Effect of direct-acting antivirals on disease burden of hepatitis C virus infection in South Korea in 2007–2021: a nationwide, multicentre, retrospective cohort study

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Summary

Background **It is unclear whether direct-acting antivirals (DAAs) treatment improves the disease burden in hepatitis C virus (HCV) infection. This study aimed to investigate the effect of DAA treatment on the reduction of disease burden in patients with HCV infection using individual participant data.**

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Methods This nationwide multicentre retrospective cohort study recruited patients with HCV infection from 29 tertiary institutions in South Korea. The data collection was done from medical records in each institution. The study included the untreated patients and the DAAs-treated patients and excluded those with a history of interferon-based treatments. Disease burden was the primary outcome, as represented by disability-adjusted life years (DALYs). Improvement in fibrosis after DAA treatment was assessed using APRI, FIB-4 index, and liver stiffness (LS) as assessed by transient elastography. Clinical outcomes were hepatocellular carcinoma (HCC), decompensation, and mortality.

Findings Between January 1, 2007, and February 17, 2022, data from 11,725 patients with HCV infection, 8464 (72%) of whom were treated with DAAs, were analysed. DAA treatment significantly improved APRI- (median 0.64 [interquartile range (IQR), 0.35–1.31]–0.33 [0.23–0.52], $p < 0.0001$), FIB-4- (median 2.42 [IQR, 1.48–4.40]–1.93 [1.31–2.97], $p < 0.0001$), and liver LS-based fibrosis (median 7.4 [IQR, 5.3–12.3]–6.2 [4.6–10.2] kPa, $p < 0.0001$). During the median follow-up period of 27.5 months (IQR, 10.6–52.4), 469 patients died (4.0%), 586 (5.0%) developed HCC, and 580 (4.9%) developed decompensation. The APRI-based DALY estimate was significantly lower in the DAA group than in the untreated group (median 4.55 vs. 5.14 years, $p < 0.0001$), as was the FIB-4-based DALY estimate (median 5.43 [IQR, 3.00–6.44] vs. 5.79 [3.85–8.07] years, $p < 0.0001$). The differences between the untreated and DAA groups were greatest in patients aged 40–60 years. In multivariable analyses, the DAA group had a significantly reduced risk of HCC, decompensation, and mortality compared with the untreated group (hazard ratios: 0.41 [95% confidence interval (CI), 0.34–0.48], 0.31 [95% CI, 0.30–0.38], and 0.22 [95% CI, 0.17–0.27], respectively; $p < 0.0001$).

Interpretation Our findings suggest that DAA treatment is associated with the improvement of liver-related outcomes and a reduction of liver fibrosis-based disease burden in patients with HCV infection. However, further studies using liver biopsy are needed to clarify the effect of DAA treatment on the reduction in the exact fibrosis-based disease burden beyond noninvasive tests.

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Keywords: Hepatitis C virus; Direct-acting antiviral; Disease burden; Liver fibrosis

Research in context

Evidence before this study

We searched PubMed for studies published until August 31, 2023, using search terms hepatitis C virus (HCV), direct-acting antivirals (DAAs), liver fibrosis, liver cirrhosis, hepatocellular carcinoma (HCC), decompensation, mortality, disease burden, disability-adjusted life years (DALYs), aspartate aminotransferase to platelet ratio (APRI) score, Fibrosis-4 (FIB-4) index, liver stiffness, and transient elastography with search terms found in abstract, title or MESH headings. We also searched references listed in the identified papers. Previous studies have indicated that the use of DAAs is associated with a lower risk of liver-related events such as HCC development, decompensation, and liver-related mortality in patients with HCV infection. However, little is known whether DAA treatment improves the disease burden, with respect to DALYs. In particular, there is lack of data on the effect of DAA treatment on disease burden considering liver fibrosis.

Added value of this study

The results of our nationwide, multicentre, retrospective cohort study suggest that DAA treatment reduces liver fibrosis-based disease burden, measured by DALYs, using individual participant data. DAA treatment in patients with HCV infection may also reduce liver-related events such as HCC development, hepatic decompensation, and liver-related mortality. Early detection of HCV infection and immediate DAA usage are crucial strategies for reducing both liver fibrosis-based disease burden and improving clinical outcomes.

Implications of all the available evidence

DAA treatment may be associated with the improvement of liver-related outcomes and the reduction of disease burden in patients with HCV infection. In this study, there is a limitation on the assessment of fibrotic burden. Liver fibrosis was assessed by noninvasive tests (APRI score, FIB-4 index, and transient elastography). Further studies using liver biopsies obtained pre- and post-DAA are needed to clarify the relationship between non-invasive fibrosis tests and liver histologic findings.

Introduction

The hepatitis C virus (HCV) is a major cause of chronic liver disease and can cause chronic hepatitis C (CHC), liver cirrhosis, hepatocellular carcinoma (HCC), decompensation, end-stage liver disease, and death. In 2019, an estimative revealed 58 million people worldwide living with CHC and 290,000 HCV-related deaths,[1] clearly indicating the high burden of HCV-related diseases.[1]

Recently, a paradigm shift from interferon-based to direct-acting antiviral (DAA) treatments for CHC occurred. Recent meta-analyses have shown that DAA therapy reduces the risk of HCC, decompensation, and mortality in patients with CHC.[2] Sustained virological response (SVR) to DAA treatment in cirrhotic patients with CHC improved portal hypertension and reduced the hepatic venous pressure gradient.[3] Resolution of ascites and hepatic encephalopathy, and an absence of variceal bleeding in decompensated cirrhosis, were evident in patients with CHC who achieved an SVR to DAA treatment.[4] SVR to DAA treatment decreased the risk of HCC in patients with CHC. The use of DAA for CHC reduced all-cause mortality and liver-related mortality in large population-based cohorts[5] and a meta-analysis.[2] In patients with CHC, recently developed DAAs have pan-genotypic efficacy, enabling the reversal of fibrosis in patients achieving SVR. Therefore, the improvement in or remainder of the fibrotic burden after DAA treatment, which determines the post-SVR long-term outcomes, has recently been of interest.[6]

The disability-adjusted life year (DALY) is a measure of overall disease burden, presented as the number of years lost due to ill health, disability, or early death, which can compare the effect of a disease on overall health and life expectancy at the population level in different countries.[7] In this study, we used individual participant data (IPD) to examine the fibrotic burden after DAA treatment and investigate whether this treatment improved the disease burden in South Korean patients with CHC. In addition, we investigated whether DAA treatment reduced the risk of liver-related events, such as HCC, decompensation, liver transplantation, and mortality.

Methods

Study design and participants

This nationwide, multicentre, retrospective cohort study recruited patients with CHC, either untreated or treated with DAA, from 29 tertiary academic institutes in South Korea between January 1, 2007, and February 17, 2022. The data collection was done from medical records in each institution. In this study, we did not include patients with a history of interferon-based therapy, because the study aim was to investigate the effect of DAA treatment on the disease burden of CHC. Because DAAs were introduced in South Korea in December 2014, patients in the "DAA group" were recruited between January 1, 2015, and February 17, 2022, whereas those in the "untreated group" were recruited between January 1, 2007, and February 17, 2022. Patients untreated during January 1, 2007, to December 31, 2014 who received DAA therapy from January 1, 2015, to February 17, 2022 were included in the "DAA group". The last follow-up date was December 31, 2022. Accordingly, there was no overlap between the "untreated group" and the "DAA group". The index date was the first appointment for patients in the "untreated group" and the date of the first DAA prescription for those in the "DAA group". Of the 12,417 patients recruited, 692 were excluded per the following exclusion criteria: 1) past HCV infection; 2) other causes of chronic liver disease; 3) history of HCC, decompensation, or liver transplantation; 4) co-infection with hepatitis B virus or human immunodeficiency virus; 5) insufficient clinical and laboratory data; and 6) insufficient follow-up of <3 months (Fig. 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Ethics

The study was carried out in accordance with the Helsinki II ethics regulations. All participants gave electronic informed consent prior to the experiment. This study was approved by the Institutional Review Board of each participating institute. The requirement for written informed consent was waived because of the retrospective nature of the study. Medical records were anonymized and de-identified before analysis.

Definitions

The "untreated group" was defined as patients who did not receive any antiviral treatment for CHC. The "DAA group" was defined as patients who were treated with DAAs with or without ribavirin; drug treatment regimens included daclatasvir + asunaprevir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir + dasabuvir, sofosbuvir, and sofosbuvir + daclatasvir. For the DAA group, SVR12 was defined as undetectable HCV RNA 12 weeks after the end of treatment.

Follow-up and surveillance

HCC surveillance was performed using ultrasonography and AFP testing every 3–6 months. If serum AFP was elevated, computed tomography or magnetic resonance imaging was done to rule out HCC depending on physician's decision. Liver cirrhosis was diagnosed based on ultrasonographic detection of small liver size, nodular liver surface, and coarse liver parenchyma. Significant alcohol consumption was defined as alcohol intake ≥210 g per week for male or ≥140 g per week for female.

Fibrosis assessment

Liver fibrosis was evaluated using noninvasive surrogate measures, including the aspartate aminotransferase to

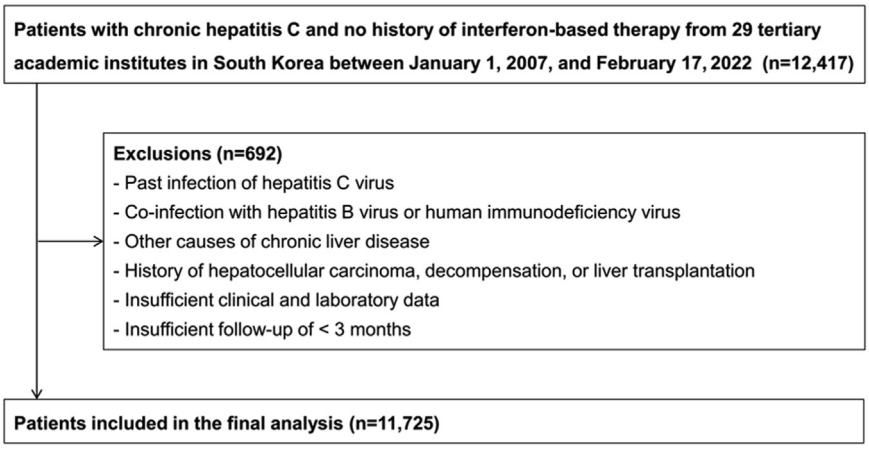


Fig. 1: **Flow diagram of study patients.**

platelet ratio index (APRI),[8] the Fibrosis-4 (FIB-4) index,[9] and liver stiffness (LS) as assessed by vibration-controlled transient elastography (TE). The fibrosis stage was determined as follows: APRI <0.7 indicated stage 0–1, 0.7–2.0 indicated stage 2–3, and ≥2.0 indicated stage 4[8]; FIB-4 index <1.45 indicated stage 0, 1.45–3.25 indicated stage 1–2, and >3.25 indicated stage 3–4[9]; and LS 6.7 kPa indicated stage 0–1, 6.8–8.5 kPa indicated stage 2, 8.6–14.4 kPa indicated stage 3, and ≥14.5 kPa indicated stage 4.[10]

Study outcomes

The primary outcome was disease burden, assessed using the DALY.[11] Of the two calculation strategies, incidence-based and prevalence-based, we selected the incidence-based approach owing to our IPD cohort (DALY_basic).[12] To compute the Years Lost due to Disability (YLD) and Years of Life Lost (YLL), the disability weights of disease, disease-onset time, disease duration, time of mortality, and expected time of mortality were determined according to the disability weights provided in the South Korea 2020 updated report[12] and the life expectancy data released by Statistics Korea in 2012.[13] Disability weights of CHC and CHC-related cirrhosis, and fibrotic burden assessed using the APRI, the FIB-4 index, and LS by TE were used for the calculations. Discounting and age weighting were also used to compute a second DALY calculation (DALY_weighted).[11] The detailed methods were described in Supplementary Materials and Supplementary Tables S1 and S2.

Additionally, we defined the survival outcomes of patients with HCC as decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome), liver transplantation, and mortality. The composite endpoint was defined as the development of any of these outcomes. We also analysed differences in the composite outcome according to fibrosis stage based on the APRI, FIB-4 index, and LS in TE.

Statistical analysis

The median value with interquartile range (IQR) was calculated for continuous variables except YLL, and frequencies with percentages were calculated for categorical variables. Details on YLL data presentation are provided in the Supplementary Materials. In this study, the variables included in the statistical analysis were defined as follows. The primary outcome was the disease burden in terms of DALYs. The secondary outcomes were clinical events such as decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome), liver transplantation, and mortality. The exposure (predictor) was antiviral treatment (use of DAAs). Potential confounders included age, sex, diabetes, hypertension, and alcohol intake. The effect modifier was the liver fibrosis stage. The Cox proportional hazards model was used to determine how DAA treatment affected time-to-event outcomes after adjusting for significant risk factors. In the multivariable analysis, the multiple imputation method was used to address missing values (Supplementary Table S3). In addition, we conducted a multivariable complete case analysis as a sensitivity analysis. To manage missing data, we used multiple imputation in the R package Amelia,[14] recognized for its effective handling of such scenarios. The detailed method using the R package Amelia was described in Supplementary Materials. The combination of estimated regression coefficients and standard errors was achieved using Rubin's rule,[15] employing the R package *mitools*. We present outcomes of gamma and Cox regressions based on the 10 imputation sets. We performed a competing risk analysis specifically for liver-related death outcomes, in which outcomes unrelated to the liver were regarded as the competing risk. Liver-related death was defined as death after one of HCC, liver transplantation, hepatic

resection, or decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome). We estimated cumulative incidence functions for the control and DAA groups and evaluated their equality across groups using Fine and Gray's proportional hazards model for the subdistributions.[16] The R package *cmprsk* was used to conduct the competing risk analysis. In addition, a propensity score matching method was also conducted to adjust for potential confounding factors with a greedy algorithm. The DALYs (DALY_basic and DALY_weighted) based on the APRI, the FIB-4 index, or LS are presented as median with IQR and compared between untreated and DAA groups using the Wilcoxon rank-sum test. We also compared the DALYs among three age groups (age <40, ≥40 and <60, and ≥60 years). Additionally, we fitted a gamma generalized linear model (GLM) with the log link function to the DALYs because they were continuous and non-negative. The detailed methods of statistical analyses were described in Supplementary Materials. All reported p-values were two-sided; a p-value <0.05 was considered significant. R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, http://cran.r-project.org/) was used for statistical analyses. The R packages MatchIt[17] and geese were used for matching analyses and generalized estimating equation model, respectively.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

Baseline characteristics

In total, 11,725 patients with CHC were recruited for this study. The baseline characteristics of the study population are presented in Table 1. The median age was 59.8 years (IQR, 51.1–69.2); 44.2% of patients (n = 5182) were male. The median APRI, FIB-4 index, and LS were 0.67 (IQR, 0.36–1.39), 2.49 (IQR, 1.49–4.57), and 7.5 (IQR, 5.3–12.5) kPa, respectively. The proportion of patients with ultrasonographic findings of cirrhosis and significant alcohol consumption was 22.5% (n = 2635) and 14.8% (n = 1482), respectively. The median HCV RNA level was 966,000 Iμ/mL (IQR, 134,338–3,280,000) and most patients had either HCV genotype 1 (53.0%, n = 5348) or 2 (45.0%, n = 4529).

Comparison between the untreated and DAA groups

Patients in the untreated group were older than those in the DAA group (median 60.6 [IQR, 50.0–70.0] vs. 59.5 [IQR, 51.4–68.6] years, p = 0.027) and more likely to be male (47.1% [n = 1536] vs. 43.1% [n = 3646], p < 0.0001). Diabetes and hypertension were more prevalent in the untreated group compared with the DAA group (21.0% [n = 684] vs. 17.2% [n = 1455], and 28.5% [n = 931] vs. 25.1% [n = 2128], respectively; both p < 0.0001). However, significant alcohol consumption was more prevalent in the DAA group compared with the untreated group (15.4% [n = 333] vs. 13.1% [n = 1149], p = 0.004). The median APRI (0.76 [IQR, 0.39–1.60] vs. 0.64 [IQR, 0.35–1.31], p < 0.0001), FIB-4 index (2.66 [IQR, 1.51–5.07] vs. 2.42 [IQR, 1.48–4.40], p < 0.0001), and LS (7.9 [IQR, 5.4–14.5] vs 7.4 [IQR, 5.3–12.3] kPa, p = 0.012) were higher in the untreated group than in the DAA group. The median follow-up periods in the untreated and DAA groups were 31.8 (IQR, 7.4–81.7) and 26.7 (IQR, 11.3–48.0) months, respectively. DAA regimens included daclatasvir/asunaprevir in 1564 (18.5%) patients, elbasvir/grazoprevir in 753 (8.9%) patients, glecaprevir/pibrentasvir in 2356 (27.8%) patients, ledipasvir/sofosbuvir in 1166 (13.8%) patients, ombitasvir/paritaprevir/ritonavir/dasabuvir in 278 (3.3%) patients, sofosbuvir in 2252 (26.6%) patients, and sofosbuvir/daclatasvir in 95 (1.1%) patients.

Liver fibrosis stage before and after DAA treatment

Liver fibrosis stage estimates before and after DAA treatment in the DAA group are summarized in Table 2. The use of DAAs in CHC improved liver fibrosis, as measured by the APRI, the FIB-4 index, and LS by TE. The proportion of patients with CHC in the DAA group who achieved SVR12 was 95.8% (n = 8105).

Comparison of disease burden between the untreated and DAA groups

Disease burden according to the fibrosis surrogate measures is summarized in Table 3. When disease burden was calculated according to the APRI, YLD was statistically similar between the two groups, whereas YLL_basic and YLL_weighted were significantly lower in the DAA group than in the untreated group (mean 0.24 ± standard deviation [SD] 2.41 vs. 1.73 ± 5.78 years, and 0.12 ± 1.24 vs. 0.85 ± 2.96 years, respectively; both p < 0.0001). When YLD and YLL were combined, DALY_basic and DALY_weighted were lower in the DAA group than in the untreated group (median 9.19 [IQR, 6.41–12.56] vs. 10.29 [IQR, 6.87–14.64] years and 4.55 [IQR, 3.00–6.44] vs. 5.14 [IQR, 3.18–7.71] years, respectively; both p < 0.0001). Similar findings were observed, when FIB-4 index was used. However, LS-based disease burden was statistically similar between the untreated and DAA groups (p > 0.050).

Independent risk factors for DALY

The use of DAAs was selected as an independent risk factor for the reduction in the APRI-, the FIB-4 index-, and LS-based DALY_basic (estimated coefficients: –0.15, 95% for ARPI, –0.10 for FIB-4 index, and –0.07 for LS;

Variables	Overall (n = 11,725)	Untreated (n = 3,261, 28%)	DAA (n = 8,464, 72%)	p-value
HCV genotype				
1	5348 (53.0)	1169 (51.7)	4179 (53.5)	
2	4529 (45.0)	1029 (45.6)	3500 (44.8)	
Others	197 (2.0)	61 (2.7)	136 (1.7)	
HCV RNA, Iμ/mL	966,000 (134,338–3,280,000)	615,000 (66,100–2,455,908)	1,117,044 (174,000–3,540,000)	<0.0001
Log (HCV RNA)	13.8 (11.8–15.0)	13.3 (11.1–14.7)	13.9 (12.1–15.1)	<0.0001
Age, years	59.8 (51.1–69.2)	60.6 (50.0–71.0)	59.5 (51.4–68.6)	0.027
Sex				
Male	5182 (44.2)	1536 (47.1)	3646 (43.1)	
Female	6543 (55.8)	1725 (52.9)	4818 (56.9)	<0.0001
BMI, kg/m^2	23.7 (21.5–26.0)	23.4 (21.2–25.7)	23.8 (21.6–26.0)	<0.0001
Diabetes mellitus	2139 (18.2)	684 (21.0)	1455 (17.2)	<0.0001
Hypertension	3059 (26.1)	931 (28.5)	2128 (25.1)	<0.0001
Significant alcohol consumption	1482 (14.8)	333 (13.1)	1149 (15.4)	0.004
Cirrhosis	2635 (22.5)	755 (23.2)	1880 (22.2)	0.28
LS in TE, kPa	7.5 (5.3–12.5)	7.9 (5.4–14.5)	7.4 (5.3–12.3)	0.012
CAP in TE, dB/m	222 (196–251)	218 (192–243)	223 (197–252)	0.011
APRI score	0.67 (0.36–1.39)	0.76 (0.39–1.60)	0.64 (0.35–1.31)	<0.0001
FIB-4 index	2.49 (1.49–4.57)	2.66 (1.51–5.07)	2.42 (1.48–4.40)	<0.0001
WBC count, $10^9/L$	5.4 (4.3–6.6)	5.5 (4.3–7.0)	5.3 (4.3–6.5)	<0.0001
Hemoglobin, g/dL	13.6 (12.5–14.7)	13.3 (12.1–14.5)	13.7 (12.7–14.7)	<0.0001
Platelet count, $10^9/L$	176 (129–223)	173 (122–223)	178 (132–223)	0.0060
AFP, ng/mL	4.4 (2.8–8.7)	4.6 (2.8–10.5)	4.4 (2.8–8.4)	0.0060
AST, IU/L	45 (28–76)	48 (30–83)	43 (28–73)	<0.0001
ALT, IU/L	38 (23–74)	42 (24–83)	37 (22–71)	<0.0001
Total bilirubin, mg/dL	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	<0.0001
Serum albumin, g/dL	4.2 (3.9–4.4)	4.1 (3.7–4.3)	4.2 (4.0–4.5)	<0.0001
Serum creatinine, g/dL	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.8 (0.6–0.9)	<0.0001
Prothrombin time, INR	1.03 (0.98–1.10)	1.05 (0.99–1.13)	1.02 (0.97–1.09)	<0.0001
Total cholesterol, mg/dL	160 (138–185)	155 (132–181)	162 (140–187)	<0.0001
Fibrosis stage by APRI score				<0.0001
Stage 0	5817 (51.4)	1470 (47.0)	4347 (53.1)	
Stage 2–3	3734 (33.0)	1070 (34.2)	2664 (32.6)	
Stage 4	1758 (15.5)	585 (18.7)	1173 (14.3)	
Fibrosis stage by FIB-4 index				
Stage 0	2707 (24.0)	738 (23.7)	1969 (24.1)	
Stage 1–2	4323 (38.3)	1069 (34.3)	3254 (39.8)	
Stage 3–4	4253 (37.7)	1307 (42.0)	2946 (36.1)	<0.0001
Fibrosis stage by LS				
Stage 0–1	2378 (42.6)	266 (40.5)	2112 (42.8)	
Stage 2	816 (14.6)	87 (13.3)	729 (14.8)	
Stage 3	1229 (22.0)	136 (20.7)	1093 (22.2)	
Stage 4	1163 (20.8)	167 (25.5)	996 (20.2)	0.024

Variables are expressed as n (%) or median (interquartile range). Abbreviations: DAA, direct acting antiviral; HCV, hepatitis C virus; BMI, body mass index; LS, liver stiffness; TE, transient elastography; kPa, kilopascal; CAP, controlled attenuation parameter; ARPI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; WBC, white blood cell; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

Table 1: **Baseline characteristics.**

$p < 0.0001$, $p < 0.0001$, and $p = 0.0026$, respectively) and DALY_weighted (estimated coefficients: –0.16 for ARPI, –0.10 for FIB-4 index, and –0.08 for LS; $p < 0.0001$, $p < 0.0001$, and $p = 0.0014$, respectively) scores in multiple imputation method (Table 4). The same tendency was shown in complete case analysis (Supplementary Table S4).

A subgroup analysis was performed based on the presence of FIB-4 index- and LS-determined advanced liver fibrosis & cirrhosis (Supplementary Tables S5 and S6). In patients with advanced fibrosis as determined by the FIB-4 index, DALY_basic and DALY_weighted scores were significantly lower in the DAA group than in the untreated group (median 12.19

Fibrosis stage	Before DAA treatment	After DAA treatment	p-value
APRI score	0.64 (0.35–1.31)	0.33 (0.23–0.52)	<0.0001
Fibrosis stage by APRI score			
Stage 0–1	3576 (52.7)	5751 (84.8)	<0.0001
Stage 2–3	2206 (32.5)	909 (13.4)	
Stage 4	1002 (14.8)	124 (1.8)	
FIB-4 index	2.42 (1.48–4.40)	1.93 (1.31–2.97)	<0.0001
Fibrosis stage by FIB-4 index			
Stage 0	1581 (23.4)	2050 (30.4)	<0.0001
Stage 1–2	2692 (39.9)	3254 (48.2)	
Stage 3–4	2474 (36.7)	1443 (21.4)	
LS (kPa)	7.4 (5.3–12.3)	6.2 (4.6–10.2)	<0.0001
Fibrosis stage by LS			
Stage 0–1	509 (37.0)	774 (56.3)	<0.0001
Stage 2	206 (15.0)	162 (11.8)	
Stage 3	318 (23.1)	251 (18.3)	
Stage 4	341 (24.8)	187 (13.6)	

Variables are expressed as median (interquartile range) or n (%). The fibrosis stage was determined as follows: APRI <0.7 indicated stage 0–1, 0.7–2.0 indicated stage 2–3, and ≥2.0 indicated stage 4; FIB-4 index <1.45 indicated stage 0, 1.45–3.25 indicated stage 1–2, and >3.25 indicated stage 3–4; and LS < 6.7 kPa indicated stage 0–1, 6.8–8.5 kPa indicated stage 2, 8.6–14.4 kPa indicated stage 3, and ≥14.5 kPa indicated stage 4. Abbreviations: DAA, direct acting antiviral; LS, liver stiffness; ARPI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4.

Table 2: **Liver fibrosis stage before and after DAA treatment.**

[IQR, 8.23–15.95] vs. 12.61 [IQR, 8.45–17.65] years, p = 0.001 and 5.74 [IQR, 3.57–7.95] vs. 5.87 [IQR, 3.72–8.89] years, p = 0.003, respectively). However, no significant difference in DALYs based on LS between the untreated and DAA groups was observed (both p = 0.16).

Disease burden variables	Overall	Untreated	DAA	p-value
APRI score-based disease burden				
YLD_basic	9.08 (6.01–12.68)	9.09 (5.41–13.33)	9.08 (6.24–12.33)	0.16
YLD_weighted	4.48 (2.79–6.53)	4.48 (2.48–6.92)	4.48 (2.90–6.35)	0.39
YLL_basic	0 (0–0) 0.71 ± 3.87	0 (0–0) 1.73 ± 5.78	0 (0–0) 0.24 ± 2.41	<0.0001
YLL_weighted	0 (0–0) 0.35 ± 1.98	0 (0–0) 0.85 ± 2.96	0 (0–0) 0.12 ± 1.24	<0.0001
DALY_basic	9.49 (6.52–13.26)	10.29 (6.87–14.64)	9.19 (6.41–12.56)	<0.0001
DALY_weighted	4.71 (3.04–6.78)	5.14 (3.18–7.71)	4.55 (3.00–6.44)	<0.0001
FIB-4 index-based disease burden				
YLD_basic	10.76 (7.74–14.16)	10.57 (7.01–14.30)	10.84 (8.01–14.10)	<0.0001
YLD_weighted	5.33 (3.58–7.28)	5.21 (3.19–7.45)	5.36 (3.75–7.23)	0.001
YLL_basic	0 (0–0) 0.70 ± 3.84	0 (0–0) 1.70 ± 5.72	0 (0–0) 0.24 ± 2.41	<0.0001
YLL_weighted	0 (0–0) 0.35 ± 1.97	0 (0–0) 0.84 ± 2.92	0 (0–0) 0.12 ± 1.25	<0.0001
DALY_basic	11.15 (8.25–14.57)	11.56 (8.41–15.42)	10.96 (8.19–14.22)	<0.0001
DALY_weighted	5.52 (3.84–7.48)	5.79 (3.85–8.07)	5.43 (3.84–7.29)	<0.0001
LS-based disease burden				
YLD_basic	10.01 (7.15–13.72)	9.94 (6.71–13.62)	10.06 (7.35–13.75)	0.17
YLD_weighted	4.99 (3.33–7.05)	4.92 (3.11–7.02)	5.02 (3.41–7.05)	0.33
YLL_basic	0 (0–0) 5.36 ± 2.91	0 (0–0) 1.04 ± 4.62	0 (0–0) 0.22 ± 2.27	<0.0001
YLL_weighted	0 (0–0) 0.24 ± 1.63	0 (0–0) 0.51 ± 2.36	0 (0–0) 0.10 ± 1.11	<0.0001
DALY_basic	10.27 (7.44–14.08)	10.56 (7.41–14.39)	10.13 (7.46–13.90)	0.19
DALY_weighted	5.09 (3.46–7.27)	5.25 (3.45–7.52)	5.04 (3.46–7.12)	0.14

Variables are expressed as median (interquartile range), and YLL is also expressed as mean ± SD. YLD, YLL, and DALY were calculated without or with age-weighting and discounting ('basic' or 'weighted'). Abbreviations: DAA, direct acting antiviral; LS, liver stiffness; ARPI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; YLD, Years Lost due to Disability; YLL, Years of Life Lost; DALY, disability-adjusted life years.

Table 3: **Comparison of disease burden between untreated and DAA group.**

Variables	APRI score-based DALY_basic		APRI score-based DALY_weighted		FIB-4 index-based DALY_basic		FIB-4 index-based DALY_weighted		LS-based DALY_basic		LS-based DALY_weighted	
	Estimated coefficient (95% CI)	p-value	Estimated coefficient (95% CI)	p-value	Estimated coefficient (95% CI)	p-value	Estimated coefficient (95% CI)	p-value	Estimated coefficient (95% CI)	p-value	Estimated coefficient (95% CI)	p-value
Male	−0.10 (−0.12, −0.07)	<0.0001			−0.13 (−0.15, −0.11)	<0.0001	−0.01 (−0.04, −0.01)	0.20	−0.10 (−0.14, −0.06)	<0.0001		
Significant alcohol consumption	0.17 (0.13, 0.20)	<0.0001			0.14 (0.11, 0.17)	<0.0001	0.17 (0.13, 0.20)	<0.0001	0.14 (0.07, 0.20)	<0.0001	0.17 (0.10, 0.24)	<0.0001
Cirrhosis	0.04 (0.01, 0.06)	0.004	0.20 (0.16, 0.24)	<0.0001	0.04 (0.02, 0.06)	0.0001	0.02 (−0.01, 0.04)	0.095	0.12 (0.07, 0.17)	<0.0001	0.10 (0.05, 0.16)	0.0001
Body mass index									0.01 (0.01, 0.02)	0.0004	0.02 (0.01, 0.02)	0.0002
Use of DAAs	−0.15 (−0.17, −0.13)	<0.0001	−0.16 (−0.18, −0.13)	<0.0001	−0.10 (−0.12, −0.08)	<0.0001	−0.10 (−0.12, −0.08)	<0.0001	−0.07 (−0.11, −0.02)	0.0026	−0.08 (−0.13, −0.03)	0.0014

In multivariable analysis, the multiple imputation method was used to treat missing values. Adjustment variables were male, significant alcohol consumption, and cirrhosis in 'APRI score-based DALY_basic'; significant alcohol consumption, and cirrhosis in 'APRI score-based DALY_weighted'; male, significant alcohol consumption, and cirrhosis in 'FIB-4 index-based DALY_basic'; male, significant alcohol consumption, and cirrhosis in 'FIB-4 index-based DALY_weighted'; male, significant alcohol consumption, cirrhosis, and body mass index in 'LS-based DALY_basic'; and significant alcohol consumption, cirrhosis, and body mass index in 'LS-based DALY_weighted'. DALY was calculated without or with age-weighting and discounting ('basic' or 'weighted'). Abbreviations: DALY, disability-adjusted life years; HCV, hepatitis C virus; BMI, body mass index; ARPI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; LS, liver stiffness; DAA, direct acting antiviral; CI, confidence interval.

Table 4: **Multivariable generalized linear model with a gamma distribution to identify the independent risk factors for DALY.**

A subgroup analysis was also performed according to age group (<40, 40–60, and ≥60 years). In the <40 years of age subgroup (Supplementary Table S7), the DALY was not different between the untreated and DAA groups (both $p > 0.05$). In contrast, in the 40–60 years of age subgroup (Supplementary Table S8), the APRI- and FIB-4 index-based DALY_basic scores were lower in the DAA group compared with the untreated group (median 11.14 [IQR, 9.16–14.12] vs. 12.65 [IQR, 9.93–17.08] years and 13.21 [IQR, 10.59–16.09] vs. 14.02 [IQR, 11.05–18.13] years, respectively; both $p < 0.0001$). Similar findings were obtained using DALY_weighted scores (median 5.84 [IQR, 4.71–7.42] vs. 6.60 [IQR, 5.26–9.10] years and 6.77 [IQR, 5.57–8.26] vs. 7.22 [IQR, 5.87–9.51] years, respectively; both $p < 0.0001$). In the ≥60 years of age subgroup (Supplementary Table S9), the APRI- and FIB-4 index-based DALY_basic scores were lower in the DAA group compared with the untreated group (median 6.46 [IQR, 4.80–8.79] vs. 7.14 [IQR, 5.13–10.39] years and 8.61 [IQR, 6.58–11.05] vs. 9.02 [IQR, 6.74–11.80] years, respectively; both $p < 0.0001$). Similar findings were obtained using the APRI- and FIB-4 index-based DALY_weighted scores (median 3.03 [IQR, 2.14–4.08] vs. 3.27 [IQR, 2.22–4.84] years, $p < 0.0001$, and 3.94 [IQR, 2.90–5.13] vs. 4.07 [IQR, 2.93–5.47] years, $p = 0.004$, respectively). The differences were greater in the 40–60 years of age subgroup than in the ≥60 years of age subgroup. LS-based DALYs did not differ between the untreated and DAA groups in either the 40–60 or ≥60 years of age subgroups (all $p > 0.050$).

Liver-related events

A total of 586 (5.0%), 18 (0.2%), 42 (0.4%), 580 (4.9%), and 469 (4.0%) patients experienced HCC, liver transplantation, hepatic resection, decompensation, and mortality, respectively (Table 5). The composite outcome was observed in 1216 patients (10.4%). The proportion of patients who experienced liver-related events, except for liver transplantation, during follow-up, was significantly lower in the DAA group than in the untreated group (2.9% [n = 243] vs. 10.5% [n = 343] for HCC, 0.3% [n = 22] vs. 0.6% [n = 20] for hepatic resection, 2.5% [n = 208] vs. 11.4% [n = 372] for decompensation, 1.4% [n = 116] vs. 10.8% [n = 353] for mortality, and 5.7% [n = 484] vs. 22.4% [n = 732] for the composite outcome).

The differences in the cumulative incidences of liver-related events according to DAA use in patients with CHC are shown in Fig. 2. The cumulative incidence of HCC was significantly lower in the DAA group compared with that in the untreated group (2.07% vs. 6.55% at 2 years, 4.44% vs. 9.99% at 4 years, 7.14% vs. 13.09% at 6 years, and 9.57% vs. 16.59% at 8 years; $p < 0.0001$ by log-rank test; Fig. 2A). Analysis of the cumulative incidence of decompensation (2.18% vs. 7.35% at 2 years, 3.60% vs. 10.86% at 4 years, 4.98% vs.

Outcomes	Overall	Untreated (n = 3261)	DAA (n = 8464)	p-value
HCC	586 (5.0)	343 (10.5)	243 (2.9)	<0.0001
Liver transplantation	18 (0.2)	8 (0.2)	10 (0.1)	0.12
Hepatic resection	42 (0.4)	20 (0.6)	22 (0.3)	0.0090
Decompensation	580 (4.9)	372 (11.4)	208 (2.5)	<0.0001
Mortality	469 (4.0)	353 (10.8)	116 (1.4)	<0.0001
Total (composite outcome)	1216 (10.4)	732 (22.4)	484 (5.7)	<0.0001

Variables are expressed as n (%). "Decompensation" was defined as one of the following manifestations: ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. The composite outcome was determined by the development of HCC or decompensation, the receipt of liver transplantation or hepatic resection, or all-cause mortality. Abbreviations: DAA, direct acting antiviral; HCC, hepatocellular carcinoma.

Table 5: **Liver-related events.**

14.89% at 6 years, and 4.98% vs. 18.64% at 8 years; p < 0.0001 by log-rank test; Fig. 2B) and the cumulative incidence of mortality (0.85% vs. 15.26% at 2 years, 2.29% vs. 22.02% at 4 years, 3.67% vs. 27.93% at 6 years, and 10.87% vs. 32.99% at 8 years; p < 0.0001 by log-rank test; Fig. 2C) yielded similar results. In addition, the

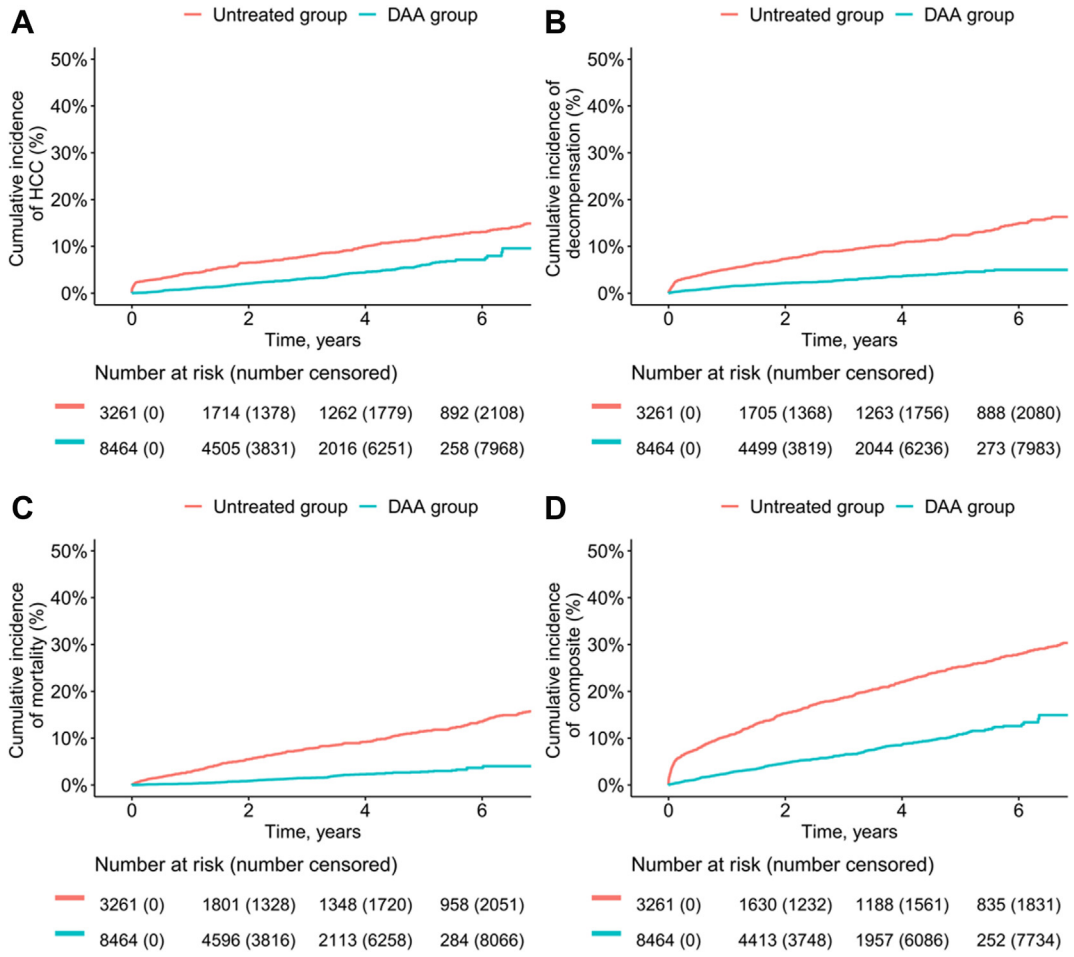


Fig. 2: Liver-related events according to the use of DAAs in patients with chronic hepatitis C: HCC development (A), decompensation development (B), mortality (C), and the composite outcome (D). "Decompensation" was defined as one of the following manifestations: ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. The composite outcome was determined by the development of HCC or decompensation, the receipt of liver transplantation or hepatic resection, or all-cause mortality. *Abbreviations*: DAA, direct-acting antiviral; HCC, hepatocellular carcinoma.

cumulative incidence of the composite outcome was significantly lower in the DAA group than that in the untreated group (4.70% vs. 15.26% at 2 years, 8.58% vs. 22.02% at 4 years, 12.59% vs. 27.93% at 6 years, and 21.01% vs. 32.99% at 8 years; $p < 0.0001$ by log-rank test; Fig. 2D). Differences in liver-related events according to fibrosis stage in the "untreated group" and "DAA group" are shown in Supplementary Figs. S1 and S2. In both groups, the risk of liver-related events increased with increasing fibrosis stage (APRI, FIB-4, and LS).

Risk factors for liver-related events

The independent predictors of liver-related events are summarized in Table 6. Multivariable analysis with multiple imputation method showed that male sex (hazard ratio [HR] = 2.14, 95% confidence interval [CI] 1.80–2.55), older age (HR = 1.04, 95% CI 1.03–1.05), diabetes mellitus (HR = 1.33, 95% CI 1.12–1.58), significant alcohol consumption (HR = 1.54, 95% CI 1.22–1.95), and cirrhosis (HR = 4.53, 95% CI 3.82–5.37) were independently associated with an increased risk of HCC development, whereas DAA use was independently associated with a decreased risk (HR = 0.41, 95% CI 0.34–0.48) (all $p < 0.0001$). Similarly, the use of DAAs was independently associated with a decreased risk of decompensation (HR = 0.31, 95% CI 0.26–0.37), mortality (HR = 0.22, 95% CI 0.17–0.27), and the composite outcome (HR = 0.34, 95% CI 0.30–0.38) (all $p < 0.0001$). The same tendency was shown in complete case analysis (Supplementary Table S10).

The number of liver-related deaths in the "untreated group" and the "DAA group" was 211 and 45, respectively, and that of liver-unrelated deaths in the "untreated group" and the "DAA group" was 142 and 71, respectively. The competing risk analysis showed that DAA treatment reduced the risk of liver-related deaths (Supplementary Fig. S3 and Supplementary Table S11). The same tendency was shown in complete case analysis (Supplementary Table S12).

Effect of DAA treatment on DALY and clinical outcomes in the matched set

Propensity score matching was performed to balance the clinical and laboratory characteristics between the groups (Supplementary Fig. S4). After matching, which yielded 896 pairs, no significant differences were observed between the groups (Supplementary Table S13, Supplementary Figs. S5 and S6). In this matched set, DAA treatment was independently associated with the reduction in the APRI- and FIB-4 index-based DALYs (Supplementary Table S14). In addition, DAA use was independently associated with decreased risks of HCC (HR = 0.51, 95% CI 0.34–0.75, $p = 0.0008$), decompensation (HR = 0.35, 95% CI 0.24–0.51, $p < 0.0001$), mortality (HR = 0.41, 95% CI 0.26–0.64, $p = 0.0001$), and the composite outcome (HR = 0.40, 95% CI 0.31–0.52, $p < 0.0001$) (Supplementary Table S15).

Discussion

This study showed that the fibrotic burden was improved after DAA treatment and that DAA treatment was independently associated with a decreased risk of HCC, decompensation, mortality, and composite outcome. In addition, we found that the disease burden was lower in patients treated with DAAs than in untreated patients. This improvement in disease burden was maintained regardless of fibrosis and was most prominent in patients aged 40–60 years.

Our study has several strengths and clinical implications. First, this was a Korean nationwide cohort study with a large sample size (n = 11,725 in total; n = 3261 in the untreated group and n = 8464 in the DAA group)

Variables	HCC		Decompensation		Mortality		Composite outcome	
	Multivariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Male	2.14 (1.80, 2.55)	<0.0001	1.39 (1.18, 1.63)	0.0001	1.43 (1.19, 1.71)	0.0001	1.61 (1.44, 1.80)	<0.0001
Age	1.04 (1.03, 1.05)	<0.0001	1.01 (1.01, 1.02)	0.0001				
Diabetes mellitus	1.33 (1.12, 1.58)	0.0014	1.56 (1.31, 1.87)	<0.0001			1.26 (1.10, 1.43)	0.0005
Hypertension			1.59 (1.33, 1.90)	<0.0001	1.74 (1.44–2.09)	<0.0001	1.61 (1.43, 1.82)	<0.0001
Significant alcohol consumption	1.54 (1.22, 1.95)	0.0003						
Cirrhosis	4.53 (3.82, 5.37)	<0.0001	3.09 (2.61, 3.65)	<0.0001	2.36 (1.96–2.84)	<0.0001	3.61 (3.22, 4.05)	<0.0001
Use of DAAs	0.41 (0.34, 0.48)	<0.0001	0.31 (0.26, 0.37)	<0.0001	0.22 (0.17–0.27)	<0.0001	0.34 (0.30, 0.38)	<0.0001

In multivariable analysis, the multiple imputation method was used to treat missing values. Adjustment variables were male, age, diabetes mellitus, significant alcohol consumption, and cirrhosis in 'HCC'; male, age, diabetes mellitus, hypertension, and cirrhosis in 'Decompensation'; male, hypertension, and cirrhosis in 'Mortality'; and male, diabetes mellitus, hypertension, and cirrhosis in 'Composite outcome'. "Decompensation" was defined as one of the following manifestations: ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. The composite outcome was determined by the development of HCC or decompensation, the receipt of liver transplantation or hepatic resection, or all-cause mortality. Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; DAA, direct acting antiviral.

Table 6: **Risk factors for liver-related outcomes.**

and a median follow-up period of 27.5 (IQR 10.6–52.4) months. In addition, our cohort was established based on IPD with serial laboratory and outcome data, including liver-related events. These factors enabled us to identify the improvement in fibrosis after DAA treatment, to investigate whether DAA treatment improves disease burden and clinical outcomes, and to explore the age group in which DAA treatment is most effective. Similarly, a French cohort study also demonstrated that DAA treatment improved all-cause mortality and reduced the development of HCC in patients with CHC.[18] However, that study did not show an improvement in decompensation by the use of DAA treatment while the findings of our study revealed the beneficial effect of DAA treatment on decompensation. We suppose that this finding might be caused by the high rate of SVR12 (95.8%) in the present study.

Second, liver fibrosis is a key factor that affects disease severity and prognosis in patients with chronic liver disease. In this study, the risk of liver-related events increased with increasing fibrosis stage in both groups. It is well known that clearing HCV infection can reduce the fibrotic burden and improve long-term outcomes in patients with CHC.[19] Based on this information, we incorporated the change in fibrotic burden after DAA treatment into the DALY analysis using noninvasive fibrosis surrogate measures. Indeed, an improvement in fibrotic burden was observed through noninvasive surrogate measures of fibrosis, leading to an improvement in disease burden in our current study.

Third, the disease burden improved following DAA treatment. Previous studies evaluated the effect of DAA treatment on disease burden at the hospital and population levels. A program for HCV screening and DAA treatment prevented 1.04 DALYs per diagnosed patient in a primary care setting in Pakistan.[20] DAA treatment also reduced the DALYs in population-based studies in Egypt, Pakistan, India, and China.[21–24] From 2010 to 2019, global DALYs for patients with acute HCV infection, HCV-related cirrhosis, HCV-related HCC, and liver-related mortality decreased significantly.[25] However, there were regional disparities in this data.[25] In East Asia, no significant reductions in the DALYs for HCV-related cirrhosis, HCV-related HCC, or liver-related mortality were observed. However, in this study, the use of DAAs reduced the DALYs of patients with CHC in South Korea. This discrepancy in the DALY trend of HCV infection might be caused by differences in study population (population-based cohort vs. hospital-based cohort). A population-based study in South Korea showed that among HCV-infected patients, the linkage-to-care rate was 65.5% and the treatment rate was 56.8%, which were below the targets of 90% and 80%, respectively.[26] The cohort in this study had easy access to medical care.

Fourth, the aim of this study was to investigate whether DAA treatment reduces disease burden, calculated based on DALYs, in patients with CHC. In terms of DALYs, the use of DAA is less beneficial in patients aged >70 years with multiple comorbidities and shorter life expectancies.[27] The data from the 2010–2019 Global Burden of Diseases Study showed that DALYs related to cirrhosis, HCC, and liver-related mortality were higher in patients with CHC aged 50–69 years compared to those aged ≥70 years.[25] These results might help establish a nationwide strategy for screening anti-HCV positivity in South Korea, where a national health screening program has not yet been set up.

Despite the clinical implications of our study, several issues remain unresolved. First, the fibrotic burden was mainly assessed using blood biomarkers to calculate the APRI and the FIB-4 index. There were correlations between the fibrosis stage and the median LS in TE, APRI score, and FIB-4 index. In addition, the proportions of fibrosis stage 4 by APRI score and LS were 15.5%, and 20.8%, respectively. However, the proportion of fibrosis stage 3–4 by FIB-4 index was higher, at 37.7%, but this was probably a result of the summing of two stages (fibrosis stages 3 and 4). Because of the lack of histological information, we cannot explain the discrepancies in the proportions of cirrhosis and advanced fibrosis according to noninvasive surrogate markers. TE information was available for only approximately 50% of the study population. Because the study population was enrolled from 2007, TE was not available at all institutions. Moreover, a small proportion of the DAA group (18%) underwent TE at both baseline and 6 months after treatment as a result of the retrospective study design. We investigated whether DAA treatment for CHC reduces the disease burden (DALYs) based on the fibrotic burden. This study tried to show that DAA can potentially reduce disease burden based on fibrosis assessment using varying noninvasive surrogates because liver biopsy, the gold standard method to measure liver fibrosis, has invasiveness and a limitation on repeatability. Indeed, FIB-4 and APRI have been used as screening tools to detect significant or advanced fibrosis in primary medical settings, because TE to measure LS is not widely available due to its high cost in primary medical settings. Therefore, we planned to include LS by TE as well as APRI and FIB-4, although a number of patients did not undergo TE. To address this issue, we conducted multivariable analyses using the multiple imputation method and including missing values. In addition, we performed a multivariable complete case analysis as a sensitivity analysis. The multiple imputation method and complete case analysis yielded similar results. In addition, we compared APRI score-based DALYs and FIB-4 index-based DALYs according to missing values of LS in TE to check the representativeness of patients without missing values (Supplementary Table S16). There was no significant difference in FIB-4 index-based DALYs according to missing values of LS by TE. Although there was a

significant difference in APRI score-based DALYs between the two groups, the difference in the absolute DALY values was small (median 9.65 vs. 9.30 years [APRI score-based DALY_basic], and median 4.80 vs. 4.63 years [APRI score-based DALY_weighted]). Therefore, we assumed that there was a negligible impact of DAA treatment on DALYs based on the APRI score, FIB-4 index, and LS in TE, although a significant difference in LS-based DALYs could not be determined because of the missing values for LS. Second, the decision to treat or observe might have been biased because of the retrospective nature of the study, although we showed that the improved disease burden in the DAA group was maintained even after appropriate adjustment. Third, after the introduction of DAAs, most patients who were diagnosed with CHC infection received DAA treatment because of the low risk of complications and short treatment duration; untreated patients were recruited mostly from the pre-DAA period, which made the follow-up durations between the untreated and DAA groups different. In the present study, we were unable to factor in the untreated state prior to starting DAA treatment because of the complexity of applying the mathematical formula for YLD in the same patients while considering the duration of no treatment in the DAA group. Our goal was to investigate whether DAA treatment can reduce the disease burden, as measured by DALYs, by comparing untreated and treated groups rather than comparing the status before and after DAA treatment within the treated group. Therefore, we analysed data from the time of DAA treatment initiation in the DAA group and from the time of enrollment in the untreated group. For a similar reason, we excluded patients who were treated with interferon-based treatments, because it can potentially cause additional bias in calculating DALYs according to varying treatment-related situations such as non-response to interferon-based treatment, intolerance to interferon-based treatment, or re-infection after SVR by interferon-based treatment. Therefore, we decided to exclude patients with a previous history of interferon-based treatments because the study aimed to investigate the pure effect of DAA treatment on the improvement of the disease burden. Fourth, we could not use the National Death Registry, mainly because of the Personal Information Protection Act.[28] Therefore, mortality was checked in the hospital. We could not check clinical events, including death, if a patient was transferred to another hospital. It was therefore difficult to obtain completely accurate all-cause mortality data in this study. Fifth, although the fibrotic burden, as determined by noninvasive tests, improved after DAA treatment, evaluation of fibrosis based on the APRI score, FIB-4 index, and LS in the post-SVR state is controversial. Noninvasive scores and LSM by TE, among other elastographic methods, are not accurate for detecting fibrosis regression after SVR in patients with HCV infection because improvements in noninvasive tests typically reflect the expected reduction of necro-inflammation but not that of fibrosis.[29] However, LS post-SVR after DAA treatment predicts HCC development and can be used to stratify cirrhotic patients with CHC according to the risk of HCC.[30] Further studies using liver biopsies obtained pre- and post-DAA are needed to clarify the relationship between non-invasive fibrosis tests and liver histologic finding. Sixth, the ultrasound-based diagnosis of liver cirrhosis might have been inaccurate in our study. However, because the present study was retrospective in nature and had a large sample size, more accurate tools such as liver biopsy or magnetic resonance elastography were not feasible. Lastly, despite statistical significance, the absolute difference in DALYs between the two groups was small. The first five decompensations were checked to calculate the DALY, which might have attenuated the different risks of decompensation between the DAA and untreated groups. In addition, we focused only on the change in fibrotic burden and not on other liver-related variables such as serum albumin and platelet counts. If all liver-related factors had been incorporated into the DALY analysis, the difference between the two groups might have been more apparent.

In conclusion, DAA treatment reduced the disease burden and improved clinical outcomes in patients with CHC in South Korea.

Contributors

SUK and SH designed the study. WS, SYP, THL, YEC, IHK, BL, KTY, JYJ, YRL, SJY, WC, SGK, DWJ, JJ, JHK, ESJ, HYK, SBC, BKJ, JGP, JL, YSS, JIL, DSS, MYK, HJY, DHS, SHA, YSK, HJ, WK, and SUK collected the data. SH performed statistical analysis. WS and SUK verified the underlying data of modeling analysis. SUK and WK critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript. The corresponding author had full access to all of the study data and took final responsibility for the decision to submit for publication.

Data sharing statement

De-identified data supporting this study may be shared based on reasonable written requests to the corresponding author (Seung Up Kim). Access to de-Articles identified data will require a Data Access Agreement and IRB clearance, which will be considered by the institutions who provided the data for this research.

Declaration of interests

All authors declare no financial or non-financial competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102671.

References

1 World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. In: *Accountability for the global health sector strategies 2016-2021: actions for impact*; 2021. https://apps.who.int/iris/rest/bitstreams/1348210/retrieve.

2 Sahakyan Y, Lee-Kim V, Bremner KE, Bielecki JM, Krahn MD. Impact of direct-acting antiviral regimens on mortality and

morbidity outcomes in patients with chronic hepatitis c: systematic review and meta-analysis. *J Viral Hepat*. 2021;28(5):739–754.
3 Lens S, Alvarado-Tapias E, Marino Z, et al. Effects of all-oral antiviral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. *Gastroenterology*. 2017;153(5):1273–12783.e1.
4 Romano J, Sims OT, Richman J, et al. Resolution of ascites and hepatic encephalopathy and absence of variceal bleeding in decompensated hepatitis C virus cirrhosis patients. *JGH Open*. 2018;2(6):317–321.
5 Hamill V, Wong S, Benselin J, et al. Mortality rates among patients successfully treated for hepatitis C in the era of interferon-free antivirals: population based cohort study. *BMJ*. 2023;382:e074001.
6 Kim NJ, Vutien P, Cleveland E, Cravero A, Ioannou GN. Fibrosis stage-specific incidence of hepatocellular cancer after hepatitis C cure with direct-acting antivirals: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2022;21(7):1723–1738.e5.
7 Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. *Bull World Health Organ*. 1994;72(3):495–509.
8 Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317–1325.
9 Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518–526.
10 Seo YS, Kim MY, Kim SU, et al. Accuracy of transient elastography in assessing liver fibrosis in chronic viral hepatitis: a multicentre, retrospective study. *Liver Int*. 2015;35(10):2246–2255.
11 Fox-Rushby JA, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy Plan*. 2001;16(3):326–331.
12 Kim YE, Jo MW, Park H, et al. Updating disability weights for measurement of healthy life expectancy and disability-adjusted life year in Korea. *J Korean Med Sci*. 2020;35(27):e219.
13 Korean Statistical Information Service. Life expectancy data. https://kosis.kr/eng/; 2012.
14 Honaker J, King G, Blackwell M. Amelia II: a program for missing data. *J Stat Software*. 2011;45(7):1–47.
15 Rubin DB. *Multiple imputation for nonresponse in surveys*. John Wiley and Sons; 2004. https://onlinelibrary.wiley.com/doi/book/10.1002/9780470316696.
16 Latouche A, Porcher R, Chevret S. A note on including time-dependent covariate in regression model for competing risks data. *Biom J*. 2005;47(6):807–814.
17 Ho D, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Software*. 2011;42(8):1–28.
18 Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet*. 2019;393(10179):1453–1464.
19 Rout G, Nayak B, Patel AH, et al. Therapy with oral directly acting agents in hepatitis C infection is associated with reduction in fibrosis and increase in hepatic steatosis on transient elastography. *J Clin Exp Hepatol*. 2019;9(2):207–214.
20 Mafirakureva N, Lim AG, Khalid GG, et al. Cost-effectiveness of screening and treatment using direct-acting antivirals for chronic Hepatitis C virus in a primary care setting in Karachi, Pakistan. *J Viral Hepat*. 2021;28(2):268–278.
21 Estes C, Abdel-Kareem M, Abdel-Razek W, et al. Economic burden of hepatitis C in Egypt: the future impact of highly effective therapies. *Aliment Pharmacol Ther*. 2015;42(6):696–706.
22 Lim AG, Scott N, Walker JG, Hamid S, Hellard M, Vickerman P. Health and economic benefits of achieving hepatitis C virus elimination in Pakistan: a modelling study and economic analysis. *PLoS Med*. 2021;18(10):e1003818.
23 Aggarwal R, Chen Q, Goel A, et al. Cost-effectiveness of hepatitis C treatment using generic direct-acting antivirals available in India. *PLoS One*. 2017;12(5):e0176503.
24 Heffernan A, Ma Y, Nayagam S, et al. Economic and epidemiological evaluation of interventions to reduce the burden of hepatitis C in Yunnan province, China. *PLoS One*. 2021;16(1):e0245288.
25 Veracruz N, Gish RG, Cheung R, Chitnis AS, Wong RJ. Global trends and the impact of chronic hepatitis B and C on disability-adjusted life years. *Liver Int*. 2022;42(10):2145–2153.
26 Lee CH, Choi GH, Choi HY, et al. Core indicators related to the elimination of hepatitis B and C virus infection in South Korea: a nationwide study. *Clin Mol Hepatol*. 2023;29(3):779–793.
27 Maor Y, Malnick SD, Melzer E, Leshno M. Treatment of chronic hepatitis C in the aged - does it impact life expectancy? A decision analysis. *PLoS One*. 2016;11(7):e0157832.
28 Huh S. Protection of personal information in medical journal publications. *Neurointervention*. 2019;14(1):1–8.
29 Singh S, Venkatesh SK, Wang Z, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol*. 2015;13(3):440–451.e6.
30 Semmler G, Meyer EL, Kozbial K, et al. HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease. *J Hepatol*. 2022;76(4):812–821.