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ORIGINAL ARTICLE

The change in the nationwide seroprevalence of hepatitis C virus and the status of linkage to care in South Korea from 2009 to 2015

Eun Sun Jang[1] · Moran Ki[2] · Hwa Young Choi[2] · Kyung-Ah Kim[3] · Sook-Hyang Jeong[1] · The Korean hepatitis epidemiology study group

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Abstract

Background Hepatitis C virus (HCV) requires epidemiological monitoring to estimate its disease burden and to develop countermeasures. This study aimed to investigate the difference between the 2015 and 2009 nationwide anti-HCV seroprevalence and to determine linkage to care estimates in South Korea.

Methods A total 268,422 examinees ≥ 20 years old were included in 2015 from 33 medical institutions nationwide. Electronically extracted data were retrospectively analyzed to calculate the age-, sex-, and area-adjusted anti-HCV prevalence. Seroprevalence in 2015 was measured using the same method as that in 2009. For anti-HCV-positive subjects, medical records were reviewed to see whether HCV RNA testing or antiviral treatment was performed.

Results Adjusted anti-HCV prevalence was 0.60% (95% confidence interval, 0.57–0.63) based on general Korean population in 2015. It showed an increasing trend according to age; 0.23% in thirties, 0.38% in forties, 0.63% in fifties, 1.08% in sixties, and 1.65% in those aged ≥ 70 years. From 2009 to 2015, the adjusted anti-HCV prevalence decreased by 30%, with odds ratio of 0.70 (95% CI 0.70–0.71). There was significant intranational regional variation and changing pattern of seroprevalence. Among 1359 anti-HCV-positive subjects, HCV RNA test was performed in 60% and 25.4% had positivity. Treatment-initiated and cured rates in 2015 were 18.5% and 10.9%, respectively.

Conclusions Anti-HCV prevalence in South Korea was 0.6% in 2015, showing a 30% decrease from that in 2009. Although the HCV RNA testing rate was increased since 2009, this remains suboptimal. Moreover, the treatment uptake rate should be improved in South Korea.

Keywords Hepatitis C virus · Epidemiology · Prevalence · Anti-HCV · HCV RNA · Antiviral treatment

Abbreviations

HCV	Hepatitis C virus
RNA	Ribonucleic acid
DAA	Direct acting antiviral drug
SVR	Sustained virologic response
AST	Aspartate aminotransferases
ALT	Alanine aminotransferases
GGT	Gamma-glutamyl transferase
CI	Confidence interval
HLA	Human leukocyte antigen
IL	Interleukin

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The members of the Korean hepatitis epidemiology study group are listed in the Acknowledgements section.

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✉ Sook-Hyang Jeong
jsh@snubh.org

[1] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro, 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, South Korea

[2] Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Gyeonggi, South Korea

[3] Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Gyeonggi, South Korea

Background

Since a clone of hepatitis C virus (HCV) genome and its detecting antibody have been identified in 1989 [1], the global incidence of HCV infection began to decline with improved transfusion blood screening, safer injection practices, and development of antiviral therapeutics. In 2013, the global prevalence of anti-HCV was 1.6% (1.3–2.1%), corresponding to 115 million persons, and the HCV ribonucleic acid (RNA) prevalence was 1.1%, corresponding to 80 million (64–103) viremic persons [2]. According to the updated modelling study in 2015, global HCV viremic prevalence was estimated to be 1.0%, corresponding to 71.1 million (62.5–79.4) persons [3], showing a decreasing trend.

However, HCV transmission persists mostly due to unsafe injection practices in healthcare and drug use. In 2015, the estimated number of newly infected persons ($n = 1.75$ million) exceeded the estimated number of persons dying from end-stage HCV infection ($n = 399{,}000$) or the number being cured ($n = 843{,}000$), resulting in an increasing global trend [4]. Therefore, continuous monitoring of HCV epidemiology is important to assess the HCV-related disease burden and to develop an optimal strategy for eliminating HCV by 2030, as suggested by the World Health Organization (WHO) agenda [5].

Although direct acting antiviral drug (DAA) therapy showed high efficacy with over 90% of real-life sustained virologic response (SVR) rate, elimination of HCV remains difficult due to lower rates of diagnosis, suboptimal linkage to care, and limited access to DAA therapy [3, 6]. According to United States data prior to 2015, 38–57% of anti-HCV-positive adults did not receive HCV RNA test; only 13–18% had received antiviral therapy [7, 8]. In Asia–Pacific countries including South Korea, linkage to care rate and related cost-effectiveness of anti-HCV treatment remain unclear.

Since the nationwide anti-HCV prevalence in South Korean adults was reported in 2009 [6], a few regional outbreaks of HCV infection related to unsafe healthcare injection developed, casting great concerns of increasing incidence and prevalence of HCV infection. This prompted a need to evaluate the prevalence of HCV and analyze its trend since 2009. Thus, the aim of this study was (1) to investigate the updated nationwide anti-HCV prevalence in 2015 and (2) to compare the seroprevalence between 2009 and 2015. Another aim of this study was to determine linkage to care of HCV infection among the anti-HCV-positive persons in South Korea.

Methods

Subjects and data collection

Initially, data of 323,892 health-check examinees with a Korean domestic address who visited 33 health checkup centers were electronically retrieved from each institution. The 33 centers were in 9 provinces, 6 metropolitan cities, and 1 capital city of South Korea on a national scale. Of them, 5049 individuals aged < 20 years and 50,421 who were not checked for anti-HCV were excluded. Finally, a total of 268,422 subjects were included for analysis of the age-, sex-, and area-adjusted anti-HCV prevalence. Demographic data, including age, sex, current address, and laboratory results, were collected electronically in each study site in accordance with the predefined case reporting form.

Serological and biochemical tests in the collected data

Anti-HCV antibody was tested using a third-generation enzyme immunoassay at each certified laboratory according to the manufacturer's instruction.

Second-stage evaluation of anti-HCV-positive subjects

For subjects with positive anti-HCV, qualitative/quantitative HCV RNA concentration in blood, HCV genotype, and history or prescription of antiviral therapy before or after the health-check examination was collected by medical record review. For those who had undergone antiviral treatment, we recorded whether SVR was achieved.

Statistical analysis

To calculate the age-, sex- and area-adjusted anti-HCV prevalence in 2015, the estimated population of 2015 by Korea National Statistical Office was used. The estimated prevalence was weighted according to age, sex, and regions to match the estimates of the distribution of these factors [9]. Positive rates by age, sex, and area were compared using Pearson's χ^2 test.

A previous study in 2009 included 291,314 adult health-check examinees in 29 centers had been conducted as the same way to this study. [6] Of 29 centers, the same 26 institutions were included in this 2015 survey, and 2 institutions were replaced with the others in the rural area of the same regions. Other 3 institutions were newly recruited from Gangwon and Jeonnam where the number of subjects was relatively small in the previous survey.

The participated institutions in the 2009 and 2015 surveys were compared in Supplementary Table 2. To compare the seroprevalence in 2009 with that in 2015, we used the standard population of year 2009.

The ratios of anti-HCV prevalence (year 2015/year 2009) were described with 95% confidence interval (CI). Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Anti-HCV prevalence rates according to age, sex, and regions in South Korea, 2015

As shown in Table 1, the age-, sex-, and area-adjusted anti-HCV prevalence was 0.60% (95% CI 0.57–0.63), which was adjusted for the 2015 South Korean population. Males (0.54%) and females (0.66%) showed similar adjusted prevalence ($p = 0.20$). The seroprevalence showed an increasing trend with age; 0.23% in their thirties, 0.38% in forties, 0.63% in fifties, 1.08% in sixties, and 1.65% in those aged ≥ 70 years ($p < 0.001$).

Table 1 Crude and adjusted anti-HCV seroprevalence among health-check examinees in 2015, South Korea

	Standard population	No. of health-check examinees	No. of subjects with positive anti-HCV	Crude rate (%)	Adjusted rate (%)	*p* value
Sex						
Male	19,595,002	161,017	792	0.49	0.54[a]	0.2
Female	20,033,409	107,405	567	0.53	0.66[a]	
Age						
20–29	6,413,832	8853	14	0.16	0.24[b]	< 0.001
30–39	7,394,623	42,139	87	0.21	0.23[b]	
40–49	8,482,862	82,701	285	0.34	0.38[b]	
50–59	8,009,071	91,670	498	0.54	0.61[b]	
60–69	4,876,816	32,499	309	0.95	1.06[b]	
70+	4,451,207	10,560	166	1.57	1.63[b]	
Area						
Seoul	7,870,641	63,941	378	0.59	0.61[c]	< 0.001
Busan	2,799,131	8608	80	0.93	0.88[c]	
Daegu	1,945,475	8009	40	0.50	0.53[c]	
Incheon	2,241,152	15,602	75	0.48	0.43[c]	
Gwangju	1,142,407	3475	24	0.69	0.75[c]	
Daejeon	1,185,708	4913	26	0.53	0.60[c]	
Ulsan	886,758	22,761	76	0.33	0.36[c]	
Gangwon	1,209,120	14,836	47	0.32	0.43[c]	
Gyeonggi	9,376,591	63,921	270	0.42	0.43[c]	
Chungbuk	1,226,148	4174	26	0.62	0.62[c]	
Chungnam	1,755,544	16,244	44	0.27	0.28[c]	
Gyeongbuk	1,434,968	10,444	37	0.35	0.96[c]	
Gyeongnam	1,417,016	8084	56	0.69	0.89[c]	
Jeonbuk	2,123,872	10,942	74	0.68	0.72[c]	
Jeonnam	2,559,114	9803	82	0.84	0.81[c]	
Jeju	454,766	2665	24	0.90	1.54[c]	
Total	39,628,411	268,422	1359	0.51	0.60[d]	

The standard population of year 2015 was used

[a]Adjusted rate for age and area

[b]Adjusted rate for sex and area

[c]Adjusted rate for age and sex

[d]Adjusted rate for age, sex and area

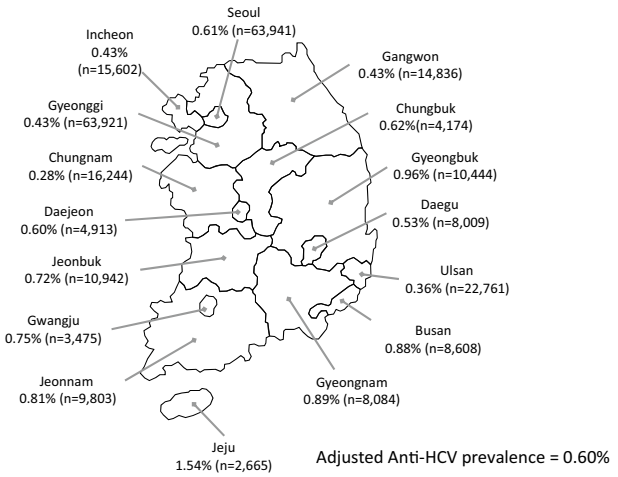

Fig. 1 Map of South Korea showing age- and sex-adjusted anti-HCV prevalence in 2015

By region, the anti-HCV prevalence showed a significant difference (Table 1 and Fig. 1). Jeju showed the highest prevalence, followed by Gyeongbuk (0.96%), Gyeongnam (0.89%), Busan (0.88%), Jeonnam (0.81%) and others. Chungnam (0.28%) showed the lowest prevalence.

Change of anti-HCV prevalence from 2009 to 2015 according to age, sex, and regions in South Korea

For the comparison of anti-HCV prevalence between 2009 and 2015, the anti-HCV-positive rates in 2015 were re-adjusted with a standard population in 2009. The adjusted anti-HCV prevalence in 2015 decreased by 30% (0.7, 95% CI 0.70–0.71) compared with that in 2009 with significant regional variation and dynamically changing regional pattern (Table 2). The age- and region-adjusted seroprevalence in males showed a greater reduction (34%) than in females (26%). Among the age groups, those in their thirties revealed the most prominent decrease in sex- and region-adjusted prevalence (0.57, 95% CI 0.56–0.58).

Notably, the pattern of regional distribution of anti-HCV prevalence had changed during the past 6 years. Seroprevalence was decreased in most regions from 2009 to 2015, with Gyeongnam, Chungnam, Gangwon, Busan, and Jeonbuk showing marked decrease; however, anti-HCV prevalence in Seoul—the capital city—remained unchanged. In contrast, Jeju showed a remarkable increase with respect to the age- and sex-adjusted anti-HCV prevalence in 2015 (1.37%) compared with 2009 (0.26%), which showed about 5 times increase (5.35, 95% CI 5.00–5.72). Moreover, Chungbuk showed an increased prevalence in 2015 (0.61%) compared with that in 2009 (0.50%).

Table 2 Comparison anti-HCV seroprevalence between 2009 and 2015, South Korea

	Adjusted anti-HCV-positive rates		Adjusted seroprevalence ratio (year 2015/year 2009)	
	Year 2015	Year 2009	Ratio	95% CI
Sex[a]				
Male	0.49[a]	0.74[a]	0.66	0.66–0.67
Female	0.61[a]	0.83[a]	0.74	0.74–0.75
Age[b]				
20–29	0.24[b]	0.34[b]	0.72	0.71–0.73
30–39	0.23[b]	0.41[b]	0.57	0.56–0.58
40–49	0.38[b]	0.60[b]	0.64	0.63–0.65
50–59	0.63[b]	0.80[b]	0.78	0.77–0.79
60–69	1.08[b]	1.53[b]	0.71	0.69–0.71
70+	1.64[b]	2.31[b]	0.70	0.70–0.71
Area[c]				
Seoul	0.54[c]	0.54[c]	1.00	0.99–1.02
Busan	0.81[c]	1.53[c]	0.52	0.52–0.53
Daegu	0.49[c]	0.69[c]	0.70	0.68–0.72
Incheon	0.40[c]	0.51[c]	0.79	0.76–0.81
Gwangju	0.68[c]	0.93[c]	0.73	0.72–0.76
Daejeon	0.61[c]	0.80[c]	0.75	0.73–0.78
Ulsan	0.32[c]	0.50[c]	0.64	0.61–0.67
Gangwon	0.40[c]	0.78[c]	0.51	0.50–0.53
Gyeonggi	0.37[c]	0.53[c]	0.70	0.69–0.71
Chungbuk	0.61[c]	0.50[c]	1.22	1.18–1.26
Chungnam	0.28[c]	0.64[c]	0.44	0.42–0.46
Gyeongbuk	0.90[c]	0.98[c]	0.92	0.89–0.94
Gyeongnam	0.86[c]	2.07[c]	0.41	0.40–0.42
Jeonbuk	0.66[c]	1.20[c]	0.55	0.54–0.56
Jeonnam	0.73[c]	1.08[c]	0.67	0.66–0.69
Jeju	1.37[c]	0.26[c]	5.35	5.00–5.72
Total[d]	0.55[d]	0.78[d]	0.70	0.70–0.71

The standard population of year 2009 was used to estimate the adjusted seroprevalence in 2009 and 2015 to compare two rates

[a]Adjusted rate for age and area

[b]Adjusted rate for sex and area

[c]Adjusted rate for age and sex

[d]Adjusted rate for age, sex and area

Pattern of the changed anti-HCV prevalence from 2009 to 2015 according to regions in South Korea

Interestingly, in Busan and Jeonnam, which were previously the two highest prevalence regions [10], the most remarkable decrease was observed in male in their thirties residing in Busan (1.96% in 2009 vs. 0.15% in 2015, Supplementary Table 1), while elderly female older than 60 years residing in Jeonnam showed a similarly high anti-HCV positivity

without significant changes (60s, 3.56% in 2009 vs. 2.11% in 2015; 70s 1.27% in 2009 vs. 2.31% in 2015, Supplementary Table 1). Moreover, the decrease of anti-HCV positivity in the other highly prevalent area (Gyeongnam and Jeonbuk) was also observed only in male.

In contrast, the anti-HCV prevalence in Jeju and Chungbuk increased from 2009 to 2015; however, the increase was significant only in male in these two areas. In Jeju, the anti-HCV-positive rates of male in their forties, sixties, and seventies were increased by 3.52-fold in 2015 compared with 2009 (0.29% in 2009 vs. 1.02% in 2015, $p=0.016$, Table 3); however, the change in female was not significant ($p=0.067$). In Chungbuk, the highest increase was observed in male, especially in those in their thirties (0.25% in 2009 vs. 0.68% in 2015) and forties (0.24% in 2009 vs. 0.78% in 2015, Table 3).

Linkage to care among anti-HCV-positive health-check examinees in 2015

Among the 1359 anti-HCV-positive subjects who were tested in 2015, HCV RNA testing was performed in 776 (57.1%, Fig. 2). Among these 776 patients, 448 (57.7%) had already undergone HCV RNA testing prior to the examination, while 328 (42.3%) underwent HCV RNA testing for the first time after the examination (data not shown).

However, a detailed review of the medical records revealed that although 100 subjects received antiviral therapy, only 64 patients underwent the HCV RNA test (Fig. 2). We assumed that they likely underwent the HCV RNA test at another institution. Hence, we assumed that those with either the HCV genotype result or previous history of receiving antiviral therapy were HCV RNA-positive patients. Therefore, we regarded those with the result of HCV genotype and/or with a history of receiving antiviral therapy as HCV RNA-positive patients. As a result, the HCV RNA testing rate was 60% (815/1359) and viremic proportion was 42.3% (345/815, Table 4 and Fig. 3). The antiviral treatment initiation rate was 72.8% (251 of 345 showing positive HCV RNA, Table 4) which was 18.5% of 1359 anti-HCV-positive subjects (treatment-initiated rate, Fig. 3). SVR was achieved in 148 out of 185 subjects evaluated (80%), which was 10.9% of total anti-HCV-positive subjects (cured rate, Fig. 3); the SVR rate was 70.2% in genotype 1 and 81.1% in genotype 2 (Table 4).

Discussion

Our study demonstrated that the age-, sex-, and region-adjusted anti-HCV prevalence of South Koreans in 2015 was 0.6%, showing a 30% decrease from 2009. The seroprevalence rate gradually increased with age; 59.4% of anti-HCV-positive persons were in their fifties and sixties. The adjusted anti-HCV seroprevalence in male and female was similar. The area in South Korea with the highest anti-HCV prevalence in 2015 was Jeju (1.54%), followed by Gyeongbuk (0.95%), Gyeongnam (0.89%), and Busan (0.88%). Among the 1359 anti-HCV-positive persons, HCV RNA was tested in 60%, in whom HCV RNA-positive rate was 42.3%. Among the viremic patients, antiviral treatment—mostly based on the pegylated interferon and ribavirin—was undertaken in 72.8%, showing SVR rate of 80%.

Since we reported the nationwide anti-HCV prevalence in 2009 as 0.78% (adults aged 20 years or older), the National Health and Nutrition Examination Survey during the 2012–2014 period reported that anti-HCV prevalence in those aged 10 years or older was 0.62%, while the prevalence in those aged 20 years or older was 0.68% [11]. This study showed that the anti-HCV prevalence in those aged 20 years or older was 0.60% in 2015. Therefore, the anti-HCV prevalence in South Korea continuously decreased from 2009 to 2015 by 30%. This rapid decrease might be related with the death of elderly HCV infected patients who had > 2% of prevalence in 2009, a low incidence of new HCV infection, as well as with an increase of antiviral treatment for middle aged patients.

Our data showed a consistent trend of increasing anti-HCV prevalence with age; however, there was quite a dynamic change in the anti-HCV prevalence among regions from 2009 to 2015. Most regions showed a decreasing seroprevalence in 2015 compared with that in 2009 with marked reduction in Gyeongnam, Chungnam, Gangwon, Busan, and Jeonbuk, while Jeju showed an increase of about 5 times of the anti-HCV prevalence in 2015 compared with 2009.

The changed anti-HCV seroprevalence showed different patterns across various regions. In Busan and Jeonnam, the decreased seroprevalence was mainly observed in male. Previous studies showed that in Busan and Jeonnam, dock-worker contact, sharing razors, and multiple sexual partners were risk factors for HCV infection in male [12, 13], whereas cosmetic tattooing and acupuncture were risk factors in female [14]. Therefore, new infection among male may be decreasing, while it may persist in female; thus, a detailed study on the risk factors for HCV infection is required. In Jeju and Chungbuk, the increased anti-HCV prevalence was shown in middle aged male, which could be related to the change of population in those areas. In Jeju, a popular tourist destination, the population size rapidly increased with an explosion of foreign tourism and the migration from the other area in Korea during the past 6 years. According to official statistics, the population growth rate of Jeju had increased as 3.2% in 2015, compared to 1.6% in 2010. In this study population, the number of tested subjects in Jeju was increased in 2015 ($n=1564$) compared to in 2009 ($n=1371$) although the study institution was exactly the

Table 3 Anti-HCV-positive rates according to sex and age group in the region showing increased prevalence in 2015 compared to 2009, South Korea

Area	Age group	Male							Female						
		Year 2009			Year 2015			*p* value	Year 2009			Year 2015			*p* value
		No. of subjects	No. of subjects with positive anti-HCV	Anti-HCV positive rate (%)	No. of subjects	No. of subjects with positive anti-HCV	Anti-HCV positive rate (%)		No. of subjects	No. of subjects with positive anti-HCV	Anti-HCV positive rate (%)	No. of subjects	No. of subjects with positive anti-HCV	Anti-HCV positive rate (%)	
Chungbuk	20–29	69	0	0.00	79	1	1.27		74	0	0.00	55	0	0.00	
	30–39	408	1	0.25	292	2	0.68		324	0	0.00	185	0	0.00	
	40–49	843	2	0.24	645	5	0.78		562	2	0.36	508	1	0.20	
	50–59	712	7	0.98	899	7	0.78		523	1	0.19	637	4	0.63	
	60–69	323	2	0.62	414	1	0.24		260	4	1.54	246	3	1.22	
	70+	91	1	1.10	121	2	1.65		70	1	1.43	93	0	0.00	
	Subtotal	2446	13	0.53	2450	18	0.73	0.370	1813	8	0.44	1724	8	0.46	0.92
Jeju	20–29	34	0	0.00	43	0	0.00		44	0	0.00	31	0	0.00	
	30–39	375	0	0.00	252	1	0.40		258	0	0.00	212	0	0.00	
	40–49	397	1	0.25	530	4	0.75		272	0	0.00	358	0	0.00	
	50–59	318	1	0.31	466	2	0.43		277	2	0.72	305	2	0.66	
	60–69	180	1	0.56	205	5	2.44		164	0	0.00	145	1	0.69	
	70+	67	1	1.49	68	4	5.88		39	0	0.00	50	5	10.00	
	Subtotal	1371	4	0.29	1564	16	1.02	0.016	1054	2	0.19	1101	8	0.73	0.067

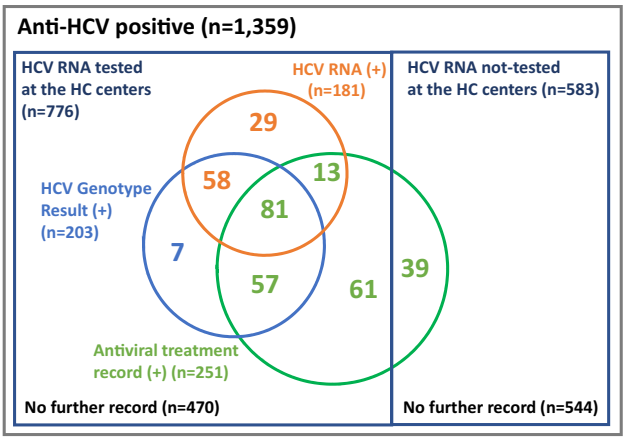

Fig. 2 HCV RNA, genotype and antiviral treatment status among 1,359 Korean anti-HCV-positive health-check examinees. For calculated rates in Table 4, 776 RNA tested subjects at the health-check center and 39 subjects who were not tested HCV RNA at the center but had history of antiviral treatment were considered as RNA-tested population ($n=815$). For RNA positivity, subjects with positive HCV RNA ($n=181$), detectable HCV genotyping ($n=7$) without antiviral treatment history, or history of antiviral treatment ($n=157$) without RNA result were considered as positive HCV RNA population ($n=345$). Orange circle, 181 HCV RNA-positive subjects; Blue circle, 203 HCV genotype-detected subjects, Green circle, 251 subjects with antiviral treatment record; HC, health-check center

Table 4 Virologic characteristics and antiviral treatment status of 1359 anti-HCV-positive health-check examinees in 2015, South Korea

	Calculated rates
RNA tested	815/1359 (60.0)
Positive RNA	345/815 (42.3)
Genotype 1/2/3	104/94/5
Antiviral treatment	251/345 (72.8)
Before health-check	170/251 (67.7)
Genotype 1/2/3[a]	69 (66.3)/68 (72.3)/1 (20)
Sustained virologic response rate	148/185 (80.0)
Genotype 1	40/57 (70.2)
Genotype 2	43/53 (81.1)
Genotype 3	1/1 (100)

For calculated rates, 776 RNA-tested subjects at the health-check center and 39 subjects who were not tested HCV RNA at the center but had history of antiviral treatment were considered as RNA-tested population ($n=815$). For RNA positivity, subjects with positive HCV RNA ($n=181$), detectable HCV genotyping ($n=7$) without antiviral treatment history, or history of antiviral treatment ($n=157$) without RNA result were considered as positive HCV RNA population ($n=345$) as shown in Fig. 2

[a]Percent is the proportion of treated subjects in each genotype

same. In Chungbuk, Sejong city was built in 2012 and most of the government offices moved from Seoul to the new city with about 2 times growth in the city-dwellers as well as a large floating population. Such population change may be related to the increase of anti-HCV prevalence in male in these areas.

Notably, the present study showed a nationwide HCV cascade of care in South Korea for the first time by providing a detailed review of medical records for 1359 anti-HCV-positive individuals. The HCV RNA testing rate had improved from 2009 (27.8%) [6] to 2015 (60.0%), though still not optimal. Considering the possibility that some of the anti-HCV-positive individuals may be tested for HCV RNA in other hospitals that did not participate in this study, this may be an underestimated figure. Marked increase of the HCV RNA testing rate suggests that doctors and health-check examinees may be more aware of the positive anti-HCV results [15]. Moreover, the use of first-generation DAA that had started in 2014 and the scale-up of reimbursement strategy for DAA therapy in 2015 might result in increased testing rates, similar to other countries [16].

In the present study, the RNA-positive rate in tested subjects was 42.3%. In a recent US study that screened 17,149,140 subjects from 2 large national laboratory companies, viremic patients accounted for 57.4% (914,285/1,592,984) of anti-HCV-positive subjects [17]. Another study from Spain, where anti-HCV seroprevalence (0.6–2.6%) is similar to South Korea, revealed RNA-positive rate of 43.3% (0.49% of the total study population) [18], which is similar to the results in this study. The Korea National Health and Nutrition Examination Survey, which included 17,764 South Korean representative subjects, showed a HCV RNA-positive rate of 32.5% in 2012–2014 [11], which is lower than that shown in this study.

Asian HCV patients, compared with their Caucasian counterparts, showed a higher spontaneous viral clearance rate or favorable antiviral treatment response rate due to genetic factors, including human leukocyte antigen (HLA) type or interleukin (IL) -28B single nucleotide polymorphism [19–22]. Nonetheless, the RNA-positive rate of this study could be underestimated because healthcare centers are generally located separately from the hepatology unit; hence, some of the anti-HCV-positive subjects may not have visited the hepatology unit in the same hospital and ended up undergoing the HCV RNA testing in another hospital. Moreover, some subjects who already were treated and achieved sustained virologic response did not visit the hepatology unit in the same hospital. A similar phenomenon was observed in terms of antiviral treatment rate in this study (18.5%), suggesting the possibility of underestimation [6, 23, 24].

To the best of our knowledge, this study showed for the first time the estimation of HCV linkage of care in South Korea, which is similar or slightly higher than the previous report from Canada (56% had tested for HCV RNA, and 12% initiated antiviral treatment [25]) or the United States (54% of RNA testing rate, and 32% of antiviral treatment rate [8]).

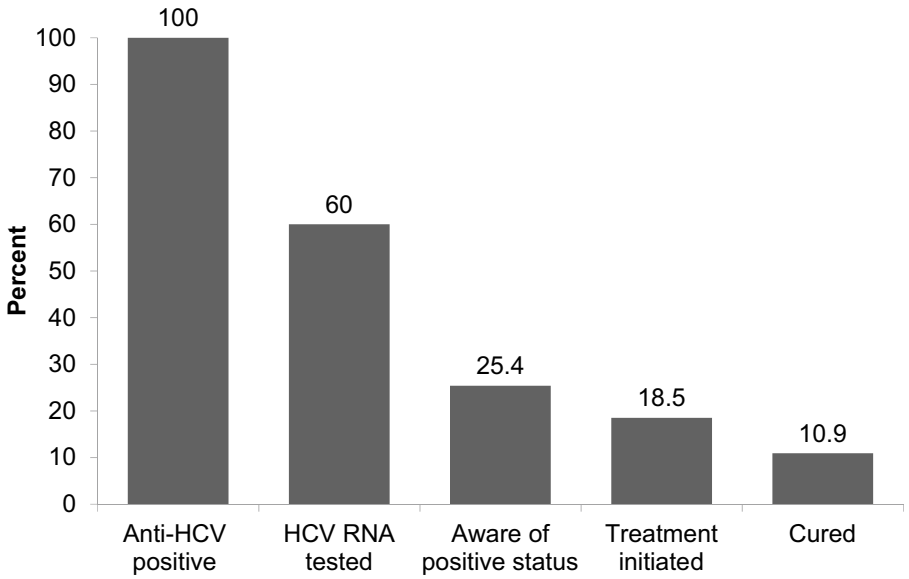

Fig. 3 Cascade of care in 1359 anti-HCV subjects of South Korea in 2015. For these calculated rates, subjects with positive RNA results, detectable HCV genotype, or history of antiviral treatment were considered as positive HCV RNA population. HCV RNA tested rate was the ratio of the number of subjects who tested for HCV RNA ($n=815$) to total anti-HCV-positive subjects ($n=1359$). The aware of positive status rate was the ratio of the number of subjects with positive HCV RNA ($n=345$) to total anti-HCV-positive subjects. The treatment-initiated rate was the ratio of the number of subjects with the antiviral treatment record ($n=251$) to total anti-HCV-positive subjects. The cured rate was the ratio of the number of subjects with successful sustained virologic response after antiviral treatment ($n=148$) to total anti-HCV-positive subjects

A more recent report from England showed a much higher HCV RNA testing (77%) and antiviral treatment uptake (21.4%) rates after the adoption of DAA therapy [26]. In South Korea, considering that the DAA therapy had been significantly increased since August 2015, and our data are from 2015, the linkage to care rate in 2019 is expected to be higher.

Our study has some limitations. First, HCV RNA test and antiviral treatment record were not complete because this data were retrospectively obtained in healthcare centers. Although retrospective follow-up had been tried for anti-HCV-positive patients, it was successful only for 776 (57.1%) subjects because a significant portion of healthcare examinees did not receive a subsequent confirmative test in the same hospital. Therefore, the HCV RNA testing rate and the treatment uptake rate may have been underestimated in this study. Contrastingly, the treatment initiation rate in our data might be overestimated because the participating centers were secondary or tertiary hospitals with hepatologists, who were highly dedicated to providing anti-HCV treatment, compared with those in primary care settings. Second, the health-check examinees might be not fully representative because some symptomatic patients were included. However, most symptomatic patients in Korea usually visit outpatient clinic firstly because the cost of health checkup is about three times more than laboratory test in the medical clinic which is reimbursable with National Health Insurance. Moreover, all employees should take a regular health checkup annually or biannually under Korean healthcare policy. Thus, health-check examinees in Korea are mostly representative of general population, especially in the middle age. Thirdly, the institutions we included in this study were not exactly same between 2015 and 2009 (Supplementary Table 2). We replaced a few institutions of 2009 survey from capital area to rural area in 2015 survey where more subjects were elderly and possibly had higher anti-HCV prevalence. However, the result showed that with a decrease of anti-HCV prevalence in 2015, the potential problem of the change of study institution between 2 surveys might be not critical in this study result. To minimize the potential selection bias with the visit for health checkup, we adjusted the number of subjects based on the age- and sex-specific composition of the general population. Thirdly, the address of health-check examinees was based on electronic medical records; therefore, their actual residence may have been different. Lastly, in-depth epidemiological investigation about behavioral risk factors was not performed due to the retrospective, cross-sectional design.

In conclusion, the anti-HCV prevalence in South Korea was 0.6% in 2015, showing a 30% decrease from that in

2009. Although the HCV RNA testing rate was increased since 2009, this remains suboptimal. Moreover, the treatment uptake rate should be improved in South Korea.

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Compliance with ethical standards

Conflict of interest Eun Sun Jang, Moran Ki, Hwa Young Choi, Kyung-Ah Kim and Sook-Hyang Jeong have nothing to declare.

Ethical approval The study protocol was reviewed and approved by the institutional review board of each hospital.

Informed consent Requirement for informed consent was waived due to the retrospective nature of this study.

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