.6)	4,016 (17.6)	5,079 (19.3)	8,512 (18.3)	583 (22.3)	4,929 (18.6)	4,166 (18.3)	0.6058
Category VI (diseases of the nervous system)	8,627 (17.5)	81 (6.7)	339 (10.5)	1,547 (14.2)	2,489 (16.3)	2,290 (20.2)	1,881 (25.7)	3,646 (15.9)	4,981 (18.9)	8,098 (17.4)	529 (20.2)	4,642 (17.5)	3,985 (17.5)	0.7704
Category II (neoplasms)	6,572 (13.3)	69 (5.7)	342 (10.6)	1,295 (11.9)	1,943 (12.7)	1,778 (15.7)	1,145 (15.6)	2,833 (12.4)	3,739 (14.2)	6,247 (13.4)	325 (12.4)	3,540 (13.4)	3,032 (13.3)	0.8815
Category VIII (diseases of the ear and mastoid process)	5,347 (10.9)	59 (4.9)	171 (5.3)	751 (6.9)	1,478 (9.7)	1,555 (13.7)	1,333 (18.2)	2,140 (9.4)	3,207 (12.2)	5,050 (10.8)	297 (11.4)	2,959 (11.2)	2,388 (10.5)	0.0312
Category III (disease of the blood and blood-forming organs and certain disorders involving the immune mechanism)	2,446 (5.0)	43 (3.5)	151 (4.7)	482 (4.4)	619 (4.1)	578 (5.1)	573 (7.8)	1,008 (4.4)	1,438 (5.5)	2,267 (4.9)	179 (6.8)	1,167 (4.4)	1,279 (5.6)	< 0.0001

Values are presented as number (%).

The mean number of comorbidities by category of disease was counted by each classified disease category. For example, if a patient had two different KCD-7 codes for comorbidities belonging to the same category of disease, the patient's number of comorbidity category was counted as one comorbidity. Category was defined using Korean Standard Classification of Diseases and Causes of Death 7th edition.

DAA, direct-acting antiviral; CHC, chronic hepatitis C.

[a]*p* value not provided.

Supplementary Table 4. Comorbidity by disease code and health conditions

Comorbidity by KCD-7 code	Total	Age group of total CHC patients						Gender		Cirrhosis status		DAA exposure		*p* value
		18–34 years	35–44 years	45–54 years	55–64 years	65–74 years	≥ 75 years	Male	Female	without cirrhosis	with cirrhosis	Unexposed	Exposed	
Hypertension	16,769 (34.1)	26 (2.1)	305 (9.5)	2,181 (20.1)	4,779 (31.3)	5,286 (46.6)	4,192 (57.2)	7,796 (34.1)	8,973 (34.0)	15,776 (33.8)	993 (38.0)	8,931 (33.7)	7,838 (34.4)	< 0.0001
Dyslipidemia	10,583 (21.5)	100 (8.2)	464 (14.4)	2,023 (18.6)	3,599 (23.6)	2,865 (25.3)	1,532 (20.9)	4,508 (19.7)	6,075 (23.0)	10,231 (21.9)	352 (13.5)	5,777 (21.8)	4,806 (21.1)	< 0.0001
Diabetes mellitus	9,777 (19.9)	29 (2.4)	237 (7.3)	1,711 (15.8)	2,961 (19.4)	2,843 (25.1)	1,996 (27.3)	5,466 (23.9)	4,311 (16.4)	9,021 (19.4)	756 (28.9)	5,047 (19.1)	4,730 (20.8)	0.0013
Peptic ulcer or gastrointestinal ulcer	3,872 (7.9)	21 (1.7)	149 (4.6)	699 (6.4)	1,156 (7.6)	1,097 (9.7)	750 (10.2)	1,727 (7.6)	2,145 (8.1)	3,640 (7.8)	232 (8.9)	2,065 (7.8)	1,807 (7.9)	< 0.0001
Ischemic heart diseases	3,052 (6.2)	–[a]	–[a]	294 (2.7)	772 (5.1)	1,109 (9.8)	847 (11.6)	1,695 (7.4)	1,357 (5.1)	2,896 (6.2)	156 (6.0)	1,746 (6.6)	1,306 (5.7)	< 0.0001
Cerebrovascular diseases	2,824 (5.7)	9 (0.7)	33 (1.0)	255 (2.3)	705 (4.6)	943 (8.3)	879 (12.0)	1,317 (5.8)	1,507 (5.7)	2,670 (5.7)	154 (5.9)	1,614 (6.1)	1,210 (5.3)	< 0.0001
Chronic renal disease	1,437 (2.9)	7 (0.6)	62 (1.9)	265 (2.4)	416 (2.7)	362 (3.2)	325 (4.4)	936 (4.1)	501 (1.9)	1,329 (2.9)	108 (4.1)	770 (2.9)	667 (2.9)	0.0066
Alcoholic liver disease	1,179 (2.4)	9 (0.7)	77 (2.4)	420 (3.9)	450 (2.9)	156 (1.4)	67 (0.9)	940 (4.1)	239 (0.9)	1,016 (2.2)	163 (6.2)	629 (2.4)	550 (2.4)	0.0214
Chronic hepatitis B	861 (1.7)	15 (1.2)	81 (2.5)	233 (2.1)	289 (1.9)	158 (1.4)	85 (1.2)	463 (2.0)	398 (1.5)	78 (1.7)	73 (2.8)	427 (1.6)	434 (1.4)	0.8114
Schizophrenia, schizotypal and delusional disorders	613 (1.2)	12 (1.0)	63 (1.9)	217 (2.0)	201 (1.3)	73 (0.6)	47 (0.6)	409 (1.8)	204 (0.8)	559 (1.2)	54 (2.1)	300 (1.1)	313 (1.4)	0.5995

Values are presented as number (%).

The mean number of comorbidities by disease code was counted if patients having at least one comorbidity using diagnostic KCD-7 disease code.

KCD, Korean version of the International Classification of Disease; CHC, chronic hepatitis C; DAA, direct-acting antiviral.

[a]As per Health Insurance Review & Assessment Service, counts/values ≤ 3 are masked.

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Supplementary Table 5. Prescribed medications by age, gender, demographic characteristics, and health conditions

	Total	Age group						Gender		Cirrhosis status		DAA exposure status		*p* value
		18–34 years	35–44 years	45–54 years	55–64 years	65–74 years	≥ 75 years	Male	Female	Without Cirrhosis	With Cirrhosis	Unexposed	Exposed	
Total hepatitis C infected patients	50,476	1,405 (2.8)	3,474 (6.9)	11,312 (22.4)	15,536 (30.80)	11,402 (22.6)	7,347 (14.6)	23,592 (46.7)	26,884 (53.3)	47,850 (94.8)	2,626 (5.2)	27,232 (54.0)	23,244 (46.0)	–[a]
Patient with ≥ 1 prescribed medication	49,846 (98.8)	1,315 (93.6)	3,360 (96.7)	11,092 (98.1)	15,380 (99.90)	11,363 (99.7)	7,336 (99.9)	23,236 (98.5)	26,610 (99.9)	47,231 (98.7)	2,615 (99.6)	26,856 (98.6)	22,990 (98.9)	–[a]
Mean number of medications	9.5	6.2	7.6	8.5	9.3	10.4	11.3	9.2	9.7	9.4	10.9	9.4	9.5	–[a]
Comedications														
Analgesics	45,669 (91.6)	1,123 (85.4)	2,940 (87.5)	9,878 (89.1)	14,053 (91.4)	10,689 (94.1)	6,986 (95.2)	20,900 (89.9)	24,769 (93.1)	43,270 (91.6)	2,399 (91.4)	24,613 (91.6)	21,056 (91.6)	< 0.0001
Gastrointestinal agents	42,347 (85.0)	955 (72.6)	2,641 (78.6)	9,018 (81.3)	13,111 (85.2)	10,042 (88.4)	6,580 (89.7)	19,140 (82.4)	23,207 (87.2)	40,031 (84.8)	2,316 (88.2)	22,866 (85.1)	19,481 (84.7)	< 0.0001
Antibacterials	40,013 (80.3)	1,032 (78.5)	2,623 (78.1)	8,574 (77.3)	12,236 (79.6)	9,421 (82.9)	6,127 (83.5)	18,075 (77.8)	21,938 (82.4)	37,851 (80.1)	2,162 (82.3)	21,591 (80.4)	18,422 (80.1)	< 0.0001
Antihistamines	36,644 (73.5)	873 (66.4)	2,352 (70.0)	7,615 (68.7)	11,163 (72.6)	8,863 (78.0)	5,778 (78.8)	16,219 (69.8)	20,425 (76.8)	34,649 (73.4)	1,995 (76.0)	19,715 (73.4)	16,929 (73.6)	< 0.0001
Anticoagulant, anti-platelet and fibrinolytic	30,987 (62.2)	699 (53.2)	1,925 (57.3)	6,512 (58.7)	9,510 (61.8)	7,532 (66.3)	4,809 (65.6)	13,946 (60.0)	17,041 (64.0)	29,395 (62.2)	1,592 (60.6)	16,812 (62.6)	14,175 (61.7)	< 0.0001
Steroids	29,152 (58.5)	651 (49.5)	1,743 (51.9)	6,027 (54.3)	9,038 (58.8)	7,138 (62.8)	4,555 (62.1)	12,586 (54.2)	16,566 (62.3)	27,605 (58.4)	1,547 (58.9)	15,704 (58.5)	13,448 (58.5)	< 0.0001
Antiarrhythmics	24,748 (49.6)	380 (28.9)	1,123 (33.4)	4,818 (43.4)	7,716 (50.2)	6,540 (57.6)	4,171 (56.9)	11,479 (49.4)	13,269 (49.9)	23,318 (49.4)	1,430 (54.5)	13,331 (49.6)	11,417 (49.7)	< 0.0001
Anxiolytics/hypnotics/ sedatives	21,737 (43.6)	265 (20.2)	1,136 (33.8)	4,414 (39.8)	6,763 (44.0)	5,376 (47.3)	3,783 (51.6)	9,525 (41.0)	12,212 (45.9)	20,369 (43.1)	1,368 (52.1)	11,762 (43.8)	9,975 (43.4)	< 0.0001
Herbals/supplements/ vitamins	21,475 (43.1)	266 (20.2)	1,050 (31.3)	4,306 (38.8)	6,419 (41.7)	5,370 (47.3)	4,064 (55.4)	10,220 (44.0)	11,255 (42.3)	19,896 (42.1)	1,579 (60.1)	11,588 (43.1)	9,887 (43.0)	< 0.0001
Hepatotonics	19,302 (38.7)	257 (19.5)	998 (29.7)	4,194 (37.8)	5,783 (37.6)	4,398 (38.7)	3,672 (50.1)	10,386 (44.7)	8,916 (33.5)	17,415 (36.9)	1,887 (71.9)	10,597 (39.5)	8,705 (37.9)	< 0.0001
Hypertension/heart failure agents	18,692 (37.5)	43 (3.3)	416 (12.4)	2,718 (24.5)	5,371 (34.9)	5,626 (49.5)	4,518 (61.6)	9,072 (39.0)	9,620 (36.2)	17,262 (36.5)	1,430 (54.5)	10,004 (37.3)	8,688 (37.3)	< 0.0001

Supplementary Table 5. Continued

	Total	Age group						Gender		Cirrhosis status		DAA exposure status		*p* value
		18–34 years	35–44 years	45–54 years	55–64 years	65–74 years	≥ 75 years	Male	Female	Without Cirrhosis	With Cirrhosis	Unexposed	Exposed	
Calcium channel blockers	14,586 (29.3)	35 (2.7)	311 (9.3)	1,989 (17.9)	4,160 (27.0)	4,446 (39.1)	3,645 (49.7)	7,125 (30.7)	7,461 (28.0)	13,652 (28.9)	934 (35.6)	7,812 (29.1)	6,774 (29.5)	< 0.0001
Lipid lowering agents	14,200 (28.5)	53 (4.0)	389 (11.6)	2,229 (20.1)	4,575 (29.7)	4,195 (36.9)	2,759 (37.6)	6,354 (27.3)	7,846 (29.5)	13,528 (28.6)	672 (25.6)	8,418 (31.3)	5,782 (25.2)	< 0.0001
Antidiabetics	9,496 (19.1)	26 (2.0)	238 (7.1)	1,686 (15.2)	2,865 (18.6)	2,744 (24.1)	1,937 (26.4)	5,409 (23.3)	4,087 (15.4)	8,698 (18.4)	798 (30.4)	4,911 (18.3)	4,585 (19.9)	0.0008
Antidepressants	9,412 (18.9)	122 (9.3)	474 (14.1)	1,913 (17.2)	2,777 (18.1)	2,275 (20.0)	1,851 (25.2)	4,044 (17.4)	5,368 (20.2)	8,823 (18.7)	589 (22.4)	5,074 (18.9)	4,338 (18.9)	< 0.0001
Beta blockers	8,576 (17.2)	64 (4.9)	315 (9.4)	1,311 (11.8)	2,404 (15.6)	2,431 (21.4)	2,051 (28.0)	4,124 (17.7)	4,452 (16.7)	7,838 (16.6)	738 (28.1)	4,618 (17.2)	3,958 (17.2)	< 0.0001
Bronchodilators	8,311 (16.7)	166 (12.6)	504 (15.0)	1,369 (12.3)	2,473 (16.1)	2,144 (18.9)	1,655 (22.6)	3,599 (15.5)	4,712 (17.7)	7,868 (16.7)	443 (16.9)	4,557 (17.0)	3,754 (16.3)	< 0.0001
Anesthetics and muscle relaxants	7,818 (15.7)	133 (10.1)	487 (14.5)	1,590 (14.3)	2,438 (15.9)	1,939 (17.1)	1,231 (16.8)	3,594 (15.5)	4,224 (15.9)	7,364 (15.6)	454 (17.3)	4,218 (15.7)	3,600 (15.7)	< 0.0001
Antifungals	7,671 (15.4)	263 (20.0)	743 (22.1)	1,891 (17.0)	2,230 (14.5)	1,601 (14.1)	943 (12.9)	2,787 (12.0)	4,884 (18.4)	7,325 (15.5)	346 (13.2)	4,194 (15.6)	3,477 (15.1)	< 0.0001
Anticonvulsants	7,386 (14.8)	63 (4.8)	311 (9.3)	1,472 (13.3)	2,140 (13.9)	1,921 (16.9)	1,479 (20.2)	3,473 (14.9)	3,91 (14.7)	6,91 1(14.6)	475 (18.1)	3,911 (14.6)	3,475 (15.1)	< 0.0001

Values are presented as number (%).
DAA, direct-acting antiviral.
[a]*p* value not provided.

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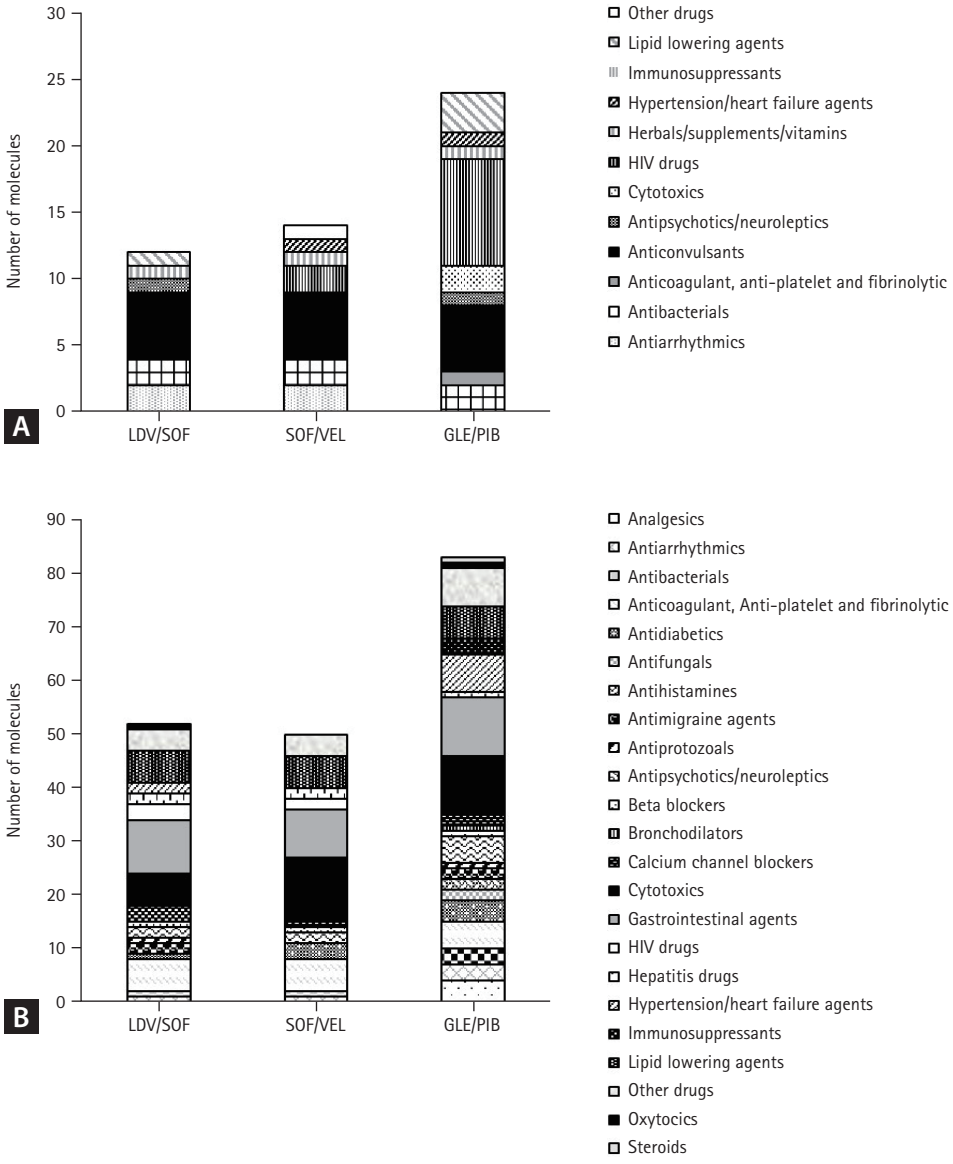
Supplementary Table 6. DDI with DAA regimen by age group in HCV diagnosed patients

Age group	Total	LDV/SOF	SOF/VEL	GLE/PIB	*p* value
Contraindication					
18–34 years	80	35 (0.1)	13 (0.0)	32 (0.1)	0.0048
35–44 years	431	186 (0.4)	42 (0.1)	203 (0.4)	< 0.0001
45–54 years	2,476	1,088 (2.2)	197 (0.4)	1,191 (2.4)	< 0.0001
55–64 years	4,981	2,142 (4.3)	346 (0.7)	2,493 (5.0)	< 0.0001
65–74 years	4,432	1,863 (3.7)	254 (0.5)	2,315 (4.6)	< 0.0001
≥ 75 years	3,006	1,198 (2.4)	266 (0.5)	1,542 (3.1)	< 0.0001
Potential					
18–34 years	2,737	880 (1.8)	877 (1.8)	980 (2.0)	0.0216
35–44 years	7,609	2,457 (4.9)	2,536 (5.1)	2,616 (5.2)	0.0724
45–54 years	25,628	8,224 (16.5)	8,878 (17.8)	8,526 (17.1)	< 0.0001
55–64 years	35,939	11,523 (23.1)	12,907 (25.9)	11,509 (23.1)	< 0.0001
65–74 years	26,876	8,624 (17.3)	9,909 (19.9)	8,343 (16.7)	< 0.0001
≥ 75 years	17,536	5,721 (11.5)	6,381 (12.8)	5,434 (10.9)	< 0.0001

Values are presented as number (%).
% of DDIs were rounded to 1 decimal place.
The proportion shows the number of patients taking DAA regimen with contraindication among HCV diagnosed patients.
DDI, drug-drug interaction; DAA, direct-acting antiviral; HCV, hepatitis C virus; LDV, ledipasvir; SOF, sofosbuvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir.



Supplementary Figure 1. Number of molecules with DDI by drug classes among HCV diagnosed patients in 2018. (A) Contraindicated DDIs with DAA regimens. (B) Potential DDIs with DAA regimens. Count indicated as the number of DDIs recorded between medications in the categories and the DAA regimens. DDI, drug-drug interaction; DAA, direct-acting antiviral; LDV, ledipasvir; SOF, sofosbuvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; HIV, human immunodeficiency virus.

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