

Retrospective Cohort Study

Chrono-optimal treatments for human immunodeficiency virus/hepatitis C virus co-infection yield comparable survival outcomes with hepatitis C virus mono-infection

Jeayeon Park, Jae Yoon Jeong, Soon Sun Kim, Jae Hyun Yoon, Hyuk Soo Eun, Jonggi Choi, Ki Tae Yoon, Young Kul Jung, Soo Young Park, Geum-Youn Gwak, Do Young Kim, Ji Hoon Kim, Jin-Woo Lee, Tae Yeob Kim, Jeong Won Jang, Su Jong Yu

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Jeayeon Park, Su Jong Yu, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul 03080, South Korea

Jae Yoon Jeong, Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Seoul 07985, South Korea

Soon Sun Kim, Department of Gastroenterology, Ajou University School of Medicine, Suwon 16499, Gyeonggi-do, South Korea

Jae Hyun Yoon, Department of Gastroenterology and Hepatology, Chonnam National University Hospital and Medical School, Gwangju 61469, South Korea

Hyuk Soo Eun, Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon 35015, South Korea

Jonggi Choi, Department of Internal Medicine, Asan Medical Center, Seoul 05505, South Korea

Ki Tae Yoon, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan 50612, South Korea

Young Kul Jung, Ji Hoon Kim, Department of Internal Medicine, Korea University College of Medicine, Seoul 02841, South Korea

Soo Young Park, Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu 41944, South Korea

Geum-Youn Gwak, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, South Korea

Do Young Kim, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul 03722, South Korea

Jin-Woo Lee, Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon 22212, South Korea

Tae Yeob Kim, Department of Internal Medicine, New Hope Internal Medicine Clinic, Seoul 03113, South Korea

Jeong Won Jang, Department of Internal Medicine, The Catholic University of Korea, Seoul 06591, South Korea

Co-first authors: Jeayeon Park and Jae Yoon Jeong.

Co-corresponding authors: Jeong Won Jang and Su Jong Yu.

Corresponding author: Su Jong Yu, MD, PhD, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 101, Daehak-Ro Jongno-Gu, Seoul 03080, South Korea. ydoctor2@snu.ac.kr

Abstract

BACKGROUND

Over recent decades, treatment for human immunodeficiency virus (HIV)/hepatitis C virus (HCV) co-infection has significantly advanced. HIV is known to accelerate liver disease progression and increase liver-related mortality in patients with HCV infection.

AIM

To reassess the effectiveness of HCV treatments by comparing outcomes between HIV/HCV co-infected and HCV mono-infected patients.

METHODS

We retrospectively included patients with HCV mono-infection or HIV/HCV co-infection at 12 tertiary referral centers from January 2009 to December 2020. The primary endpoint was overall survival (OS). Secondary endpoints included achievement of a sustained virologic response (SVR), time-to-occurrence of hepatocellular carcinoma (HCC), and the changes in fibrosis-4 (FIB-4) index.

RESULTS

A total of 904 patients were included: 792 with HCV mono-infection and 112 with HIV/HCV co-infection, of whom 97 (86.6%) had received prior HIV treatment. HCV treatment was administered to 741 (93.6%) mono-infected and 86 (76.8%) co-infected patients. Among treated patients, SVR was achieved in 93.4% of mono-infected and 81.4% of the co-infected group [$P = 0.114$ after inverse probability of treatment weighting (IPTW) adjustment]. OS and HCC occurrence showed no significant differences between groups, regardless of the HCV treatment method, after IPTW [hazard ratio (HR) = 0.37, 95% confidence interval (95%CI): 0.05-3.07, $P = 0.360$ for OS; HR = 0.19, 95%CI: 0.02-1.48, $P = 0.113$ for HCC occurrence]. The FIB-4 index significantly improved 1 year after achieving SVR with direct-acting antivirals in both groups.

CONCLUSION

With optimal HIV/HCV treatment regimens, HCC occurrence and mortality risks in co-infected patients have become comparable to those in patients with HCV mono-infection.

Key Words: Peginterferon; Direct-acting antivirals; Overall survival; Hepatocellular carcinoma; Liver fibrosis

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Core Tip: Proactive hepatitis C virus (HCV) treatment in human immunodeficiency virus (HIV)/HCV co-infected patients may contribute to improved long-term prognosis. With optimal HIV/HCV treatment regimens, hepatocellular carcinoma occurrence and mortality risks in co-infected patients have become comparable to those in patients with HCV mono-infection.

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INTRODUCTION

Owing to overlapping transmission routes, approximately 20%-30% of patients with human immunodeficiency virus (HIV) are co-infected with hepatitis C virus (HCV), particularly among intravenous drug users, where the co-infection

rate reaches 70%-95% [1,2]. Previous studies have demonstrated that HIV infection accelerates the progression of HCV-related liver disease, leading to an increased risk of cirrhosis, liver-related complications, and mortality [3]. Consequently, HIV/HCV co-infection represents a significant global public health threat [4]. Over time, there have been substantial improvements in the treatment options for both HIV and HCV, particularly with the advent of highly active antiretroviral therapy (ART) and the introduction of direct-acting antivirals (DAAs). However, while the efficacy of DAAs in achieving sustained virologic response (SVR) in HIV/HCV coinfection is well-established, real-world evidence on long-term clinical outcomes, such as overall survival (OS) and hepatocellular carcinoma (HCC) incidence, from large multicenter cohorts, particularly in Asian populations, remains valuable yet limited [5].

Achieving SVR with peginterferon and ribavirin therapy for HCV treatment has been shown to reduce liver-related complications and mortality [6,7]. However, in patients with HIV, the peginterferon plus ribavirin regimen showed disappointing rates of SVR and a high incidence of intolerable adverse events [8,9]. Additionally, ribavirin caused drug-drug interactions with ART [10-12], and these limitations led to a low number of patients receiving HCV treatment [13].

The development of DAAs has dramatically changed the treatment landscape for HIV/HCV co-infected patients [14]. DAAs achieve high SVR rates and, as demonstrated by the MINMON study, address concerns regarding drug-drug interactions between HIV and HCV medications while enabling the use of a simplified HCV treatment algorithm in these patients [15-18]. Some studies have reported higher rates of early occurrence and recurrence of HCC with DAA therapy compared to interferon-based therapy; however, these findings remain highly controversial [19-21].

Therefore, using a long-term multicenter cohort of HIV and HCV patients in South Korea, we aim to evaluate how changes in treatment strategies over time have influenced clinical outcomes in patients with HIV/HCV co-infection, in comparison to those with HCV mono-infection.

MATERIALS AND METHODS

Study population

The study retrospectively included patients diagnosed with HCV, with or without HIV at 12 tertiary referral centers between January 2009 and December 2020. Due to the very low prevalence of HIV in South Korea, patients with HIV/HCV co-infection were enrolled from all 12 centers, whereas patients with HCV mono-infection were included from two of these centers. The participating centers are listed in the [Supplementary material](#). HCV and HIV were diagnosed and treated according to the most up-to-date guidelines available at the time of this study [17,22,23]. This study conformed to ethical guidelines of the World Medical Association Declaration of Helsinki. This study was approved by the institutional review board of each tertiary referral center and was integrated under the approval of Institutional Review Board of Seoul National University Hospital. The requirement to obtain informed consent from patients was waived by the institutional review board due to the retrospective nature of this study.

Inclusion criteria: (1) Age > 18 years; (2) Unequivocal diagnosis of HCV or HIV based on guidelines; (3) Administration of peginterferon plus ribavirin or a DAA as the initial treatment for HCV, or opting for observation without treatment; and (4) Longitudinal follow-up of more than 6 months.

Exclusion criteria: (1) Presence of HCC or another malignancy at the time of diagnosis; (2) Concurrent hepatitis B virus infection; (3) Discontinuation of treatment due to poor compliance or severe adverse events; (4) Prior liver transplantation; or (5) Insufficient clinical data.

Treatment regimens

The decision to initiate HCV treatment for co-infected patients was made by physicians at each institution based on national and international guidelines [22-24]. Eligibility criteria for HCV treatment in HIV/HCV co-infected patients included no history of hepatic decompensation, a CD4+ cell count greater than 200 cells/ μ L (a criterion primarily applied during the peginterferon/ribavirin era, as current DAA-era international guidelines no longer require a minimum CD4 count due to high efficacy across all CD4 strata), at least 6 weeks of stable ART, and the absence of active opportunistic infections. Peginterferon was administered for 24 weeks or 48 weeks depending on the HCV genotype, and ribavirin was dosed either weight-based or fixed, depending on the HCV genotype or the type of peginterferon used [17,22,25]. Since its approval for use in South Korea in late 2015, DAA has been employed as an initial treatment option. The selection of an appropriate DAA was guided by factors such as HCV genotype, the presence of liver cirrhosis (LC), renal function, and potential drug-drug interactions with other medications [22-24]. HCV treatment was discontinued in patients who experienced fatal adverse events, or liver failure.

Assessments and outcomes

The primary endpoint was OS. Secondary endpoints included the achievement of SVR, the incidence of HCC, and changes in the fibrosis-4 (FIB-4) index. An SVR is defined as the absence of detectable HCV RNA in the blood 24 weeks after peginterferon plus ribavirin treatment or 12 weeks after DAA treatment. The FIB-4 index is a non-invasive scoring system used to estimate liver fibrosis in patients with HCV [26]. It is calculated using the following formula: $FIB-4 = [age \times \text{aspartate aminotransferase (IU/L)}] / [\text{platelet (} 10^9/\text{L)} \times \sqrt{\text{alanine aminotransferase (IU/L)}}]$ [26]. All patients included in the study underwent regular laboratory, including alpha-fetoprotein (AFP) measurements, and abdominal ultrasound or computed tomography every 6 months for surveillance of malignancies, including HCC.

The index date was defined as the date of achieving SVR for patients who underwent HCV treatment. Patients were censored on the earliest of the following dates: The date of last follow-up, death, or the date cutoff date (February 29, 2024).

Statistical analysis

Baseline clinical and demographic characteristics were compared between groups stratified by the presence or absence of HIV co-infection. Categorical variables are presented as *n* (%). Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables were compared using Pearson's χ^2 test and continuous variables were compared using Student's *t*-test. Inverse probability of treatment weighting (IPTW) was applied to minimize potential confounding factors in the propensity score calculation by incorporating variables such as age, sex, diabetes mellitus status, HCV treatment method, categorized scores for FIB-4, albumin-bilirubin score, AFP level, presence of LC, Child-Pugh score, and HCV genotype[27,28]. Stabilized weights were used, and extreme weights were truncated at the 1st and 99th percentiles to minimize the influence of outliers. The Kaplan-Meier estimator and log-rank test were used to analyze OS and the incidence of HCC among patients who achieved SVR. The Firth method was employed to address issues of separation and small sample sizes in our logistic regression analysis, adjusting the likelihood function to reduce bias in the maximum likelihood estimate[29]. For risk factor analysis, multivariate analysis was performed using Cox regression for covariables found to be significant in the univariable analysis or to have a low degree of collinearity. To assess within-patient changes in FIB-4 index across time points, a repeated measures analysis of variance (ANOVA) was performed, allowing for the control of inter-individual variability.

All the statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). *P* values less than 0.05 indicated statistically significant differences.

RESULTS

Study population

A total of 904 patients were included in this study. Of these, 792 patients were classified into the HCV mono-infected group, and 112 into the HIV/HCV co-infected group (Figure 1). In the HIV/HCV co-infection group, 97 (86.6%) had received HIV treatment prior to inclusion in the study. The median follow-up duration was 58.4 months (IQR: 34.1-91.3). The baseline characteristics of the study population are presented in Table 1. The HIV/HCV co-infected group showed a younger average age, and a higher proportion of males compared to the HCV mono-infected group. A larger proportion of HIV/HCV co-infected patients were untreated for HCV infection compared to the HCV mono-infected group. The AFP and FIB-4 levels were significantly elevated in the HCV mono-infected group. HCV genotype 1 and Child-Pugh score of A5 were the most prevalent in both groups. After the IPTW adjustment, there were no significant differences between the two groups across all variables.

Achievement of SVR

Among the treated patients, 93.4% of those in the HCV mono-infected group achieved SVR, compared with 81.4% in the HIV/HCV co-infected group as shown in Table 2. Before the IPTW adjustment, there was a significant difference between the two groups ($P < 0.001$). However, after adjusting for IPTW, no significant differences were observed between the groups ($P = 0.114$). In the group treated with peginterferon plus ribavirin, 80.2% of the HCV mono-infected group achieved SVR, while 60.0% of the HIV/HCV co-infected group reached SVR. Even after adjusting for IPTW, the proportion of patients who achieved SVR was significantly higher in the HCV mono-infected group ($P = 0.039$). In the DAA treated group, 98.7% of the HCV mono-infected group achieved SVR, whereas 92.9% of the HIV/HCV co-infected group achieved SVR. Before the IPTW adjustment, there was a significant difference in SVR rates between the two groups ($P = 0.015$); however, after IPTW adjustment, no difference was found between the groups ($P = 0.139$).

OS

During the follow-up period, among patients who achieved SVR, 41 out of 762 patients died. This included 40 patients (5.8%) from the HCV mono-infected group and 1 patient (1.4%) from the HIV/HCV co-infected group. The median OS was not reached in either group. The OS between the two groups showed no statistically significant difference before IPTW [hazard ratio (HR) = 0.32; 95% confidence interval (95%CI): 0.04-2.30, $P = 0.255$, Supplementary Figure 1A]. Even after adjusting with IPTW, OS was not significantly different between the two groups (HR = 0.37, 95%CI: 0.05-3.07, $P = 0.360$, Figure 2A). Multivariate analyses showed no significant differences in OS between the two groups either before IPTW [adjusted HR (aHR) = 0.63, 95%CI: 0.08-4.71, $P = 0.658$, Supplementary Tables 1 and 2] or after IPTW (aHR = 0.46, 95%CI: 0.11-1.91, $P = 0.280$, Tables 3 and 4). Both before and after IPTW, being over the age of 65 and the presence of LC were independently shown to be poor prognostic factors for OS (aHR = 2.45, 95%CI: 1.21-4.96, $P = 0.009$ for age ≥ 65 years old; aHR = 2.72, 95%CI: 1.34-5.52, $P = 0.005$ for LC, Tables 3 and 4). When patients were categorized and analyzed based on treatment with either peginterferon plus ribavirin or DAA, there was still no significant difference in OS between the HCV mono-infected group and the HIV/HCV co-infected group even after IPTW adjustment (HR = 3.89, 95%CI: 0.41-37.42, $P = 0.239$ for peginterferon plus ribavirin treated group, Supplementary Figure 2; HR = 0.75, 95%CI: 0.002-2194.25, $P = 0.937$ for DAA treated group, Supplementary Figure 3).

Table 1 Baseline characteristics, *n* (%)

Variables	Before IPTW		<i>P</i> value	SMD	After IPTW		<i>P</i> value	SMD
	HCV mono-infection (<i>n</i> = 792)	HIV/HCV co-infection (<i>n</i> = 112)			HCV mono-infection (<i>n</i> = 792)	HIV/HCV co-infection (<i>n</i> = 112)		
Age, years	58.0 (51.0-67.0)	44.0 (36.0-53.5)	< 0.001	0.96	46.0 (37.0-54.0)	44.0 (36.0-53.0)	0.829	0.04
Sex			< 0.001	1.16			0.465	0.09
Male	339 (42.8)	101 (90.2)			691 (87.3)	101 (90.2)		
Female	453 (57.2)	11 (9.8)			101 (12.7)	11 (9.8)		
Diabetes mellitus			0.35	0.11			0.891	0.02
Absent	685 (86.5)	101 (90.2)			710 (89.7)	101 (90.2)		
Present	107 (13.5)	11 (9.8)			82 (10.3)	11 (9.8)		
Hypertension			0.187	0.15			0.975	0.004
Absent	657 (86.5)	99 (88.4)			699 (88.3)	99 (88.4)		
Present	107 (13.5)	13 (11.6)			93 (11.7)	13 (11.6)		
Genotype			< 0.001	0.4			0.428	0.2
1	507 (64.0)	52 (46.4)			430 (54.3)	52 (46.4)		
2	233 (29.4)	42 (37.5)			281 (35.5)	42 (37.5)		
Others	52 (6.6)	18 (16.1)			81 (10.2)	18 (16.1)		
Treatment			< 0.001	0.47			0.808	0.11
None	51 (6.4)	26 (23.2)			151 (19.9)	26 (23.2)		
Peginterferon plus ribavirin	212 (26.8)	30 (26.8)			247 (31.2)	30 (26.8)		
DAA	529 (66.8)	56 (50.0)			386 (48.8)	56 (50.0)		
Liver cirrhosis			< 0.001	0.23			0.109	0.31
Absent	639 (80.7)	96 (85.7)			706 (89.2)	96 (85.7)		
Present	153 (19.3)	11 (9.8)			86 (10.8)	11 (9.8)		
Unknown	0 (0.0)	5 (4.5)			0 (0.0)	5 (4.5)		
Child-Pugh score			0.282	0.16			0.295	0.23
A5	663 (87.8)	34 (81.0)			689 (87.0)	91 (81.1)		
A6	65 (9.0)	8 (19.0)			89 (11.2)	15 (13.3)		
B7	15 (2.1)	4 (4.3)			10 (1.2)	5 (4.4)		
B8	6 (0.8)	1 (1.1)			4 (0.5)	1 (1.1)		
B9	2 (0.3)	0 (0.0)			2 (0.2)	0 (0.0)		
AFP (ng/mL)	4.6 (2.9-8.4)	2.9 (2.1-5.4)	< 0.001	0.14	4.3 (2.5-6.8)	2.8 (2.0-5.3)	0.253	0.09
ALBI score	-2.8 (-3.0 to -2.5)	-2.8 (-3.1 to -2.5)	0.306	0.05	-2.9 (-3.0 to -2.6)	-2.8 (-3.1 to -2.5)	0.78	0.04
APRI	0.7 (0.4-1.4)	0.7 (0.3-1.3)	0.346	0.04	0.5 (0.3-1.0)	0.7 (0.3-1.3)	0.085	0.23
Fibrosis-4 index	2.4 (1.5-4.2)	1.6 (1.0-2.7)	< 0.001	0.18	1.3 (0.8-2.4)	1.6 (1.0-2.7)	0.23	0.16

IPTW: Inverse probability of treatment weighting; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; DAA: Direct-acting antiviral; AFP: Alpha-fetoprotein; ALBI: Albumin-bilirubin score; APRI: Aspartate aminotransferase to platelet ratio index.

Time to occurrence of HCC

HCC occurred in 44 out of 762 patients who achieved SVR during the follow-up period. Of these patients, 43 (6.2%) were in the HCV mono-infected group, and 1 (1.4%) was in the HIV/HCV co-infected group. The median time to occurrence of HCC was not reached in either group. There was no significant difference between the occurrence of HCC before IPTW (HR = 0.18, 95% CI: 0.02-1.30, *P* = 0.089, [Supplementary Figure 1B](#)) and after IPTW (HR = 0.19, 95% CI: 0.02-1.48, *P* = 0.113, [Figure 2B](#)). There was no statistically significant association with the occurrence of HCC for either HCV mono-infection or

Table 2 Achievement of sustained virologic response according to treatment in hepatitis C virus mono-infected and human immunodeficiency virus/hepatitis C virus co-infected groups, *n* (%)

	Not achieved	Achieved
All treated		
Before IPTW		
HCV mono-infection (<i>n</i> = 741)	49 (6.6)	692 (93.4)
HIV/HCV co-infection (<i>n</i> = 86)	16 (18.6)	70 (81.4)
<i>P</i> value	< 0.001	
After IPTW		
HCV mono-infection (<i>n</i> = 741)	49 (6.6)	692 (93.4)
HIV/HCV co-infection (<i>n</i> = 86)	11 (13.1)	75 (86.9)
<i>P</i> value	0.114	
Treated with Peginterferon plus ribavirin		
Before IPTW		
HCV mono-infection (<i>n</i> = 212)	42 (19.8)	170 (80.2)
HIV/HCV co-infection (<i>n</i> = 30)	12 (40.0)	18 (60.0)
<i>P</i> value	0.024	
After IPTW		
HCV mono-infection (<i>n</i> = 212)	42 (19.8)	170 (80.2)
HIV/HCV co-infection (<i>n</i> = 30)	13 (42.9)	17 (57.1)
<i>P</i> value	0.039	
Treated with DAA		
Before IPTW		
HCV mono-infection (<i>n</i> = 529)	7 (1.3)	522 (98.7)
HIV/HCV co-infection (<i>n</i> = 56)	4 (7.1)	52 (92.9)
<i>P</i> value	0.015	
After IPTW		
HCV mono-infection (<i>n</i> = 529)	7 (1.3)	522 (98.7)
HIV/HCV co-infection (<i>n</i> = 56)	2 (3.7)	54 (96.3)
<i>P</i> value	0.139	

IPTW: Inverse probability of treatment weighting; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; DAA: Direct-acting antiviral.

HIV/HCV co-infection in the multivariable analysis conducted before and after IPTW adjustment (aHR = 0.28, 95%CI: 0.04-2.07, *P* = 0.212 before IPTW, [Supplementary Tables 1 and 2](#); aHR = 0.22, 95%CI: 0.03-1.69, *P* = 0.144 after IPTW, [Tables 3 and 4](#)). LC was the only factor independently associated with the occurrence of HCC (aHR = 2.54, 95%CI: 1.35-4.77, *P* = 0.004). Both peginterferon plus ribavirin and DAA treated patients showed no difference in the time to occurrence of HCC after IPTW adjustment (HR = 0.04, 95%CI: NA-NA, *P* = 1.000 for peginterferon plus ribavirin treated group, [Supplementary Figure 4](#); HR = 0.40, 95%CI: 0.06-2.64, *P* = 0.342 for DAA treated group, [Supplementary Figure 5](#)).

Changes in the FIB-4 index

Among patients who achieved SVR12, the mean baseline FIB-4 was 3.54 ± 3.63 in the HCV mono-infected group and 2.54 ± 4.90 in the HIV/HCV co-infected group ([Figure 3](#)). After 1 year, the FIB-4 significantly decreased in both the HCV mono-infected group (*P* < 0.001) and the HIV/HCV co-infected group (*P* < 0.001). When followed up at 3 years and 5 years, the FIB-4 remained decreased in both the HCV mono-infected group and the HIV/HCV co-infected group. When treated with peginterferon plus ribavirin, the FIB-4 significantly decreased after 1 year in the HCV mono-infected group (*P* < 0.001, [Supplementary Figure 6A](#)). In the HIV/HCV co-infected group, although no statistically significant difference was observed, a decreasing tendency was demonstrated (*P* = 0.398, [Supplementary Figure 6B](#)). However, when treated with DAA, the FIB-4 significantly decreased after 1 year in both groups (*P* < 0.001 in both groups), and this reduction was

Table 3 Cox regression analysis of factors associated with overall survival of hepatitis C virus after inverse probability of treatment weighting in patients who achieved sustained virologic response

Variables	Crude HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Group		0.360		0.280
HCV mono-infection	1 (reference)		1 (reference)	
HIV/HCV co-infection	0.37 (0.05-3.07)		0.46 (0.11-1.91)	
Age (year)		0.002		0.009
< 65	1 (reference)		1 (reference)	
≥ 65	3.35 (1.54-7.30)		2.45 (1.21-4.96)	
Sex		0.288		
Male	1 (reference)			
Female	0.68 (0.33-1.39)			
Diabetes mellitus		0.002		0.042
Absent	1 (reference)		1 (reference)	
Present	3.11 (1.54-6.27)		2.04 (1.03-4.05)	
Hypertension		0.104		
Absent	1 (reference)			
Present	0.35 (0.10-1.24)			
Child-Pugh score		0.804		
A	1 (reference)			
B	1.02 (0.90-1.14)			
Treatment		0.035		0.184
Peginterferon plus ribavirin	1 (reference)		1 (reference)	
DAA	2.76 (1.07-7.09)		1.95 (0.74-5.15)	
Fibrosis-4 index		< 0.001		0.649
≤ 3.25	1 (reference)		1 (reference)	
> 3.25	1.26 (1.24-1.97)		1.13 (0.67-1.93)	
Liver cirrhosis		< 0.001		0.005
Absent	1 (reference)		1 (reference)	
Present	5.18 (2.81-9.55)		2.72 (1.34-5.52)	
AFP (ng/mL)		0.580		
< 20	1 (reference)			
≥ 20	1.04 (0.91-1.17)			
ALBI score		< 0.001		0.039
≤ -2.60	1 (reference)		1 (reference)	
> -2.60	3.55 (1.82-6.91)		1.97 (1.04-3.73)	
APRI		0.026		0.791
< 1	1 (reference)		1 (reference)	
≥ 1	2.21 (1.10-4.44)		1.10 (0.54-2.25)	

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; DAA: Direct-acting antiviral; AFP: Alpha-fetoprotein; ALBI: Albumin-bilirubin score; APRI: Aspartate aminotransferase to platelet ratio index; HR: Hazard ratio; 95%CI: 95% confidence interval.

Table 4 Cox regression analysis of factors associated with time-to-occurrence of hepatitis C virus after inverse probability of treatment weighting in patients who achieved sustained virologic response

Variables	Crude HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Group		0.113		0.144
HCV mono-infection	1 (reference)		1 (reference)	
HIV/HCV co-infection	0.19 (0.02-1.48)		0.22 (0.03-1.69)	
Age (year)		0.692		
< 65	1 (reference)			
≥ 65	1.21 (0.47-3.13)			
Sex		0.200		
Male	1 (reference)			
Female	0.58 (0.25-1.34)			
Diabetes mellitus		0.034		0.107
Absent	1 (reference)		1 (reference)	
Present	2.44 (1.07-5.58)		1.81 (0.88-3.73)	
Hypertension		0.217		
Absent	1 (reference)			
Present	1.72 (0.73-4.08)			
Child-Pugh score		0.922		
A	1 (reference)			
B	1.01 (0.89-1.14)			
Treatment		0.507		
Peginterferon plus ribavirin	1 (reference)		1 (reference)	
DAA	1.31 (0.59-2.94)		1.95 (0.74-5.15)	
Fibrosis-4 index		0.016		0.736
≤ 3.25	1 (reference)		1 (reference)	
> 3.25	1.41 (1.07-1.86)		1.08 (0.68-1.73)	
Liver cirrhosis		0.002		0.004
Absent	1 (reference)		1 (reference)	
Present	3.80 (1.63-8.85)		2.54 (1.35-4.77)	
AFP (ng/mL)		0.758		
< 20	1 (reference)			
≥ 20	0.98 (0.87-1.11)			
ALBI score		0.149		
≤ -2.60	1 (reference)			
> -2.60	1.83 (0.81-4.14)			
APRI		0.015		0.068
< 1	1 (reference)		1 (reference)	
≥ 1	3.33 (1.26-8.77)		2.13 (0.95-4.80)	

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; DAA: Direct-acting antiviral; AFP: Alpha-fetoprotein; ALBI: Albumin-bilirubin score; APRI: Aspartate aminotransferase to platelet ratio index; HR: Hazard ratio; 95%CI: 95% confidence interval.

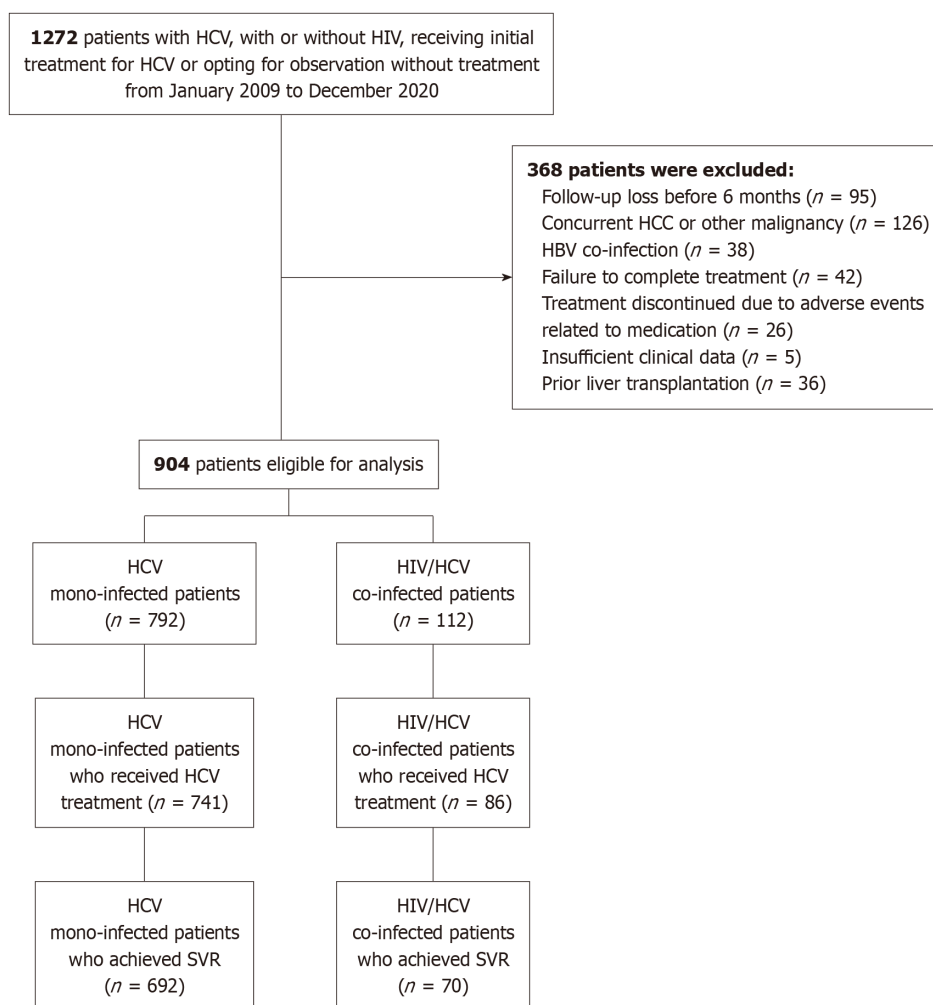


Figure 1 Flow diagram of patient selection for the study. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SVR: Sustained virologic response.

maintained at 3 and 5 years of follow-up (Supplementary Figure 7).

DISCUSSION

This study is the first to utilize a multicenter cohort enrolled over an extended period from 12 tertiary referral centers in South Korea, to evaluate how changes in optimal treatment strategies over time have influenced clinical outcomes in patients with HIV/HCV co-infection. In the HIV/HCV co-infection group, patients treated with pegylated-interferon had a significantly lower SVR rate than those in the HCV mono-infection group after IPTW adjustment ($P = 0.04$). In contrast, those treated with DAAs showed no significant difference ($P = 0.14$). Once SVR was achieved, there were no statistically significant differences in OS or HCC incidence between the HCV mono-infection group and HIV/HCV co-infection groups, regardless of whether the patients were treated with peginterferon plus ribavirin or DAA. Following the achievement of SVR, changes in the FIB-4 index showed a significant reduction 1 year after DAA treatment, which remained stable over time. This retrospective analysis demonstrated that, although the HIV/HCV co-infection has been known to have poorer clinical outcomes, the introduction of DAAs has led to higher SVR rates and clinical outcomes comparable to those with HCV mono-infection. Therefore, proactive HCV treatment in HIV/HCV co-infected patients could contribute to improving prognosis.

Both interferon-based antiviral and DAA therapies are known to reduce the incidence of HCC, hepatic decompensation, and liver-related mortality, even in patients with advanced fibrosis and compensated LC, provided that SVR is achieved[6,7,30,31]. However, previous studies have shown that HIV/HCV co-infected patients have lower SVR rates compared to HCV mono-infected patients when treated with peginterferon plus ribavirin[8,9]. Consistent with these findings, our study also demonstrated that the SVR rate in the HIV/HCV coinfection group remained significantly lower than that in the HCV mono-infection group, even after IPTW adjustment. The underlying reasons include, first, the higher levels of viral replication observed in HIV/HCV co-infection[32-34]. Second, the impaired immune status associated with HIV infection results in delayed clearance of HCV[35]. Third, interferon exerts its antiviral effects by activating genes that regulate both the innate and adaptive immune responses. However, in immunocompromised HIV

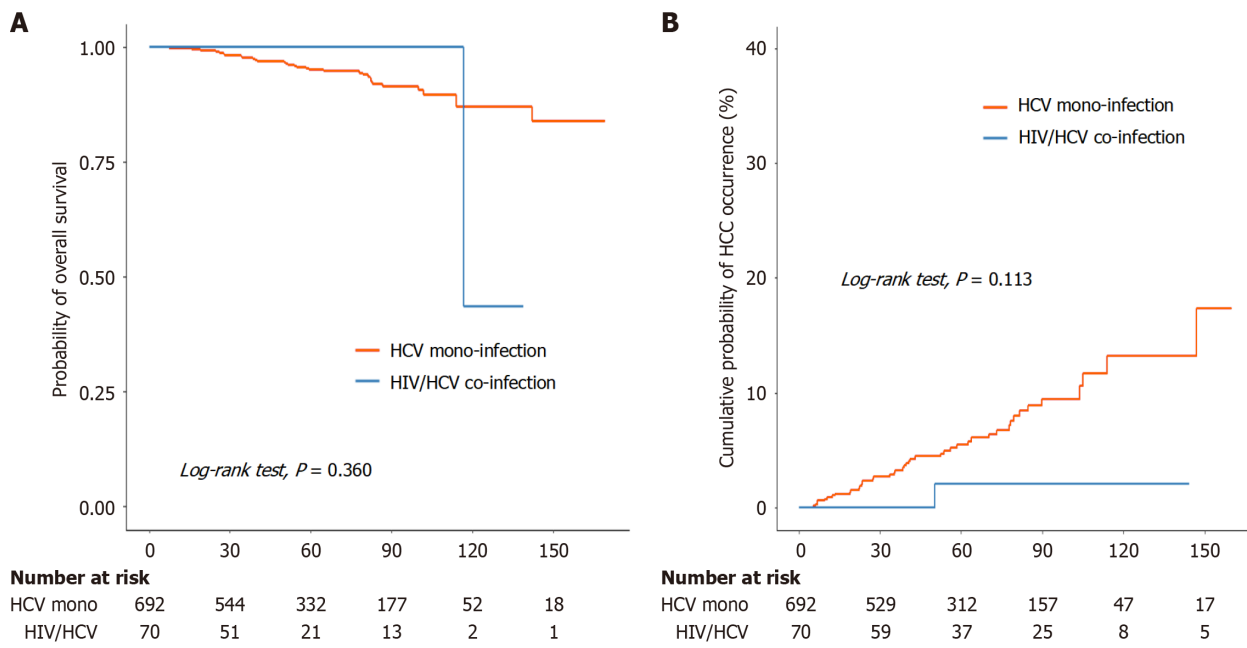


Figure 2 Clinical outcomes in hepatitis C virus patients achieving sustained virologic response stratified by human immunodeficiency virus co-infection status. A and B: Kaplan-Meier estimates of overall survival (A) and time to the occurrence of hepatocellular carcinoma (B) in hepatitis C virus (HCV) patients who achieved sustained virologic response after treatment, stratified by human immunodeficiency virus co-infection status, after inverse probability of treatment weighting adjustment. Propensity scores of inverse probability of treatment weighting were computed using the age, sex, diabetes mellitus status, HCV treatment method, categorized scores for the fibrosis-4 index, the albumin-bilirubin score, and alpha-fetoprotein levels, presence of liver cirrhosis, Child-Pugh score, and HCV genotype. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

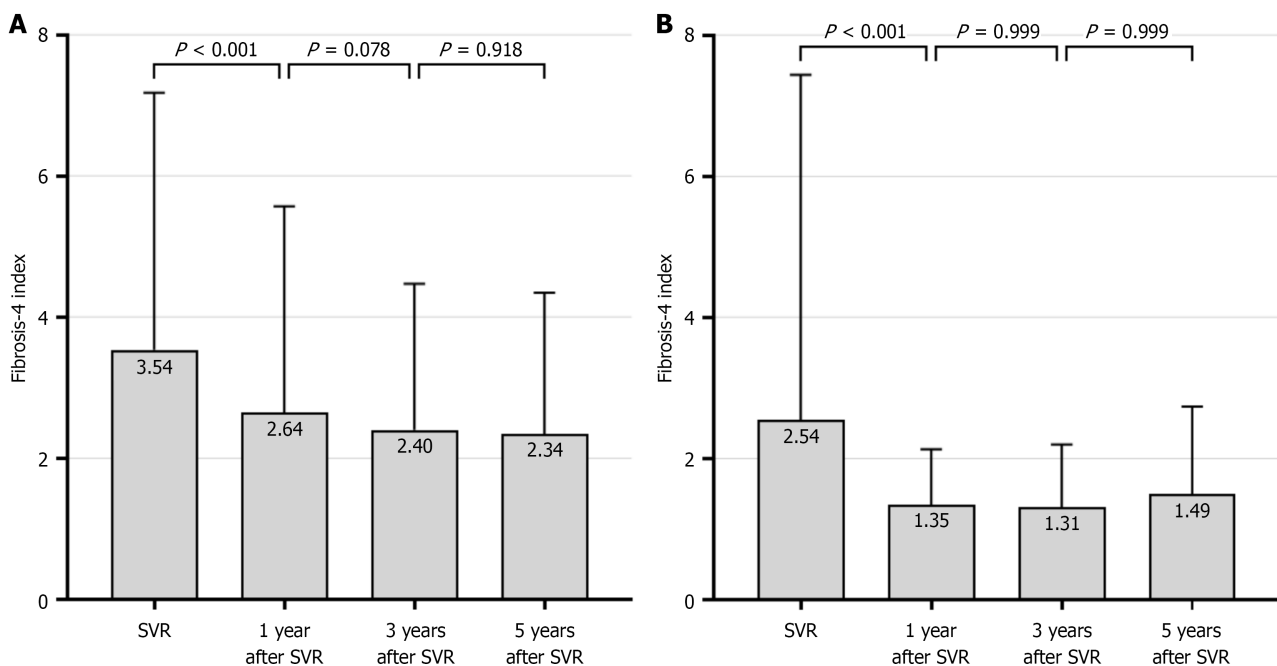


Figure 3 Changes in the fibrosis-4 index in hepatitis C virus patients achieving sustained virologic response. A and B: Changes in the fibrosis-4 (FIB-4) index in hepatitis C virus mono-infected patients (A) and human immunodeficiency virus/hepatitis C virus co-infected patients (B) who achieved sustained virologic response after treatment. Within-patient changes in the FIB-4 index over time were assessed using repeated measures analysis of variance. The mean FIB-4 index is presented at the top of each bar in the graph. SVR: Sustained virologic response.

patients, the standard dose and duration of treatment may fail to achieve optimal therapeutic outcomes[9,36]. In contrast, DAAs directly target HCV non-structural proteins essential for replication, enabling HIV/HCV co-infected patients to achieve SVR rates comparable to HCV mono-infected patients[31].

Early reports raised concerns about a potentially increased risk of HCC following DAA therapy; however, subsequent large-scale cohort studies and meta-analyses have shown that this apparent risk was attributable to the inclusion of patients with more advanced liver disease rather than a direct causal effect of the DAAs[37,38]. Current consensus indicates that although DAA-induced SVR reduces the risk of HCC, it does not eliminate it in patients with established cirrhosis. In the present study, LC was identified as the sole independent factor associated with HCC occurrence. Neither HIV co-infection status nor the type of HCV treatment regimen had an independent impact on HCC occurrence. Therefore, we performed IPTW adjustment using inverse probability weighting based on propensity scores to balance the distribution of LC and other covariates, thereby enhancing the statistical power. Consequently, no statistically significant difference in time to HCC occurrence was observed between the two groups, regardless of HCV treatment method.

Patients with HIV/HCV co-infection have been known to progress to LC more rapidly than those with HCV mono-infection[3]. Several studies have shown that this accelerated progression results from HIV signaling through coreceptors on hepatocytes in a TGF- β 1-dependent manner, leading to increased HCV replication, reactive oxygen species generation, and hepatocyte apoptosis[33]. While many studies have reported improvements in liver fibrosis after achieving SVR[30,39,40], data on fibrosis changes in HIV/HCV co-infection patients remain scarce. Therefore, this study analyzed the changes in the FIB-4 index, a non-invasive method for assessing liver fibrosis, at one-year intervals. DAA treatment significantly decreased the FIB-4 index 1 year after achieving SVR in both the HCV mono-infection and HIV/HCV coinfection groups, with reductions sustained at three and 5 years of follow-up. In contrast, peginterferon plus ribavirin treatment resulted in a significant decrease in FIB-4 levels only in the HCV mono-infection group. The reduction in fibrosis following HCV treatment was due to improved hepatic inflammation resulting from decreased viral replication [33,39]. Our findings showed that similar improvements occurred in HIV/HCV co-infection patients after DAA treatment. Moreover, the significant and sustained reduction in the FIB-4 index following SVR in our cohort aligns with a growing body of evidence from both mono-infected and co-infected populations, demonstrating that viral eradication with DAAs leads to histological regression of fibrosis and a reduction in liver-related complications[25]. Previous studies have reported greater declines in liver stiffness among HCV-mono-infected patients treated with DAAs compared with those treated with peginterferon plus ribavirin, which has been attributed to DAAs' ability to rapidly clear viremia and lead to hepatic inflammation resolution[30,40]. Similarly, this study demonstrated that DAA treatment significantly improved the FIB-4 index compared to peginterferon plus ribavirin in HIV/HCV co-infected patients, consistent with the findings of previous studies. Therefore, active HCV treatment with DAAs in HIV/HCV co-infected patients is expected to produce reductions in FIB-4 that are suggestive of fibrosis improvement in this population, thereby substantially reducing liver-related complications.

In patients with HIV/HCV coinfection, OS may be influenced by cardiovascular diseases, malignancy, opportunistic infections caused by HIV, or the progression of liver disease due to HCV, such as the development of LC or HCC[41,42]. In this study, all patients included in the OS analysis were receiving HIV treatment and had achieved SVR following HCV treatment. No significant difference in OS was observed between the HCV mono-infection group and the HIV/HCV coinfection group. In the multivariate analysis, only older age and the presence of LC were identified as independent factors affecting OS. Because OS encompasses deaths from all causes, comparable OS between the groups should not be interpreted as reflecting liver-related mortality alone. Instead, these findings likely reflect the combined impact of effective HIV suppression, successful HCV eradication, and stabilization of the underlying liver disease. Previous studies have shown that patients with HIV/HCV coinfection experienced more rapid liver disease progression and higher mortality[3]; however, our results suggest that coordinated and proactive management of both infections may mitigate these risks, leading to OS outcomes comparable to those observed in HCV mono-infected patients.

Our findings in the Asian cohort were consistent with those observed in cohorts of other ethnicities. In a multicenter, prospective, nationwide French cohort of HIV/HCV coinfecting patients, following the achievement of SVR with DAA therapy, HIV/HCV co-infected patients and HCV mono-infected patients exhibited a similar risk of liver-related mortality and events[43]. Likewise, a multicenter cohort study from Spain reported that, among HIV/HCV co-infected patients who achieved SVR, the leading causes of death were non-liver- and non-acquired immune deficiency syndrome-related events[44]. In that study, the risk of hepatic decompensation and HCC development increased progressively increased from patients with advanced fibrosis to those with decompensated cirrhosis. Taken together, our findings provide additional real-world insight from an Asian cohort, contributing to broader evidence on the long-term benefits of DAA-induced SVR in HIV/HCV coinfection.

The key strength of this study is that it is the first to compare HIV/HCV co-infected patients with HCV mono-infected patients within a multicenter cohort with long-term patient enrollment in South Korea. However, there are some limitations inherent to its retrospective design. Although the overall cohort size was substantial, the number of HIV/HCV co-infected patients who received HCV treatment and completed follow-up was relatively small, which may have limited the statistical power of the analysis; moreover, the low number of HCC events in this subgroup may have affected the precision of the corresponding hazard estimates. Furthermore, patients with HCV mono-infection were enrolled from only two of the participating centers, rather than from all centers, potentially introducing selection bias. To address these limitations, IPTW methods were applied to improve the reliability of the statistical analysis despite the smaller, unevenly distributed sample size. In addition, direct methods for assessing liver fibrosis, such as liver biopsy and elastography, were not widely utilized in this cohort. Liver biopsy was rarely performed due to the risk of procedure-related complications, and elastography was not consistently available during the earlier years of the study period. Given these limitations, the FIB-4 index was adopted as a standardized, non-invasive measure to allow uniform longitudinal assessment across the participating centers. Notably, international clinical guidelines endorse FIB-4 as a validated tool for risk stratification and for monitoring fibrosis dynamics over time, particularly in large, retrospective multi-center studies where harmonization of elastography measurements is difficult to achieve. Finally, as the study period spanned both the interferon-based and DAA eras, temporal variability in treatment practices may remain an unmeasured factor,

warranting future era-specific analyses.

CONCLUSION

In conclusion, the introduction of DAAs, characterized by their high efficacy and favorable safety profiles, has dramatically advanced the management of HCV in patients with HIV/HCV co-infection. Achieving SVR has demonstrated prognostic improvements comparable to those observed in patients with HCV mono-infection. These findings suggest that the timely initiation of HCV treatment and achievement of SVR can lead to similar clinical outcomes in HIV/HCV co-infected patients. Therefore, HIV infection should not be considered a barrier to timely HCV therapy in this population.

FOOTNOTES

Author contributions: Park J and Jeong JY contribute equally to this study as co-first authors; Yu SJ and Jang JW contribute equally to this study as co-corresponding authors and they have full access to all study data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; study concepts and design were performed by Park J, Jeong JY, Kim SS, Yu SJ, and Jang JW; provision of study materials or patients were performed by Park J, Jeong JY, Kim SS, Yoon JH, Eun HS, Choi J, Yoon KT, Jung YK, Park SY, Gwak GY, Kim DY, Kim JH, Lee JW, Kim TY, Yu SJ, and Jang JW; collection and management of the study data were performed by Park J, Jeong JY, Kim SS, Yu SJ, and Jang JW; data analysis and interpretation were performed by Park J, Jeong JY, and Kim SS; manuscript writing was performed by Park J, Jeong JY, Kim SS, Yu SJ, and Jang JW.

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Informed consent statement: The requirement to obtain informed consent from patients was waived by the institutional review board due to the retrospective nature of this study.

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Data sharing statement: All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Country of origin: South Korea

ORCID number: Jae Yoon Jeong 0000-0002-3624-3261; Soon Sun Kim 0000-0002-6862-1896; Jae Hyun Yoon 0000-0002-4993-2496; Hyuk Soo Eun 0000-0003-0485-0072; Ki Tae Yoon 0000-0002-8580-0239; Young Kul Jung 0000-0002-6566-1382; Soo Young Park 0000-0002-4944-4396; Geum-Youn Gwak 0000-0002-6453-3450; Ji Hoon Kim 0000-0003-3924-0434; Jin-Woo Lee 0000-0002-7227-4938; Tae Yeob Kim 0000-0001-7978-5303; Jeong Won Jang 0000-0002-0305-5846; Su Jong Yu 0000-0001-8888-7977.

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