The global prevalence of hepatitis C virus (HCV) infection is approximately 1.0%, corresponding to 71.1 million people. About 70% to 85% of patients with HCV infection develop chronic hepatitis, and 30% of these patients progress to end-stage liver disease such as liver cirrhosis or hepatocellular carcinoma (HCC). Because an effective HCV vaccination is not yet available, prevention of transmission and appropriate treatment are the best way to reduce the burden of HCV-related liver diseases. Fortunately, highly efficacious all-oral direct antiviral agents (DAA) have been available since the mid-2010s, resulting in markedly improved treatment of HCV infection. Therefore, current international guidelines recommend early detection and treatment of patients with HCV infection to prevent end-stage liver diseases and new HCV infection. This is a major component of the global strategy to eliminate HCV infection by 2030 promoted by the World Health Organization. To achieve HCV infection elimination, it is crucial to establish a cascade of care for patients. This requires HCV screening and testing to identify HCV-infected individuals, linkage to care, treatment with highly efficacious antiviral treatment, and preventing disease progression by achieving a clinical cure. However, multiple barriers still impede implementation of this cascade of care leav-

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ing many HCV-infected patients untreated. The barriers include a low awareness of HCV infection, failure to refer patients to a hepatologist, and low treatment uptake rates. A recent Korean study reported that about half of HCV-infected patients did not receive antiviral treatment. This means that the DAA-era does not significantly differ from the pre-DAA era.\footnote{Choi J, et al: Status and 20-Year Trends of Korean HCV Care Cascade} Therefore, other factors in the cascade of care might be more important than the potency of antiviral treatment, to achieving effective treatment coverage of patients with HCV infection.

Therefore, we aimed to comprehensively explore the cascade of care for patients with HCV infection over the past 20 years and to assess the current state of HCV care in a large cohort from a single tertiary referral center.

1. Study design and outcomes

This study was approved by the institutional review board of Asan Medical Center, Seoul, Korea (IRB number: 2020-1639) and was exempt from obtaining consent by the institutional review board. This was a retrospective study. The study examined changes over the past 20 years and the current status in four categories: (1) anti-HCV-testing, (2) linkage to care for HCV, (3) characteristics of HCV infection and treatment for HCV, and (4) long-term outcome in patients with HCV.

For anti-HCV testing, we analyzed yearly trends in the number of patients who had anti-HCV tests, the number of patients who had HCV RNA tests, the number of patients confirmed with HCV infection, the proportion of patients tested for HCV RNA among anti-HCV-positive patients, and the distribution of HCV genotypes.

For linkage to HCV care, we calculated the linkage time for HCV RNA testing defined as median days between the date of anti-HCV-positivity and the date of HCV RNA testing. The flow of patients with confirmed HCV infection between hospital departments was also evaluated. In addition, we estimated the median period between the date of anti-HCV-positivity and the date of HCV treatment among patients who received antiviral treatment. Moreover, we explored the clinical and demographic characteristics of patients who were not tested for HCV RNA despite anti-HCV-positivity.

For characteristics of HCV infection and treatment for HCV, we investigated disease status at the time of HCV diagnosis, treatment uptake rate, antiviral treatment regimen types, and the rate of achieving sustained virological response (SVR).

For the long-term outcomes focusing on patients without a history of HCC before the diagnosis of HCV infection, the cumulative incidence of HCC and death were estimated. In addition, these outcomes were compared based on the presence of baseline cirrhosis and achievement of SVR.

2. Study population

Data were collected on 1,144,468 patients who had anti-HCV tests between January 2001 and June 2020 at Asan Medical Center (Fig. 1). This is a 2,700-bed academic tertiary referral hospital in Seoul, Korea. The anti-HCV test was performed as a routine screening test before invasive procedures or surgery. The medical department generally tests anti-HCV in cases of abnormal liver function test. Additionally, the health check-up department performed anti-HCV testing for routine health screening.

3. Clinical and laboratory variables and follow-up evaluation

Data on clinical information and outcomes were obtained from the electronic medical records of the Asan Medical Center database. Demographics including age and sex, and laboratory variables including aspartate aminotransferase, alanine aminotransferase (ALT), total bilirubin, serum albumin, platelet count, prothrombin time, hepatitis B virus (HBV) surface antigen. Human immunodeficiency virus status, anti-HCV (real-time polymerase chain reaction with a single strand linear probe; Abbott RealTime kit, Abbott, Chicago, IL, USA), and serum HCV RNA levels (AMPLICOR HCV Test v2.0, Roche, Basel, Switzerland) were extracted from the electronic medical records. The HCV genotype was determined using the restriction fragment mass polymorphism assay.

We collected clinical information regarding previous or concurrent diagnosis of HCC or non-HCC malignancy and liver transplantation at the time of anti-HCV testing. To assess the long-term outcome of patients with HCV infection, the index date was defined as the first date of anti-HCV-positivity. Patients were followed up from the index date to the date of confirmation of HCC, liver transplantation, death, or last follow-up (December 31, 2020), whichever came first.

4. Statistical analysis

The baseline characteristics of patients were compared between patients with HCV infection and patients who were not tested for HCV RNA despite anti-HCV-positivity, and between patients who did and who did not receive antiviral treatment. Continuous variables were compared using the Student t-test, and categorical variables were compared by the chi-square test or the Fisher exact test as appropriate. The cumulative incidence rates of HCC and
death or transplantation were estimated using the Kaplan-Meier method. They were compared by the log-rank test according to age group, treatment uptake, achievement of SVR, coinfection with HBV, presence of liver cirrhosis at the time of HCV diagnosis, and time between the diagnosis of HCV and SVR achievement. To evaluate the impact of SVR on the risk of HCC and to avoid immortal time bias,\(^9\) we performed two landmark analyses. All data analyses were performed using R software (https://cran.r-project.org/). All reported p-values are two-sided, and p-values \(<0.05\) were considered statistically significant.

**RESULTS**

1. HCV testing

Of the 1,144,468 patients tested for anti-HCV during the study period, 21,363 patients (1.8%) were anti-HCV-positive. Positivity rates of anti-HCV ranged from 0.9% to 2.2% between 2001 and 2020, showing a decreasing trend after 2015 (Fig. 2A).

Of the 21,363 anti-HCV-positive patients, 14,983 (70.1%) were referred for an HCV RNA test. However, despite this, 99 patients (0.4%) did not perform the confirmatory test. In addition, 6,379 patients (29.9%) were not referred for an HCV RNA confirmatory test. The proportion of HCV RNA testing among anti-HCV-positive patients was 70.1%, ranging from 65.4% to 72.4% annually (Fig. 2B).

Genotype 1b (48.5%) and 2 (45.5%) were the most frequent genotypes, in patients with confirmed HCV infection, followed by 1a (2.2%), 3 (1.2%), mixed (1.2%), and 6 (1.1%) (Fig. 2C).

Of the 14,884 patients who took the HCV RNA test, 9,747 (65.5%) were confirmed. The absolute number of newly identified HCV infections has been gradually decreasing since 2016 (Fig. 2D).

2. Linkage to care for HCV

Of anti-HCV-positive patients, the gastroenterology department ordered an HCV RNA test in 60.0% of patients, followed by general surgery 10.8%, internal medicine (not gastroenterology) 9.7%, other surgery 5.4%, family medicine 5.4%, pediatrics 3.1%, and emergency medicine 2.2% (Supplementary Fig. 1). The linkage time for HCV RNA testing was 3 days, 1 day, and 7 days in patients tested for HCV RNA, in patients with confirmed HCV infection, and in patients with HCV RNA negativity, respectively. The linkage time for HCV RNA testing showed a decreasing trend during the study period, showing less than 1 week since 2005 (Fig. 3A). Of the 6,379 patients who were not tested for HCV RNA despite anti-HCV-positivity, anti-HCV testing was ordered from other surgical departments. The rates were, for family medicine, gastroenterology, general surgery,
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Table 1 shows baseline characteristic comparisons between patients with confirmed HCV infection and patients who did not perform HCV RNA testing. The latter patients showed a lower prevalence of liver cirrhosis and lower levels of aspartate aminotransferase, ALT compared with patients with HCV infection. However, a history of non-HCC ma-

internal medicine not gastroenterology, and emergency medicine, 1,541 (24.2%), 1,150 (18.0%), 991 (15.5%), 974 (15.3%), 818 (12.8%), and 463 (7.3%) patients, respectively (Fig. 3B).

Fig. 2. Trends of testing and diagnosis of hepatitis C virus (HCV). [A] Positive rates of anti-HCV test. [B] Proportions of patients with confirmed HCV infection, patients with HCV RNA negativity, and patients who did not perform HCV RNA testing. [C] Distribution of HCV genotypes. [D] Annual number of patients newly diagnosed with HCV infection.

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Lignancy was significantly higher in patients not performing HCV RNA testing than in those with HCV infection. Normal ALT proportions were 81.7%, 72.9%, and 46.5% in patients with anti-HCV+ but no HCV RNA testing, anti-HCV+ HCV RNA−, and HCV infection, respectively. Of the 13,892 patients with normal ALT, 8,707 (62.2%) tested HCV RNA (Supplementary Table 1). Multivariable analysis showed that older patients, males, history of non-HCC malignancy, and HBV coinfection were associated with not undergoing HCV RNA testing in the case of normal ALT (Supplementary Table 2).

**Fig. 3.** Linkage to care for hepatitis C virus (HCV). (A) Median period from the detection of anti-HCV-positivity to HCV RNA testing. (B) Distribution of departments where HCV RNA was not ordered in patients with anti-HCV-positivity.

Other surgery, cardiothoracic surgery, otorhinolaryngology, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedic surgery, plastic surgery, urology; FM, family medicine, including health-screening department; GI, gastroenterology department; GS, general surgery; IM not GI, internal medicine not gastroenterology department; EM, emergency medicine.

**Table 1.** Demographic and Laboratory Characteristics of Patients Who Tested Positive for Anti-HCV by the Result of the Following HCV RNA Confirmation Test

| Characteristics                      | Confirmed HCV infection (n=9,747) | Anti-HCV-positivity, HCV RNA not done (n=6,478) | p-value |
|--------------------------------------|-----------------------------------|--------------------------------------------------|---------|
| **Demographics**                     |                                   |                                                  |         |
| Age, yr                              | 59.0±12.7                         | 60.1±15.8                                        | <0.001  |
| Male sex                             | 5,428 (55.7)                      | 3,446 (53.2)                                     | 0.003   |
| Liver cirrhosis                      | 2,956 (30.3)                      | 325 (5.0)                                        | <0.001  |
| History of HCC                       | 2,146 (22.0)                      | 218 (3.4)                                        | <0.001  |
| History of non-HCC malignancy        | 1,208 (12.4)                      | 1,585 (24.5)                                     | <0.001  |
| History of liver transplantation     | 65 (0.6)                          | 8 (0.1)                                          | <0.001  |
| HBV coinfection                      | 460 (5.0)                         | 417 (6.4)                                        | <0.001  |
| HIV coinfection                      | 15 (0.2)                          | 5 (0.1)                                          | <0.001  |
| **Laboratory parameters**            |                                   |                                                  |         |
| AST, U/L                             | 83.7±140.4                        | 40.1±77.0                                        | <0.001  |
| ALT, U/L                             | 77.6±148.2                        | 33.9±70.8                                        | <0.001  |
| Albumin, g/L                         | 3.6±0.6                           | 3.8±0.6                                          | <0.001  |
| Total bilirubin, mg/dL               | 1.4±2.7                           | 1.0±1.8                                          | <0.001  |
| Prothrombin time, %                  | 87.0±18.4                         | 96.3±18.2                                        | <0.001  |
| Prothrombin time, INR                | 1.1±0.2                           | 1.1±0.3                                          | <0.001  |

Data are presented as mean±SD or number (%). HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HIV, human immunodeficiency virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.
Supplementary Fig. 2 shows how the anti-HCV-positive patients were referred from the department where the anti-HCV test was ordered to the destination department where the HCV RNA test was ordered. The gastroenterology department had 41.1% anti-HCV-positive patients, whereas HCV RNA was ordered by the department in 51.9% of cases.
3. Clinical characteristics of patients with HCV infection

The clinical characteristics of patients with HCV infection are presented in Table 1. Among 9,747 HCV-infected patients, 5,428 (55.7%) were male, and the mean age was 59.0 years (Supplementary Fig. 3). Coinfection with HBV and human immunodeficiency virus was present in 460 (5.0%) and 15 (0.2%) patients, respectively. At the time of HCV infection diagnosis, 2,146 patients (22.0%) had a previous history of HCC or were diagnosed with HCC. In addition, 2,956 (30.3%) had liver cirrhosis at the time of HCV infection diagnosis. The proportion of patients with HCC when HCV was diagnosed has shown an increasing trend since 2015 (Fig. 4A). The mean ALT level was 83.7 U/L, and 4,529 (46.5%) showed an ALT <40 U/L, being within the upper limit of normal. Only 6.1% of patients had a very high level of ALT (>5 × upper limit of normal) (Fig. 4B).

4. Treatment of patients with HCV infection

Of the patients with HCV infection, 3,113 (31.9%) received antiviral treatment for HCV infection. The clinical characteristics of those treated for HCV were compared with those not treated (Supplementary Table 3). Compared with patients receiving antiviral treatment, patients who were not treated were significantly older, and significantly more of them had higher levels of ALT, cirrhosis, a history of HCC, and history of non-HCC malignancy (Table 2). No difference was found in the yearly distribution between

Table 2. Summary of Incidences of Hepatocellular Carcinoma

| Variable                                           | Patient | Hepatocellular carcinoma | Person-year | Incidence (per 100 person-years) |
|----------------------------------------------------|---------|--------------------------|-------------|----------------------------------|
| Entire population                                  | 5,302   | 504                      | 32,548      | 1.55                             |
| Liver cirrhosis at the time of HCV diagnosis       |         |                          |             |                                  |
| Yes                                                | 981     | 286                      | 5,198       | 4.19                             |
| No                                                 | 4,321   | 218                      | 27,351      | 1.05                             |
| Age at the time of HCV diagnosis, yr               |         |                          |             |                                  |
| <40                                                | 542     | 7                        | 3,920       | 0.18                             |
| 40–49                                              | 990     | 47                       | 7,061       | 0.24                             |
| 50–59                                              | 1,509   | 141                      | 10,033      | 0.67                             |
| 60–69                                              | 1,403   | 201                      | 8,093       | 1.41                             |
| ≥70                                                | 858     | 108                      | 3,443       | 2.48                             |
| Antiviral treatment                                |         |                          |             |                                  |
| Received                                           | 2,421   | 228                      | 17,821      | 1.28                             |
| Interferon-based                                   | 1,206   | 115                      | 9,847       | 1.17                             |
| DAA-based                                          | 930     | 61                       | 5,438       | 1.12                             |
| Interferon-failed, then DAA                        | 285     | 52                       | 2,535       | 2.05                             |
| Not received                                       | 2,881   | 276                      | 14,728      | 1.87                             |
| Achievement of SVR                                 |         |                          |             |                                  |
| SVR achieved                                       | 2,319   | 176                      | 17,205      | 1.02                             |
| SVR not achieved                                   | 2,983   | 328                      | 15,343      | 2.14                             |
| Achievement of SVR and baseline cirrhosis          |         |                          |             |                                  |
| SVR achieved without baseline cirrhosis            | 1,948   | 117                      | 14,413      | 0.81                             |
| SVR achieved with baseline cirrhosis               | 371     | 59                       | 2,792       | 2.11                             |
| No SVR without baseline cirrhosis                 | 2,373   | 169                      | 12,938      | 1.31                             |
| No SVR with baseline cirrhosis                    | 610     | 159                      | 2,405       | 6.61                             |
| Coinfection with HBV                               |         |                          |             |                                  |
| HBV + HCV                                          | 237     | 39                       | 1,682       | 2.32                             |
| HCV infection only                                 | 5,065   | 445                      | 30,867      | 1.51                             |
| Landmark analysis at 2 yr (n=3,970)                |         |                          |             |                                  |
| SVR achieved                                       | 1,094   | 47                       | 7,537       | 0.62                             |
| No SVR                                            | 2,876   | 317                      | 23,542      | 1.35                             |
| Landmark analysis at 5 yr (n=2,582)                |         |                          |             |                                  |
| SVR achieved                                       | 924     | 36                       | 8,894       | 0.41                             |
| No SVR                                            | 1,658   | 174                      | 17,648      | 0.99                             |
| Time between the diagnosis of HCV and SVR          |         |                          |             |                                  |
| SVR achievement <2 yr                              | 1,430   | 67                       | 7,855       | 0.85                             |
| SVR achievement <5 yr                              | 376     | 33                       | 3,152       | 1.05                             |
| SVR achievement <10 yr                             | 279     | 37                       | 2,895       | 1.28                             |
| SVR achievement >10 yr                             | 205     | 39                       | 3,085       | 1.26                             |

HCV, hepatitis C virus; DAA, direct antiviral agents; SVR, sustained virological response; HBV, hepatitis B virus.
the two groups. Patients treated for HCV infection had significantly more liver biopsies performed than patients who were not treated. Among patients with HCV infection, 934 patients had a liver biopsy for histologic examination. Of the patients treated for HCV infection, 798 (25.6%) had a liver biopsy before antiviral treatment, whereas only 136 (2.1%) untreated patients underwent liver biopsy.

The average yearly rate of antiviral treatment for HCV was 32.1%, ranging from 28.3% in 2011 to 38.8% in 2016. (Supplementary Fig. 4) However, after excluding patients diagnosed with HCC, the average yearly rate of antiviral treatment for HCV was 35.4% (Fig. 4C).

Of the patients treated for HCV infection, 1,931 patients were treated with an interferon-containing regimen, whereas 1,439 patients were treated with an interferon-free DAA regimen. The number of patients treated with an interferon-containing regimen has remarkably decreased since 2015 (Fig. 4D). The number of patients treated with the DAA regimen showed a peak in 2016, then gradually decreased in subsequent years (Fig. 4D). The clinical characteristics of patients diagnosed with HCC before the DAA-era and after DAA-era are presented in Supplementary Table 4. The average rate of antiviral treatment in the post-DAA era was significantly higher than in the pre-DAA era.

5. Long-term outcome of patients with HCV infection

The long-term outcomes of 5,302 patients who did not have a history of HCC at more than 6 months of follow-up were analyzed. The median follow-up period was 6.1 years. Annual incidences of HCC in the entire population and various subgroups are summarized in Table 2. Overall, 504 patients developed HCC for 32,548 person-years (PYs), with an annual incidence of 1.55/100 PYs. Among various subgroups, cirrhotic patients not achieving SVR had the highest risk of HCC, with an annual incidence of 6.61/100 PYs.

Landmark analyses at years 2 and 5 were performed to evaluate the impact of SVR on the risk of HCC and death or transplantation. At the 2-year landmark, patients achieving SVR within 2 years of the diagnosis of HCV infection showed a significantly lower risk of HCC (0.62/100 PYs) and risk of death or transplantation (0.44/100 PYs) than patients who did not achieve SVR (1.35/100 PYs and 1.88/100 PYs),
respectively (Fig. 5A and C). At the 5-year landmark, patients achieving SVR within 5 years of HCV diagnosis had a significantly lower risk of HCC (0.41/100 PYs) and death or transplantation (0.27/100 PYs) than patients not achieving SVR (1.20/100 PYs and 0.99/100 PYs), respectively (Fig. 5B and D).

**DISCUSSION**

The present study comprehensively explored the changes in the HCV care cascade and current status, including HCV testing, linkage to care, and treatment and long-term prognosis for the past 20 years from the data of a tertiary referral hospital (Table 3).

The overall seroprevalence of anti-HCV-positivity was 1.8% in the present study, which was higher than that of population studies. This may be from the nature of our hospital cohort and the age distribution in the present study since the seroprevalence increases with age. Our hospital is a tertiary referral and transplant center, where about 400 cases of liver transplantation are performed annually. Therefore, patients with comorbidities and advanced liver disease due to HCV were included in the present study. However, the recent decreasing trend in the seroprevalence of anti-HCV-positivity in the present study is in line with previous reports.

In this study, 69.6% of anti-HCV-positive patients underwent HCV RNA testing. This rate is higher than that in previous studies (27.8% to 42.9%). Reasons for not undergoing HCV RNA testing can be postulated based on the characteristics of these patients. First, anti-HCV-positive patients not undergoing HCV RNA testing tended to have a lower mean ALT level (33 U/L) and a greater proportion of normal ALT levels (81.7%) than those with HCV infection (78 U/L and 46.5%). Physicians might have misconceptions that a normal ALT reflects a lack of liver damage, thereby not requiring further tests.

Second, 24.5% of patients without HCV RNA testing were diagnosed with non-HCC malignancy at the time of anti-HCV-positivity. Presumably, these patients underwent testing to prepare for invasive procedures or surgery for treating underlying malignancy. Therefore, further
HCV evaluation might not be prioritized in these patients. Third, among these patients without non-HCC malignancy, 44.1% and 23.6% underwent anti-HCV testing in surgery departments and health check-up, respectively. This suggests a low referral rate to hepatology from other departments, which is a well-known barrier in the HCV care cascade.\textsuperscript{14,15}

Interestingly, older patients and patients with non-HCC malignancy tended not to undergo HCV RNA when they showed normal ALT. This may be affected by physicians’ individual perception about prioritization of comorbidities that patients have at the time of testing. In contrast, patients with cirrhosis or a history of HCC were more likely to undergo HCV RNA testing despite normal ALT. This phenomenon appears reasonable. Regardless of ALT level, HCV confirmatory test should have been conducted since HCV infection is a major cause of cirrhosis and HCC.

An encouraging change over the past 20 years is that the linkage time from anti-HCV-positivity to HCV RNA testing has dramatically improved. This continuous improvement might be partly due to the advancement of the general caring system and increase in HCV infection awareness among physicians in our center, albeit the level of awareness is still unsatisfactory. The linkage time from HCV diagnosis to antiviral treatment has also markedly decreased since 2015, when all-oral DAA was introduced. In the pre-DAA era, several clinical aspects had to be considered to select a good candidate for interferon treatment and liver biopsy was usually required. However, in the post-DAA era, the decision process for treatment has been simplified and liver biopsy is generally no longer necessary.

As HCV infection progresses to chronic liver disease, liver cirrhosis, or HCC, early detection is associated with improved outcomes.\textsuperscript{16} We found that 14.3% and 22.6% of patients with HCV infection had liver cirrhosis and HCC at the time of diagnosis, respectively. This prevalence of advanced liver disease was higher than previous studies, was higher than previous studies. Because our cohort was from tertiary referral and transplant center. Our study showed that the average treatment uptake rate for the past 20 years was 35.4% in patients without HCC. The treatment uptake rate was slightly higher in the post-DAA era.

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**Table 3. Summary of Key Metrics of HCV Care Cascade Steps**

| Cascade steps | Metric | Results |
|---------------|--------|---------|
| Anti-HCV testing, % | Anti-HCV-positivity, mean (range) | 1.8 (0.9–2.2) |
| | Performed HCV RNA testing, mean (range) | 69.6 (65.4–72.4) |
| | HCV RNA positivity, mean (range) | 65.7 (55.7–83.2) |
| | Distribution of HCV genotypes | 1b 48.4 |
| | | 2 45.3 |
| | Linkage time for HCV RNA from the detection of anti-HCV-positivity, median | Before 2010 7.5 |
| | | 2010–2014 3.0 |
| | | After 2015 1.0 |
| | Linkage time for antiviral treatment from confirmed HCV infection, median | Before 2010 226 |
| | | 2010–2014 192 |
| | | After 2015 84 |
| | Liver disease status at the time of HCV diagnosis | Chronic hepatitis, mean proportion | 63.1 |
| | | Liver cirrhosis, mean proportion | 14.3 |
| | | HCC, mean proportion | 22.6 |
| | Rate of antiviral treatment (without HCC) | Before DAA-era 33.9 |
| | | DAA-era 38.9 |
| | SVR rate | Interferon-based regimen 71.2 |
| | | DAA-based regimen 93.1 |
| | Annual incidence of HCC | With SVR 1.02 |
| | | Without SVR 2.14 |
| | Annual incidence of death or transplantation | With SVR 0.55 |
| | | Without SVR 4.34 |

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; DAA, direct antiviral agents; SVR, sustained virological response.
(38.9%) than in the pre-DAA era (33.9%) and increased further up to 45.2% recently. This appears to be unsatisfactory considering the high effectiveness of DAA. However, Nam et al. also reported a slight difference in treatment uptake rate between pre-DAA (52.8%) and post-DAA (56.1%) eras. Reasons for the lack of a remarkable increase in the treatment uptake rate might be complex. Physicians might not recommend HCV treatment to patients who are older or have several comorbidities. The Korean national health insurance covers DAA in patients with serologically confirmed HCV who are treatment-naive or interferon-experienced since 2015. However, these reimbursement criteria are applied only once in a lifetime, indicating no further coverage in case of DAA failure. Despite the coverage by the Korean national insurance, DAA costs are still expensive, amounting to about $3,000. Moreover, the poor HCV care referral system may still contribute to this relatively low treatment uptake rate. Therefore, expanding the reimbursement criteria and reducing DAA costs will increase the treatment uptake rate in Korea.

Another expected finding was that the treatment pattern has also changed since the introduction of DAA. Interferon use markedly decreased, and DAA use sharply increased after 2015.

Regarding the long-term prognosis of patients with HCV infection, it is well-known that liver cirrhosis, old age, not achieving SVR, and coinfection with HBV are associated with a higher risk of HCC and death or transplantation. Our large-scale cohort confirmed these findings and showed that earlier SVR achievement after HCV diagnosis is associated with a lower risk of HCC.

Further interventions could be implemented to apply a more effective care cascade for HCV. Recently, pilot studies examined the effectiveness of alarm systems or automatic response systems to increase the uptake of HCV diagnosis. We also developed an automatic alarm system with reflex testing in patients being admitted to our hospital. For example, if a patient is anti-HCV positive without previous HCV RNA testing in our electronic medical record database, the laboratory will perform an HCV RNA test on the same specimen. If the HCV RNA test comes back positive, a notification will be sent to an attending physician recommending a hepatology department consultation. This will enhance the HCV link to care, and more patients who are unaware of their HCV infection will be diagnosed and treated. However, this reflex system did not permit us to show the improvement in the HCV care due to the recent introduction in our center.

Our study has several strengths. First, we analyzed patients with HCV infection and anti-HCV-positive patients who did not undergo HCV RNA testing. Therefore, we could evaluate the prevalence and characteristics of patients not tested for HCV RNA and where these patients were lost in the process of HCV diagnosis. Second, our study included about 10,000 HCV-infected patients, the largest cohort so far in Korea. Third, we showed serial changes in the important metrics of the HCV care cascade, including linkage times for HCV RNA testing from anti-HCV positivity and HCV treatment from diagnosis. In addition, we were able to analyze patient flow between various departments after detecting anti-HCV positivity. Therefore, we could identify where the patients were missed in the care cascade. Lastly, we investigated the long-term prognosis of more than 5,000 patients with HCV infection.

However, our study also has limitations. First, our cohort was derived from a tertiary referral hospital where liver transplantation was available. Therefore, our results might differ from the results of a population-based study. However, considering the lack of universal screening for HCV infection in Korea, increasing awareness of HCV diagnosis and treatment uptake in tertiary referral or university-setting hospitals could prevent further disease transmission and progression from HCV infection. Second, patients who underwent HCV RNA testing outside our hospital could not be captured in our database. Therefore, patients in whom HCV infection was confirmed in other hospitals may have been categorized as those not receiving HCV RNA testing if they did not repeat HCV RNA testing in our hospital.

In conclusion, the seroprevalence of anti-HCV and linkage times for HCV RNA testing from anti-HCV positivity and for treatment from HCV diagnosis have been decreasing for the past 20 years. However, the rates of HCV RNA testing in anti-HCV-positive patients have shown little improvement. The uptake of treatment began to increase in the post-DAA era. To enhance the care cascade of HCV infection, more effort should be put into developing a systematic approach to change the status quo.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: J.C., J.P. Data curation: J.C., J.P. Formal analysis: J.C. Methodology: J.C., J.P. Project administration: J.C., J.P. Visualization: J.C. Writing - original draft:
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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl210416.

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