

## Review Article

# Hepatitis C infection in hemodialysis patients in Iran: A systematic review

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### Abstract

Hemodialysis (HD) patients are recognized as one of the high-risk groups for hepatitis C virus (HCV) infection. The prevalence of HCV infection varies widely between 5.5% and 24% among different Iranian populations. Preventive programs for reducing HCV infection prevalence in these patients require accurate information. In the present study, we estimated HCV infection prevalence in Iranian HD patients. In this systematic review, we collected all published and unpublished documents related to HCV infection prevalence in Iranian HD patients from April 2001 to March 2008. We selected descriptive/analytic cross-sectional studies/surveys that have sufficiently declared objectives, a proper sampling method with identical and valid measurement instruments for all study subjects, and proper analysis methods regarding sampling design and demographic adjustments. We used a meta-analysis method to calculate nationwide prevalence estimation. Eighteen studies from 12 provinces (consisting 49.02% of the Iranian total population) reported the prevalence of HCV infection in Iranian HD patients. The HCV infection prevalence in Iranian HD patients is 7.61% (95% confidence interval: 6.06–9.16%) with the recombinant immunoblot assay method. Iran is among countries with low HCV infection prevalence in HD patients.

**Key words:** Hepatitis C, hemodialysis, prevalence, Iran

## INTRODUCTION

Hepatitis C virus (HCV) infection is one of the main health problems worldwide.<sup>1–3</sup> Hemodialysis (HD) patients belong to high-risk groups for HCV infection and have a significantly higher HCV prevalence than the general population.<sup>4,5</sup> HCV infection has been recognized as an emerging problem in dialysis patients and its prevalence varies considerably among different regions of the world. HD patients are at a risk of HCV infection due to

some factors such as impairment of their cellular immunity, blood transfusion, frequent hospitalization, and underlying diseases such as diabetes or chronic renal failure. These factors increase chances of exposure to nosocomial infection.<sup>6,7</sup> HCV has an impact on the life expectancy of HD patients. HD patients with HCV infection have 1.4 times more chance of dying than uninfected HD patients.<sup>8</sup>

The percentage of HCV prevalence in HD patients varies across several countries and even across dialysis centers.<sup>9</sup> HCV infection prevalence in HD patients is between 7% and 40% in some developed countries.<sup>10,11</sup> HCV infection prevalence in Iranian HD patients is higher than that in the general population.<sup>12,13</sup> This infection prevalence varies widely from 5.5% to over 24% among different Iranian provinces.<sup>13–15</sup>

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We do not have an overall estimation of HCV infection prevalence in HD patients in Iran. Current studies have reported HCV infection prevalence in specific regions or selected groups. The overall estimation of HCV infection in the general population will help health policymakers create or modify prevention programs for Iranian HD patients. In the present systematic review, we have reviewed papers and reports related to HCV infection prevalence in an Iranian general population.

## MATERIAL AND METHODS

We estimated the prevalence of HCV in an Iranian general population in a comprehensive systematic review of literature and evidences, followed by integration of data and analysis of the findings.

### Study question

Our study population comprised an Iranian general population, and the desired outcome was the presence of a positive HCV antibody in blood samples of the study population, based on any blood test such as enzyme-linked immunosorbent antibody (ELISA) or recombinant immunoblot assay (RIBA)/polymerase chain reaction (PCR), although other laboratory tests have not been identified clearly, from April 2001 to March 2008.

### Search strategy

For electronic and hand search, we used key words such as "Hepatitis C," "HCV," and "Iran" (or names of its provinces) in the titles and/or the abstracts as MeSH words. We also used different textwords (specifically when searching national databases) to increase the sensitivity of the search. After obtaining all papers on HCV prevalence in Iran, we used the word "hemodialysis" for extracting related papers on the prevalence of HCV in hemodialysis patients.

### Electronic databases

We searched 15 electronic databases of health and biological sciences including Google Scholar, ISI, Scopus, EMBASE, Medline, WHO, CINAHL, DOAJ, CABI, High-Wire Press, EBM Review, EMRmedex, Cochrane, NLM Gateway, and DARE. Furthermore, four Iranian databases of the medical and life sciences literature were used, including Iranmedex, SID, Magiran, and IranDoc. Hence, the study covered all registered and certified life sciences and medical journals at the national level.

## Gray literature search

In the gray literature search, we found 243 national, regional, and international Iranian medical science congresses in the study time period. Sixty-seven out of 243 relevant congress' abstract books were selected and hand searched by 2 independent reviewers. We also searched the research projects of 29 out of 40 Iranian universities of medical sciences from their websites. We contacted the Center for Diseases Control (CDC) of the Iran Ministry of Health and Iran Blood Transfusion Organization (IBTO) for searching national reports in the study time period. Medical students' theses were also evaluated by 2 independent reviewers from the Iranian center for scientific documents and records (IranDoc). Finally, we consulted 8 experts in HCV researchers in Iran and searched their personal archives for additional citations. Forward and backward citations of the searched items were also performed.

## Critical appraisal and selection of studies

We revised the criteria developed by V. Sharifi et al (unpublished data) for this purpose. All citations were reviewed thoroughly by 2 independent reviewers and checked for eligibility criteria to include the studies in the analysis. The inclusion criteria were all descriptive/analytical cross-sectional studies/surveys that has specified temporal and geographic specifications of the study, sufficiently declared objectives, proper sampling methods that could generalize findings to the target population with valid measurement instruments for all study subjects, and proper analysis methods regarding the sampling design and demographic properties. Studies that did not fulfill these specifications were not included in our meta-analysis due to low quality.

## Data extraction

After study evaluation, we included studies and extracted findings to excel spreadsheets. The extracted data included the year of the study, first author, province and district of the study, sample population, sampling method, sample size, HCV antibody detection method, HCV antibody kit name, mean age and standard error (SE) of subjects, percentage of male subjects, HCV point prevalence in study subjects and/or in males/females, and its SE. If parameters other than SE were reported, such as standard deviation, confidence interval (CI), and/or P value, proper modifications were performed to calculate the SE.

## Statistical analysis

We analyzed extracted data to estimate the point prevalence of HCV infection and its 95% CI, and used the Cochrane Q test with a significance level of  $<0.1$  for checking the statistical heterogeneity of the results. We used the meta-analysis method with the “meta” command using a fixed/random model based on the results of the heterogeneity test. The analysis was performed using STATA 9.1 software (STATA Corp. LP, TX, USA). The results are shown in geographic maps using Arc View 3.2a software (ESRI Inc., New York, NY, USA).

## RESULTS

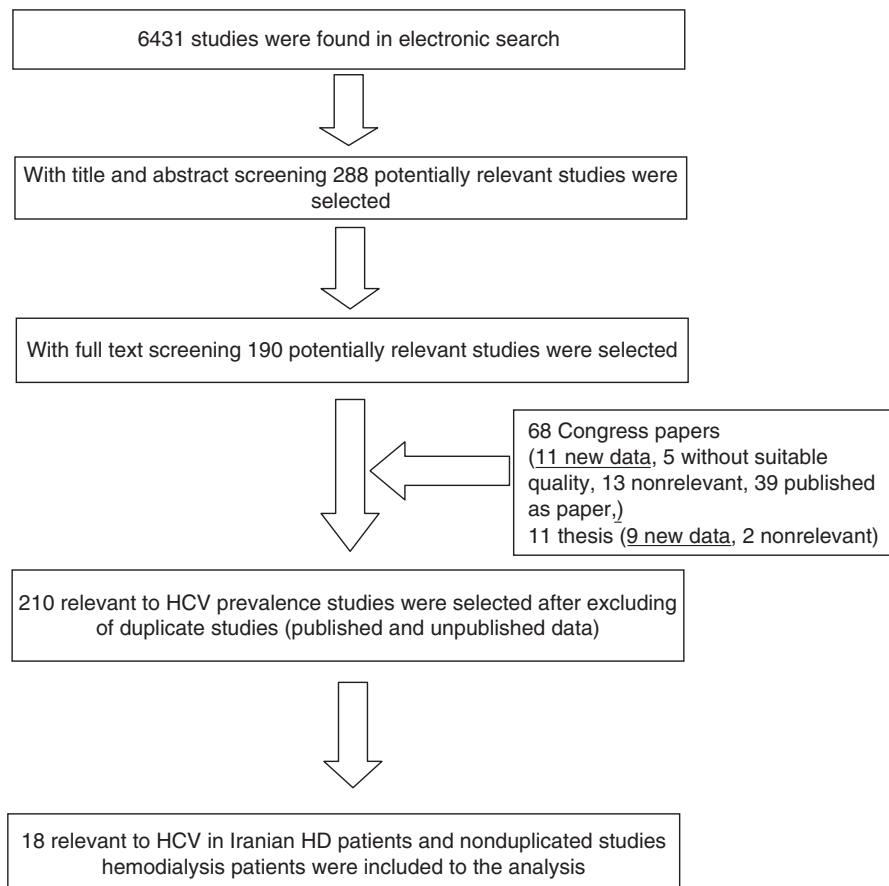
### Search results

In our primary search in electronic databases with our search strategy, we found 6431 documents. After assessing documents according to their titles and abstracts, we

excluded 6143 unrelated documents. We assessed the rest of the 288 studies, and after reading their full texts, we excluded 98 unrelated or duplicated documents again. We added gray literature (68 congress documents and 11 medical theses) to the rest of the documents. Among the congress documents, five were of low quality, 13 were unrelated, and 39 were published as papers and found in a previous database. In medical theses, 2 documents were duplicated. At this stage, 11 congress documents and 9 medical theses were added to the rest of the documents and included 220 unduplicated and relevant to HCV infection prevalence documents. Finally, 18 documents relevant to HCV prevalence in Iranian HD patients remained in our database (Diagram 1).

### Studies

After excluding duplicate and overlapping reports to avoid double counting, we finally selected 18 studies (15 published and 3 unpublished studies) from twelve provinces



**Diagram 1** Systematic review and searches for hepatitis C virus (HCV) infection prevalence in Iranian hemodialysis patients.

with Iranian HD patients as subjects<sup>16–33</sup> (Diagram 1). The 12 provinces that were studied in our study consisted of 49.02% of the Iranian total population.<sup>34</sup>

## HCV infection prevalence

According to official reports of the Iranian Health Ministry, there are 14413 HD patients in 2666 beds in our country (Iranian Health Ministry, unpublished data) (Table 1). This means that there is 1 dialysis bed for every 5.41 patients. The HCV prevalence range in Iranian provinces varied from 4.9% in Markazi<sup>31</sup> to 26.4% in Kermanshah.<sup>29</sup> The reported percentages were heterogeneous and showed statistical significance (test for heterogeneity:  $Q=397.174$ ,  $df=17$ ,  $P<0.001$ ) (Figure 1).

The overall estimation of HCV prevalence in Iran hemodialysis patients according to the data of 12 provinces was 13.57% (95% CI: 9.86–17.21%) with ELISA and 7.61% (95% CI: 6.06–9.16%) with the RIBA/PCR method (Figure 2). All papers that used ELISA for HCV detection had implemented second or third generations.

## DISCUSSION

In the present study, the HCV infection prevalence in Iranian HD patients was 13.57% with ELISA and 7.61% with the RIBA/PCR method. The HCV prevalence in HD patients varies widely in different countries. Although Bahrain has a lower prevalence than Iran, our country is among the countries with the lowest prevalence of HCV in HD patients in the Eastern Mediterranean Region. However, this prevalence is lower than that in most Asian, American, and European countries, except Germany, the United Kingdom, and Australia. The same pattern exists when we consider ELISA as an HCV infection-detecting method; only Germany and England have a lower prevalence than Iran (Table 2).

In our study period from April 2001 to March 2008 and even before that (according to searching in PubMed, Scopus, SID and Iranmedex), our data were restricted to the north, west, and central provinces of Iran. We do not have any studies from provinces that are located in the south or the east of Iran. Next, we need to follow studies in these parts of Iran for a more accurate estimation of HCV prevalence in HD patients. Kermanshah (Western province), Guilan and Golestan (Northern provinces), and West Azarbaijan (Northwest province) had the highest HCV infection prevalence in HD patients.

In our 12 provinces studied, there is one dialysis bed for every 5.68 Iranian HD patients. Provinces with higher HCV infection prevalences (according to RIBA/PCR) such

as West Azarbaijan and Golestan also had a higher dialysis bed usage rate than its national average. Kermanshah and Guilan had a high HCV prevalence but it was not higher than the national dialysis bed usage. This may be due to the method of evaluating HCV infection (ELISA and not determined, respectively), which can be interpreted as a falsely high HCV infection prevalence. Both Semnan and Markazi (Central provinces) have a lower HCV infection prevalence and a lower dialysis bed usage rate, which seems completely logical and is probably due to better accessibility to dialysis beds and having less contact with neighbors of Iran due to their geographical location. However, some provinces such as Ghazvin have a higher usage of dialysis bed units but a lower HCV prevalence. It seems that there are some other prevention modalities in these provinces for HCV infection control (Table 1).

According to the data presented in Table 1, there is a discrepancy (in East Azarbaijan) between the results of RIBA and ELISA in detecting HCV prevalence. This difference might be due to the nature (screening or confirmatory) of these tests. HCV prevalences in HD patients of western and northern provinces were higher than those of central provinces. Factors such as hepatitis care plans, usage rate of dialysis beds, dialysis durations, and HCV-detecting tests may be responsible for these rates (Table 1). Differences in HCV infection prevalence might be due to local risk factors in different Iranian regions.<sup>45</sup>

Different sources play important roles in HCV infection transmission in HD patients and units. Transmission of HCV in HD patients was associated with blood transfusion in the past.<sup>46,47</sup> But in recent years, the need for transfusion in HD patients has decreased due to enhanced safety of blood products, although HCV infection has been proven to still be in circulating among HD patients via other routes of transmission.<sup>48,49</sup> Olmer reported blood transfusion to be a risk factor for HCV infection.<sup>50</sup> But Forns found no relationship between HCV infection and blood transfusion.<sup>51</sup> Some HCV-infected patients were reported to have no history of blood transfusion.<sup>52</sup> In Iran, screening of blood donors for anti-HCV started from 1996. In previous reports, blood transfusion was considered to be a risk factor for HCV transmission in Iranian HD patients.<sup>14,53</sup> Nowadays, blood transfusion does not appear to be a proven risk factor for HCV transmission in Iranian HD patients.<sup>45</sup>

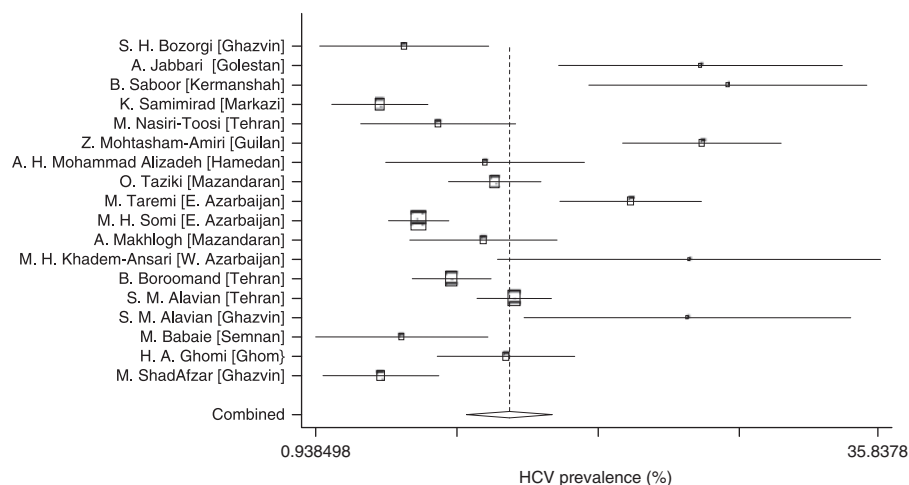
Nosocomial transmission of hepatitis C in HD patients is common in some countries.<sup>54</sup> Increased number of patients under treatment per unit, patients attending more than one treatment unit, contact with the hepatitis B virus, type of dialysis equipment used and their sterilization, and duration of HD treatment are presented as more important nosocomial transmission risk factors for HCV

**Table 1** HCV infection prevalence in several provinces of Iran

Province	Author (year)	Kit	Sample size	Prevalence (95% CI)	Number of patients/ dialysis beds in province <sup>a</sup>	References
All 12 provinces <sup>b</sup>	Present study	PCR/RIBA/ WB/ELISA	5280	12.91 (10.25–15.56)	8238/1451 (5.68)	—
Kermanshah	Saboor et al (2003)	PCR/RIBA/WB	3286	12.19 (9.26–15.12)	308/55 (5.6)	29
Guilan	Mohtasham Amiri et al (2003)	ELISA	560	13.57 (9.89–17.21)	581/94 (6.18)	26
Golestan	Jabbari et al (2008)	ELISA	140	26.4 (17.74–37.73)	419/60 (6.98)	27
West Azarbaijan	Khadem-Ansari and Omrani (2006)	ND	298	24.8 (19.9–29.7)	654/91 (7.19)	33
East Azarbaijan <sup>b</sup>	Somi et al (2008)	RIBA	93	24.7 (16.37–34.76)	769/115 (6.69)	24
		PCR	50	24 (13.06–38.17)		25
		PCR	753	7.3 13.96 (0.86–26.53)		35
	Taremi et al (2005)	ELISA	324	20.4		23
Qom	Azadegan-Ghomi (2006)	RIBA	236	12.7 (8.74–17.65)	284/65 (4.36)	22
Mazandaran <sup>c</sup>	Taziki and Espahbodi (2008)	ND	1006	12 11.8 (9.38–14.22)	685/132 (5.19)	28
Hamadan	Makhlough et al (2008)	PCR	186	11.3	313/50 (6.26)	17
Tehran <sup>b</sup>	Mohammad Alizadeh et al (2002)	ELISA	96	11.4 (5.26–18.83)	3563/661 (5.39)	16
	Nasiri-Toosi et al (2007)	ND	130	8.5 10.66 (7.61–13.71)		18
	Boroormand et al (2002)	PCR	548	9.33		19
Ghazvin <sup>b</sup>	Alavian et al (2003)	RIBA	838	13.2	207/28 (7.39)	20
	Alavian et al (2001)	RIBA	68	23.9 10.3 (2.18–18.42)		21
	Bozorgi et al (2006)	RIBA	89	6.4		31
	Shadafzar (2007)	RIBA	141	4.96		30
Semnan	Babaie and Saadedin (2004)	RIBA	80	6.25 (2.06–13.98)	149/34 (4.38)	
Markazi	Samimirad et al (2006)	RIBA	204	4.9 (2.38–8.83)	306/65 (4.71)	

<sup>a</sup>Statistics from Transplantation and Specific Disorders Office of Iranian Health Ministry.<sup>b</sup>Results are according to the random model (test of heterogeneity,  $P < 0.001$ ).<sup>c</sup>Results are according to the fixed model (test of heterogeneity,  $P > 0.1$ ).

ELISA = enzyme-linked-immunosorbant antibody; HCV = hepatitis C virus; ND = not determined; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay; WB = Western blot.

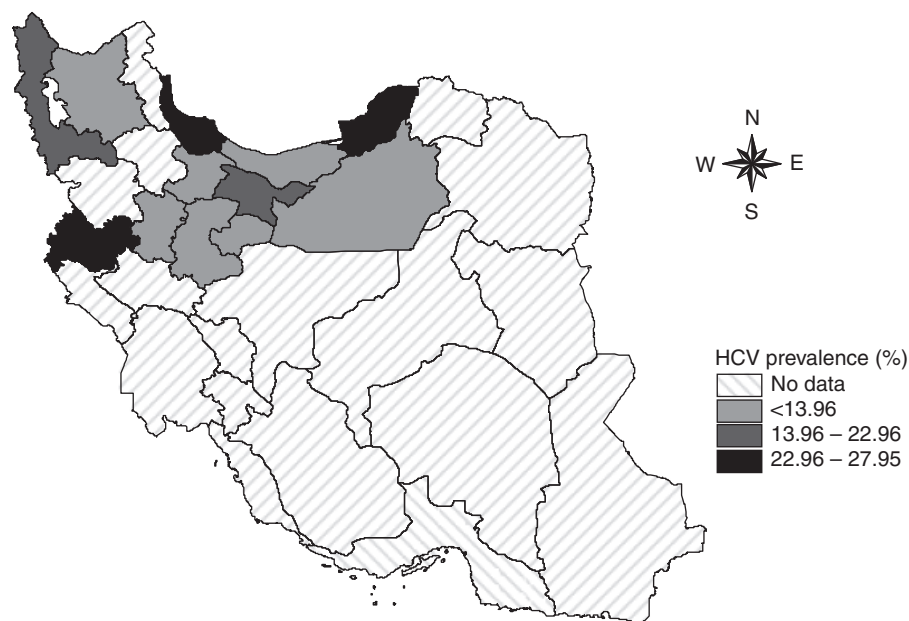


**Figure 1** Prevalence of hepatitis C virus (HCV) infection in Iranian hemodialysis patients and different related studies according to recombinant immunoblot assay/polymerase chain reaction for HCV RNA.

infection.<sup>55,56</sup> The mechanism that is responsible of HCV infection transmission in Iranian HD units has not been understood properly. Some studies have reported that cross infection through dialysis machines may be responsible for HCV infection in our country.<sup>18</sup> It seems that in a prevention program, more attention should be focused on sterilization and control of infection in HD units.

Prevention programs that have been initiated in Iran for evaluation and reduction of HCV infection prevalence in

Iranian HD patients have 3 main parts. The first part involves the diagnosis of all HD patients who are infected with HCV infection and their treatment, even with kidney transplantation.<sup>8,57</sup> The second part involves education of all nurses and health providers of dialysis centers on HCV infection and transmission routes.<sup>58</sup> The last part involves organization of prevention programs and their planning according to the natural characteristics of each Iranian province.<sup>8</sup> Iranian preventive programs will reduce HCV



**Figure 2** Prevalence of hepatitis C virus (HCV) in Iranian hemodialysis patients and different provinces of Iran according to a recombinant immunoblot antibody/recombinant immunoblot assay/polymerase chain reaction test.

**Table 2** HCV infection prevalence in hemodialysis patients from several papers in the literature

Author (yr)	Country/region	Kit	Sample size	Prevalence %	References
Present study	Iran/EMR	RIBA	5280	12.19	—
		ELISA	5280	13.57	
Souqiyyeh et al (2001)	Saudi Arabia/EMR	ELISA	6694	50.49	36
Saxena and Panhotra (2004)	Kuwait/EMR	ND	198	43.3	37
Bdour (2002)	Jordan/EMR	RIBA	283	32.51	38
Khokhar et al (2005)	Pakistan/EMR	ND	97	23.7	39
Yakaryilmaz et al (2006)	Turkey/EMR	ELISA	188	20.2	40
Bergman et al (2005)	USA/America	ND	860	16.8	41
Reddy et al (2005)	India/Asia	RIBA	151	13.23	42
Qadi et al (2004)	Bahrain/EMR	PCR	81	7.4	43
Amin et al (2004)	Australia	RIBA	2800	2.3	44
Fissell et al (2004)	7 European countries and USA <sup>a</sup>	ELISA	8615	Inserted in foot note	11

<sup>a</sup>Countries: France (14.7), Germany (3.9%), Italy (22.2%), Japan (19.9%), Spain (22.2%), the United Kingdom (2.7%), and the United States (14%).

ELISA=enzyme-linked-immunosorbant antibody; EMR=Eastern Mediterranean Region; HCV=hepatitis C virus; ND= not determined; RIBA= recombinant immunoblot assay.

infection in Iranian HD patients. Successful control of infection requires further studies to assess the effectiveness of different preventive policies.<sup>8</sup>

Some factors such as treatment of chronic renal patients, screening test in dialysis units, viremia detection in non-HCV-infected HD patients, and better dialysis equipment can help us in the diagnosis and management of HCV infection in HD patients.<sup>8,59,60</sup>

Several prevention programs were initiated across the world for the prevention and control of HCV infection in HD patients. Some stressed on isolating HD patients<sup>50,61</sup> and other programs attempted to use some equipment specific for these patients, disinfection of dialysis centers, and the use of consumer tools only for one patient.<sup>9,62,63</sup> Strict infection control might be sufficient to control HCV infection spread in HD units.<sup>9,64,65</sup> Calabrese<sup>66</sup> and Harmankaya<sup>67</sup> found that dialyzing HCV-infected patients with separate equipment in a dedicated area but not a separate room can reduce the incidence of HCV infection.

The main reason for the heterogeneity in the prevalence of findings in different studies may be the different prevalence in blood donors and general populations in those provinces and different universal infection control precaution status. There is no surveillance system to quantify the HCV infection in HD patients in our country, which is a limitation.

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