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REVIEW

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# Seroepidemiology of hepatitis E virus infection in patients undergoing maintenance hemodialysis: Systematic review and meta-analysis

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**Abstract**

Patients undergoing regular hemodialysis (HD) are at an extreme risk of acquiring bloodstream infections compared to the general population. Hepatitis E virus (HEV) infection is an important emerging health issue in these patients. To date, numerous studies have investigated the seroprevalence of HEV among HD patients across the world; however, the data are conflicting. The present study aimed to measure the exposure rate of HD patients to HEV infection by estimating the overall seroprevalence of HEV in this high-risk group. A systematic literature search was carried out using five electronic databases from inception to January 10, 2020, with standard keywords. Pooled seroprevalence estimates with 95% confidence intervals (CIs) were calculated using a random intercept logistic regression model. The seroprevalence of HEV increased from 6.6% between the years of 1994 and 2000 to 11.13% from 2016 to 2020. Blood transfusion was associated with a nearly 2-fold increase in the rate of HEV seropositivity (OR = 1.99; 95% CI: 1.50-2.63, $P < .0001$, $I^2 = 6.5\%$). HEV seroprevalence among patients with HD for more than 60 months was significantly higher than those with HD for less than 60 months (27.69%, 95% CI: 20.69%-35.99% vs 15.78%, 95%CI: 8.85%-26.57%, respectively) ($P = .06$). Our results indicated increased exposure of HD patients with HEV infection over the last decade. We concluded that blood transfusion and duration of HD are considerable risk factors for acquiring HEV infection among HD patients.

**KEYWORDS**

hemodialysis, hepatitis E virus, meta-analysis, seroprevalence

## 1 | INTRODUCTION

Hepatitis E, which is a result of infection with the Hepatitis E virus (HEV), is an important public health concern and the major etiologic agent of acute liver damage and inflammation in humans worldwide. It has been estimated that about 20 million people are infected with HEV globally each year, leading to 3.3 million symptomatic cases and around 44 000 deaths.[1] In developing countries, HEV is mainly transmitted through the consumption of

contaminated water and food due to poor hygiene conditions that result in large-scale outbreaks.[2,3] In industrialized countries, transmission usually occurs via alternative routes, such as the consumption of undercooked pork as a foodborne zoonosis, which likely contributes to the sporadic cases of acute hepatitis and fulminant hepatic failure, particularly among immunosuppressed individuals.[4] Transmission via blood transfusion and blood products, such as packed red blood cells and platelets, has also been demonstrated, especially in developed countries.[2,5]

Chronic kidney disease and resulting end-stage renal disease (ESRD) have been recognized as serious challenges in global public health, and hemodialysis (HD) continues to be the predominant therapeutic approach for the treatment of ESRD patients in most countries. Peritoneal dialysis and renal transplantation are two other major types of renal replacement therapies for ESRD patients and constitute 20% of overall dialysis treatment.[6,7] It is well known that patients on HD are at increased risk for acquiring viral infections, and sharing dialysis machines, frequent blood transfusions, repeated hospitalizations, and impaired cellular immunity make them particularly prone to bloodborne viruses.[8] Previous studies have documented that chronic liver diseases caused by the hepatitis C (HCV) and hepatitis B (HBV) viruses are more prevalent in HD and thalassemia major patients than the general population.[8–11]

HEV infection is another emerging health issue in HD patients, which can deteriorate patients' conditions. To date, there are some varying reports of the seroprevalence of HEV in HD patients from different countries worldwide. However, there is a need for an updated study reporting the pooled seroprevalence of HEV in this high-risk group. Hence, this systematic review and meta-analysis aimed at estimating the seroprevalence of HEV among HD patients throughout the world.

## 2 | MATERIALS AND METHODS

### 2.1 | Search strategy

We performed a systematic review and meta-analysis of the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[12] The searches were limited to English-language studies reporting the seroprevalence of HEV among HD patients around the world. PubMed, Web of Science, Scopus, Embase, and Google Scholar were searched from inception until January 10, 2020. The full

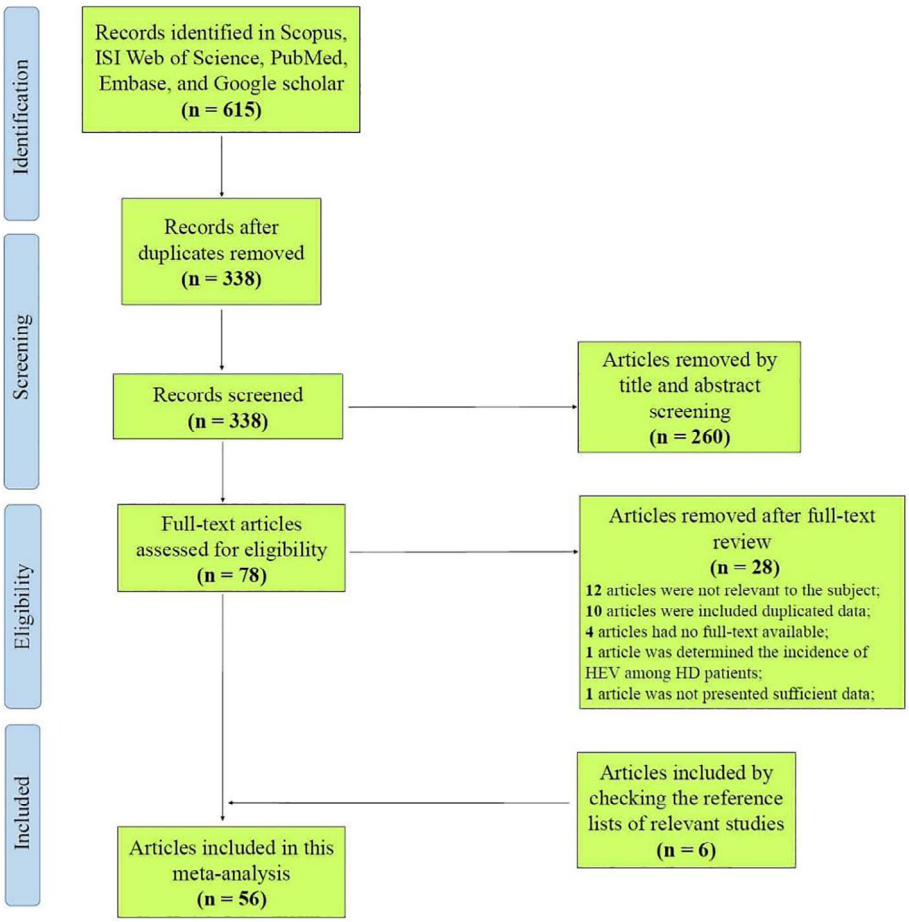


**FIGURE 1** Flowchart presenting the steps of literature search and selection [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Characteristics of studies included in the systematic review and meta-analysis

| Author (ref.) | Year | Study location | Sample size | Mean age (y) | Detection method | No. of HEV seropositive cases | Mean duration of HD (mo) |
|---|---|---|---|---|---|---|---|
| Halfon (21) | 1994 | France | 147 | 62.3 | ELISA/Western blot | 16 | — |
| Knödler (22) | 1994 | Germany | 150 | — | ELISA/Western blot | 5 | — |
| Buti (23) | 1995 | Spain | 50 | — | ELISA/Western blot | 3 | — |
| Cengiz (24) | 1996 | Turkey | 72 | 45.5 | ELISA | 10 | 56.4 |
| Fabrizi (25) | 1996 | Italy | 204 | — | ELISA | 6 | — |
| Gessoni (26) | 1996 | Italy | 193 | 59.5 | ELISA | 18 | — |
| Guiserix (27) | 1996 | France | 62 | — | ELISA | 2 | — |
| Psichogiou (19) | 1996 | Greece | 420 | 57.3 | ELISA | 27 | 61.4 |
| Fabrizi (28) | 1997 | Italy | 204 | 61.1 | ELISA | 6 | 39 |
| Parana (29) | 1997 | Brazil | 392 | — | ELISA | 0 | — |
| Abdel Hady (30) | 1998 | Egypt | 96 | — | ELISA | 38 | — |
| Arinsoy (31) | 1998 | Turkey | 52 | — | ELISA | 9 | — |
| Gessoni (32) | 1998 | Italy | 247 | — | ELISA | 23 | — |
| Dalekos (33) | 1998 | Greece | 211 | — | ELISA/Western blot | 7 | — |
| Sylvan (34) | 1998 | Sweden | 182 | — | ELISA | 11 | — |
| Agarwal (35) | 1999 | India | 64 | 38 | ELISA | 26 | — |
| Kilic (36) | 1999 | Turkey | 70 | — | ELISA | 4 | — |
| Mateos (37) | 1999 | Spain | 63 | — | ELISA/Western blot | 4 | 62 |
| Trinta (38) | 2001 | Brazil | 65 | 65.1 | ELISA | 4 | — |
| Irshad (39) | 2002 | India | 58 | — | ELISA | 21 | — |
| Ayoola (40) | 2002 | Saudi Arabia | 83 | 39 | ELISA | 6 | — |
| Kiesslich (41) | 2002 | Brazil | 192 | — | ELISA | 1 | — |
| Ding (42) | 2003 | Japan | 60 | 46.2 | ELISA | 18 | — |
| Mitsui (43) | 2004 | Japan | 416 | 60.1 | ELISA | 39 | 91.2 |
| Stefanidis (44) | 2004 | Greece | 351 | 60 | ELISA | 17 | 49 |
| Lee (45) | 2005 | Taiwan | 400 | 57 | ELISA | 124 | 32 |
| Taremi (46) | 2005 | Iran | 324 | 53.5 | ELISA | 24 | 53.45 |
| Kikuchi (47) | 2006 | Japan | 300 | 60.1 | ELISA | 57 | 116.4 |
| Pourahmad (48) | 2009 | Iran | 43 | 59.3 | ELISA | 3 | 108 |
| Uçar (49) | 2009 | Turkey | 92 | 55 | ELISA | 19 | 66 |
| Mina (50) | 2010 | Greece | 366 | 60.5 | ELISA | 15 | 49.2 |
| Khameneh (51) | 2011 | Iran | 65 | — | ELISA | 22 | — |
| El Sayed Zaki (20) | 2013 | Egypt | 30 | — | ELISA | 0 | — |
| Harrison (52) | 2013 | United Kingdom | 76 | — | ELISA | 28 | — |
| Mobaien (53) | 2013 | Iran | 93 | 57 | ELISA | 25 | — |
| Scotto (54) | 2013 | Italy | 104 | 65.1 | ELISA/Western blot | 10 | — |
| Zekavat (55) | 2013 | Iran | 80 | 55.69 | ELISA | 5 | 15.6 |
| Ben-Ayed (56) | 2014 | Tunisia | 286 | 54.86 | ELISA | 29 | — |
| Kelishadi (57) | 2014 | Iran | 149 | 56 | ELISA | 0 | — |
| Mousavi (58) | 2014 | Iran | 47 | 55.27 | ELISA | 5 | — |
| Alavian (59) | 2015 | Iran | 274 | 59.9 | ELISA | 78 | 34.6 |
| El Sayed Zaki (60) | 2015 | Egypt | 96 | 46.6 | ELISA | 22 | — |

**TABLE 1** (Continued)

| Author (ref.) | Year | Study location | Sample size | Mean age (y) | Detection method | No. of HEV seropositive cases | Mean duration of HD (mo) |
|---|---|---|---|---|---|---|---|
| Eini (61) | 2015 | Iran | 153 | — | ELISA | 30 | 33 |
| Scotto (62) | 2015 | Italy | 231 | — | ELISA/Western blot | 14 | — |
| Debes (63) | 2016 | Argentina | 81 | — | ELISA | 8 | — |
| Hajiahmadi (64) | 2016 | Iran | 149 | 55.09 | ELISA | 6 | — |
| Pisano (65) | 2016 | Argentina | 82 | 60 | ELISA | 8 | — |
| Naziri (66) | 2016 | Iran | 300 | 54 | ELISA | 12 | — |
| Ricco (67) | 2016 | Italy | 88 | 74.3 | ELISA | 22 | — |
| Yılmaz (68) | 2017 | Turkey | 66 | — | ELISA | 28 | — |
| Sheng (69) | 2017 | China | 170 | — | ELISA | 82 | — |
| Altuğlu (70) | 2018 | Turkey | 68 | 49.2 | ELISA | 1 | 37.9 |
| de Oliveira (71) | 2018 | Brazil | 310 | — | ELISA/Western blot | 8 | — |
| Kuznetsova (72) | 2018 | Estonia | 176 | 50.9 | ELISA/Western blot | 7 | — |
| Lemos (73) | 2019 | Brazil | 286 | — | ELISA | 70 | — |
| Mrzljak (74) | 2020 | Croatia | 394 | 70.5 | ELISA | 110 | — |

Abbreviations: HEV, hepatitis E virus.

details of the search strategy for each database are given in the Appendix. The bibliographies of retrieved articles were also reviewed for additional relevant studies that were likely missed in the primary search. All identified articles were imported to the EndNote software version X8 (Thomson Reuters, California) for further evaluation.

## 2.2 | Selection criteria

The inclusion criteria were as follows: (a) studies reporting the seroprevalence rate of anti-HEV IgG among HD patients across the world; (b) conference abstracts, letters to the editor, short communications, and English abstracts with sufficient data; and (c) studies performed by enzyme-linked immunosorbent assay (ELISA) and Western blot. Studies meeting one of the following criteria were excluded: (a) reviews and case reports; (b) studies investigating the seroprevalence rate of anti-HEV IgM among HD patients; (c) studies investigating the molecular prevalence of HEV in HD patients; (d) studies on patients under other types of dialysis such as peritoneal dialysis; and (e) studies assessing the incidence of HEV among patients undergoing HD, such as prospective studies.

## 2.3 | Data extraction and quality assessment

Titles and abstracts were screened independently by two reviewers, and studies that were not relevant to the study were excluded. Then, the full texts of all potentially eligible studies were obtained and further evaluated, and any disagreements were resolved by consultation with a third reviewer. A checklist based on the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used for quality assessment of the retrieved studies.[13] The checklist contains 12 questions that cover different methodological aspects. According to the checklist, the highest score was 12, representing the highest quality, and the minimum acceptable score was 8. Finally, studies obtaining the minimum score and over were considered eligible for the main meta-analysis. For each eligible study, we extracted data on the following variables: author name, publication year, study location, total sample size, gender and age of patients, duration of HD, detection method, number of HEV-positive cases, and a history of blood transfusion. The extracted data were imported into a predesigned Excel spreadsheet (Microsoft Corporation, Redmond, Washington).

## 2.4 | Statistical methods

To estimate the pooled HEV seroprevalence among HD patients, a random intercept logistic regression model was implemented.[14] The logit transformation was used to stabilize the variance and normalize their distribution, and the Clopper-Pearson method was applied to estimate the 95% exact confidence intervals (CIs) for proportions.[15] A standard continuity correction of 0.5 was added to the studies with a prevalence of zero.[16] To explore the

possible sources of heterogeneity, subgroup analyses were performed based on the publication year, gender, age, detection method, study location, history of blood transfusion, and duration of HD. To measure the heterogeneity among the included publications, I-square statistics ($I^2$) was performed, in which the result is presented as a percentage. $I^2$ values of 25%, 50%, and 75% are indicative of low, moderate, and high levels of heterogeneity, respectively.[17] All statistical tests and time-trend graph productions were performed using R package Meta[18] (version 4.9.9, R Foundation for Statistical Computing, Vienna, Austria), and $P$ values of less than 0.05 were considered statistically significant.

## 3 | RESULTS

### 3.1 | Literature search

In the initial search, 615 articles were identified from five international electronic databases. A total of 277 duplicates was excluded, and then, 338 articles were screened by title and abstract, which led to the elimination of 260 articles. The remaining 78 articles were checked for agreement with the inclusion and exclusion criteria through the full-text review. After full-text screening, 28 articles were excluded because: 12 articles were not relevant to the subject, 10 articles included duplicated data, 4 articles had no full-text available, 1 article determined the incidence of HEV among HD patients, and one article did not present sufficient data. In addition, six relevant articles were found and included by a manual search of the reference lists of the identified articles. Finally, 56 articles were included in this systematic review and meta-analysis. Figure 1 represents the process of literature retrieval and screening using a flow chart.

### 3.2 | Study characteristics

In this meta-analysis, a total of 56 studies, with a total of 9483 patients from 20 countries, were included. The publication date of articles ranged from 1994 to 2020. The characteristics of eligible studies in this systematic review and meta-analysis are summarized in Table 1. The largest study[19] included 420 patients, and the smallest[20] included 30 HD patients. Most studies investigating the seroprevalence of HEV among patients undergoing HD were from Iran (n = 11), Italy (n = 7), and Turkey (n = 6). Of the 56 studies included, 17 provided information on patients' gender, 7 studies provided data on patients' age, 4 had information on the duration of HD, and 6 studies presented data on the history of blood transfusion. Overall, 53.5% of the studies (n = 30) were performed before 2010, and 46.5% of the studies (n = 26) were performed after 2010.

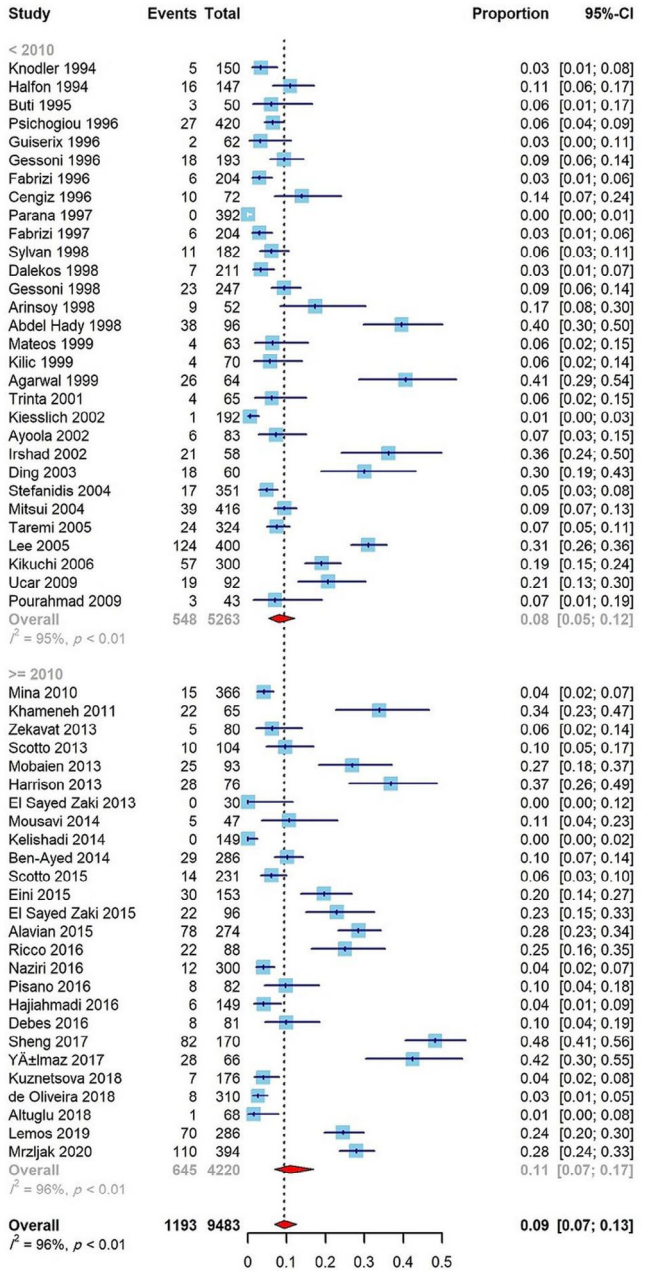


**FIGURE 2** Forest plot of the seroprevalence of hepatitis E virus (HEV) infection among HD patients, according to the random-effect model, stratified by study year (before and after 2010) [Color figure can be viewed at wileyonlinelibrary.com]

### 3.3 | Seroprevalence of HEV infection among HD patients

The pooled estimated seroprevalence of HEV infection in HD patients around the world was 9.31% (95% CI: 6.83%-12.57%), and the range was from 48.24%[20] to 0%[19,21,22]in

**TABLE 2** Subgroup analysis of the seroprevalence of HEV infection in HD patients

| Characteristics | Categories | No. of studies | Pooled prevalence (%) (95% CI) | Heterogeneity test $I^2$%, *P*-value | Differences between subgroups; $\chi^2$ test (*P*-value) |
|---|---|---|---|---|---|
| **Overall** | | 56 | 9.31 (6.83-12.57) | 95.9%, $P < .01$ | |
| **Diagnostic method** | ELISA | 47 | 10.37 (7.30-14.54) | 96.6%, $P < .01$ | ***P* = .005†** |
| | ELISA/Western blot | 9 | 5.14 (3.62-7.25) | 55.4%, $P = .01$ | |
| **Duration of HD (mo)** | <60 | 4 | 15.78 (8.85-26.57) | 87.8%, $P < .01$ | $P = .06$ |
| | >60 | 2 | 27.69 (20.69-35.99) | 0%, $P = .1$ | |
| **Age (y)** | <40 | 6 | 4.91 (1.76-12.97) | 52.9%, $P = .09$ | $P = .1$ |
| | >40 | 7 | 12.19 (6.42-21.93) | 94.9%, $P < .01$ | |
| **Gender** | Male | 17 | 10.86 (6.66-17.20) | 94.0%, $P = .01$ | $P = .7$ |
| | Female | 17 | 9.54 (5.62-15.74) | 91.5%, $P = .01$ | |
| **Study year** | 1994-2000 | 18 | 6.60 (3.82-11.16) | 92.9%, $P < .01$ | $P = .6$ |
| | 2001-2005 | 9 | 9.81 (4.54-19.93) | 96.4%, $P < .01$ | |
| | 2006-2010 | 4 | 10.77 (5.16-21.12) | 89.4%, $P < .01$ | |
| | 2011-2015 | 13 | 11.70 (6.15-21.15) | 95.5%, $P < .01$ | |
| | 2016-2020 | 12 | 11.13 (5.59-20.94) | 96.8%, $P < .01$ | |
| **Study location** | Argentina | 2 | 9.82 (6.10-15.42) | 0%, $P = .98$ | ***P* < .0001†** |
| | Brazil | 5 | 1.77 (0.23-12.31) | 96.2%, $P < .01$ | |
| | China | 1 | 48.24 (40.82-55.73) | NA, NA | |
| | Croatia | 1 | 27.92 (23.71-32.55) | NA, NA | |
| | Egypt | 3 | 12.78 (1.54-57.82) | 96.6%, $P = .05$ | |
| | Estonia | 1 | 3.98 (1.91-8.11) | NA, NA | |
| | France | 2 | 7.63 (3.29-16.72) | 28.2%, $P = .09$ | |
| | Germany | 1 | 3.33 (1.39-7.76) | NA, NA | |
| | Greece | 4 | 4.90 (3.86-6.19) | 0%, $P = .30$ | |
| | India | 2 | 38.52 (30.32-47.43) | 0%, $P = .62$ | |
| | Iran | 11 | 9.11 (4.53-17.49) | 95.0%, $P < .01$ | |
| | Italy | 7 | 7.52 (4.39-12.58) | 85.8%, $P < .01$ | |
| | Japan | 3 | 17.26 (9.87-28.44) | 88.7%, $P < .01$ | |
| | Saudi Arabia | 1 | 7.23 (3.28-15.17) | NA, NA | |
| | Spain | 2 | 6.19 (2.98-12.43) | 0%, $P = .94$ | |
| | Sweden | 1 | 6.04 (3.38-10.58) | NA, NA | |
| | Taiwan | 1 | 31.00 (26.66-35.70) | NA, NA | |
| | Tunisia | 1 | 10.14 (7.14-14.21) | NA, NA | |
| | Turkey | 6 | 12.92 (5.65-26.87) | 89.6%, $P < .01$ | |
| | United Kingdom | 1 | 36.84 (26.79-48.18) | NA, NA | |

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HEV, hepatitis E virus; NA, Not applicable.
†Statistically significant (indicated as bold values) .

the selected individual studies. The results of the heterogeneity test indicated a significant heterogeneity among all studies that were analyzed in this meta-analysis, so the random-effects model was used to pool the data. The highest and lowest seroprevalence rates of HEV were found in HD patients from China and Brazil, respectively (48.24%, 95% CI: 40.82%-55.73% vs 1.77%, 95% CI: 0.23%-12.31%). To explore responsible factors for heterogeneity, a subgroup analysis was conducted. This analysis showed that the diagnostic method, duration of HD, age, study year, and study location are responsible for heterogeneity.

We divided the individual studies into two time periods of publication, before and after 2010. The polled estimated seroprevalence rates of HEV infection before and after 2010 were different, 8.1% (95% CI: 5.36%-12.05%) and 10.94% (95% CI: 6.91%-16.89%), respectively (Figure 2). However, the difference was not statistically significant ($P = .3$). Among studies performed after 2010, the maximum and minimum seroprevalence of HEV among HD patients were found in China and Estonia, respectively (48.24%, 95%CI: 40.82%-55.73% vs 3.98%, 95% CI: 1.91%-8.11%).

The seroprevalence of HEV among patients with HD for more than 60 months was significantly higher than those with HD for less than 60 months (27.69%, 95%CI: 20.69%-35.99% vs 15.78%, 95%CI: 8.85%-26.57%, respectively) ($P = .06$). Furthermore, the proportion of HEV seropositivity among male cases undergoing HD was slightly higher than female cases (10.86%, 95%CI: 6.66%-17.20% vs 9.54%, 95%CI: 5.62%-15.74%, respectively) ($P = .7$). With respect to HEV serodetection techniques in blood samples of HD patients, ELISA with or without Western blot assay as a confirmatory test was used. HEV seroprevalence rates were 10.37% (95%CI: 7.30%-14.54%) and 5.14% (95%CI: 3.62%-7.25%) when ELISA and ELISA/Western blot assays were used, respectively, and the difference was statistically significant ($P = .005$). Table 2 indicates more detailed information on the seroprevalence of HEV infection among HD patients for subgroups. In addition, our results showed that blood transfusion is associated with a nearly 2-fold increase in the rate of HEV seropositivity (OR = 1.99; 95%CI: 1.50-2.63, $P < .0001$, $I^2 = 6.5\%$) (Figure 3).

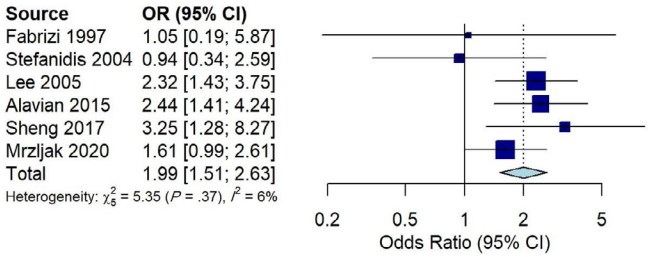


**FIGURE 3** Forest plot of the association between blood transfusion and hepatitis E virus (HEV) seropositivity according to the random-effect model [Color figure can be viewed at wileyonlinelibrary.com]

## 3.4 | Time trend analysis

Time trend analysis was performed to investigate changes in the seroprevalence of HEV infection over time in the world (Figure 4). According to this analysis, the seroprevalence of HEV was the lowest (6.6%; 95% CI: 3.82%-11.16%) between 1994 and 2000. From 2001 until 2020, the number of HEV-seropositive cases among HD patients dramatically increased, and the seroprevalence was 11.13% (95% CI: 5.59%-20.94%) between 2016 and 2020 (Table 2).

## 4 | DISCUSSION

The present study, for the first time, estimated the seroprevalence of HEV in HD patients in a systematic review and meta-analysis setting. Patients undergoing HD are characterized by abnormalities in both the adaptive and innate immune systems, making them susceptible to infections.[75] After cardiovascular complications, infections are the second major leading cause of death in HD patients.[76] Among the different bloodborne viral infections, hepatitis and human immunodeficiency viruses are the most common problems in HD units, as well as the general population.[77] Hepatitis E is generally considered an acute self-limited liver disease with no progression to chronic stages. However, recent studies have shown that chronic HEV infection and cirrhosis may occur,

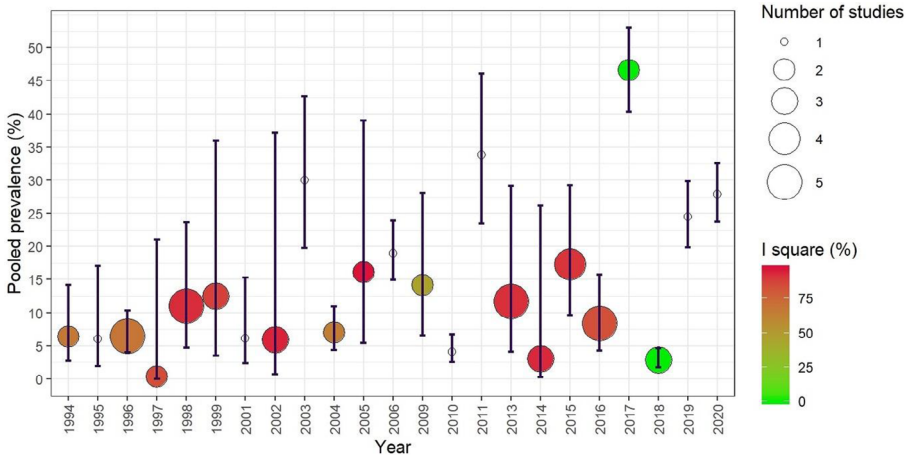


**FIGURE 4** Time trend in the seroprevalence of hepatitis E virus (HEV) among HD patients [Color figure can be viewed at wileyonlinelibrary.com]

especially in immunocompromised individuals such as HD patients.[78] A meta-analysis conducted by Haffar et al showed a positive relationship between HD and HEV seroprevalence.[79] According to their findings, the seroprevalence of HEV was more prevalent in HD patients compared with the non-HD control (OR 2.47, 95% CI: 1.79-3.40, $I^2 = 75.2\%$, $P < .01$). In another review study by Hosseini-Moghaddam et al, several risk factors have been identified for HEV infection in HD patients, including older age, living in rural vs urban areas, low education, and duration of HD.[80]

One of the most important findings of our study is that the overall seroprevalence of HEV infection in patients on HD has been increasing over the last few years around the world, which should be considered an emerging public health threat. According to our findings, the pooled seroprevalence of HEV among HD patients was 9.31%, and the highest rate of seroprevalence was seen among Chinese patients, followed by Indian, British, and Taiwanese patients. Interestingly, some European countries, such as the United Kingdom and Croatia, show a high seroprevalence of HEV among their HD patients. This can be explained by the fact that, over the past decade, the incidence and prevalence of HEV infection, particularly with genotype 3 (G3) HEV, has been steadily growing in many developed countries, including countries of the European Union.[81] It should be noted that HEV G3 is associated more with the establishment of persistent infection in immunocompromised patients, leading to the development of chronic hepatitis and serious liver complications.[82]

Our analysis suggested that the seroprevalence of HEV in HD units varies throughout the world. In the past, HEV infection was thought to be limited to developing countries with poor hygiene and sanitary conditions. Nowadays, this assumption has been challenged because most developed countries are also experiencing a high prevalence rate of HEV. As an explanation, differences in culinary culture in different regional areas can result in a wide variety of HEV prevalence rates. In developed countries, the transmission of HEV to humans occurs mainly via the consumption of raw pork products, particularly pork liver.[83] Zoonotic HEV G3 strains were documented to mostly circulate between humans, swine, and wild boar in Europe.[84]

Generally, immunization is an effective and safe measure in controlling infectious diseases, and HEV infection is not spared. There is no FDA-approved vaccine currently available against HEV, and most HEV vaccine candidates are based on recombinant expressed HEV-capsid proteins. HEV 239 is the only recombinant HEV vaccine approved in China since 2011, which exhibited high effectiveness in preventing HEV infection in the general population in China.[85] Therefore, vaccination schedules in HD patients can play an effective role in reducing HEV prevalence. Another suggestion for preventing hepatitis E transmission is taking preventive measures at the level of the community (eg, water decontamination, improved hygiene and sanitation) and the personal level (eg, avoid eating raw or undercooked meat).

HEV is recognized as a serious public health concern in HD patients both in developed and developing countries. Generally, global immunization in humans and animals, especially in pigs; improvements in sanitation conditions in HEV-endemic areas; and avoiding the consumption of suspicious HEV-infested drinking water and undercooked shellfish, meat, vegetables, and fruits can be considered the best strategies for decreasing the prevalence rate. On the other hand, it should be noted that our estimation can be affected by some limitations, such as a small number and low geographical coverage of the studies. Until now, there are no published data on the seroprevalence of HEV in this high-risk population in a large number of countries, and performing updated investigations in these areas is highly suggested.

## 5 | CONCLUSIONS

In conclusion, the overall seroprevalence of HEV in patients undergoing HD is increasing over the past years in the world, which should be considered an emerging public health issue. We also demonstrated that blood transfusion is significantly associated with an increased rate of HEV seropositivity. There are no data regarding the seroprevalence of HEV in HD patients in some countries. Therefore, performing screening tests for HEV in HD patients in other regions of the world is highly recommended to obtain more reliable estimates of the overall seroprevalence of HEV.

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### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### AUTHOR CONTRIBUTIONS

A.T and S.M.A. designed the study. M.F. and S.M. performed statistical analyses. A.T. and M.M. wrote, reviewed, and edited the manuscript. A.T. and S.M.A. performed data interpretation. A.T., M.F., S.A., and M.M. performed search strategy. S.M.A. performed critical revision. All authors were involved in the acquisition of data and read and approved the final draft.

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## APPENDIX A.: THE DETAILS OF SEARCH TERMS FOR EACH DATABASE

| Databases | Search criteria |
|---|---|
| PubMed | (“renal dialysis”[mesh terms] OR dialyses, renal OR renal dialyses OR dialysis, renal OR hemodialysis OR Hemodialyses OR dialysis, extracorporeal OR dialyses, extracorporeal OR extracorporeal dialyses OR extracorporeal dialysis) AND (“hepatitis E”[mesh terms] OR “hepatitis E virus”[mesh terms] OR hepatitis, water-borne OR Hepatitides, water-borne OR hepatitis, water borne OR water-borne Hepatitides OR water-borne hepatitis OR ET-NANBH OR hepatitis, viral, non-A, non-B, Enterically-transmitted OR Enterically-transmitted non-A, non-B hepatitis OR Enterically transmitted non A, non B hepatitis OR epidemic non-A, non-B hepatitis OR epidemic non A, non B hepatitis OR HEV) |
| Embase | (“hepatitis e”/exp OR “enterically transmitted non a non b hepatitis” OR “epidemic non a non b hepatitis” OR ‘hepatitis e’ OR “hepatitis e virus”/exp OR “hev [hepatitis]” OR ‘hepatitis e virus’ OR “hepatitis virus e”) AND (“hemodialysis”/exp OR “blood dialysis” OR “chronic haemodialysis” OR “chronic hemodialysis” OR “chronic intermittent haemodialysis” OR “chronic intermittent hemodialysis” OR “dialysis center” OR “dialysis, blood” OR “extracorporeal blood cleansing” OR “extracorporeal dialysis” OR ‘haemodialysis' OR “haemodialysis center” OR “haemodialysis Centre” OR “haemodialysis department” OR “haemodialysis unit” OR “haemodialysis units, hospital” OR “hemodialyse” OR ‘hemodialysis’ OR “hemodialysis center” OR “hemodialysis department” OR “hemodialysis unit” OR “hemodialysis units, hospital” OR “hemorenodialysis” OR “hemotrialysate” OR “intermittent chronic haemodialysis” OR “intermittent chronic hemodialysis” OR ‘intermittent haemodialysis' OR ‘intermittent hemodialysis’ OR “renal dialysis”) |
| Scopus | TITLE-ABS-KEY ((“hepatitis e” OR “enterically transmitted non a non b hepatitis” OR “epidemic non a non b hepatitis” OR “hepatitis e virus” OR “hev [hepatitis]” OR “hepatitis e virus” OR “hepatitis virus e”) AND (“hemodialysis” OR “blood dialysis” OR “chronic haemodialysis” OR “chronic hemodialysis” OR “chronic intermittent haemodialysis” OR “chronic intermittent hemodialysis” OR “dialysis center” OR “dialysis, blood” OR “extracorporeal blood cleansing” OR “extracorporeal dialysis” OR “haemodialysis” OR “haemodialysis center” OR “haemodialysis Centre” OR “haemodialysis department” OR “haemodialysis unit” OR “haemodialysis units, hospital” OR “hemodialyse” OR “hemodialysis” OR “hemodialysis center” OR “hemodialysis department” OR “hemodialysis unit” OR “hemodialysis units, hospital” OR “hemorenodialysis” OR “hemotrialysate” OR “intermittent chronic haemodialysis” OR “intermittent chronic hemodialysis” OR “intermittent haemodialysis” OR “intermittent hemodialysis” OR “renal dialysis”)) |
| Web of science | TS = ((“hepatitis e” OR “enterically transmitted non a non b hepatitis” OR “epidemic non a non b hepatitis” OR “hepatitis e” OR “hepatitis e virus” OR “hev [hepatitis]” OR “hepatitis e virus” OR “hepatitis virus e”) AND (“hemodialysis” OR “blood dialysis” OR “chronic haemodialysis” OR “chronic hemodialysis” OR “chronic intermittent haemodialysis” OR “chronic intermittent hemodialysis” OR “dialysis center” OR “dialysis, blood” OR “extracorporeal blood cleansing” OR “extracorporeal dialysis” OR “haemodialysis” OR “haemodialysis center” OR “haemodialysis Centre” OR “haemodialysis department” OR “haemodialysis unit” OR “haemodialysis units, hospital” OR “hemodialyse” OR “hemodialysis” OR “hemodialysis center” OR “hemodialysis department” OR “hemodialysis unit” OR “hemodialysis units, hospital” OR “hemorenodialysis” OR “hemotrialysate” OR “intermittent chronic haemodialysis” OR “intermittent chronic hemodialysis” OR “intermittent haemodialysis” OR “intermittent hemodialysis” OR “renal dialysis”)) |

(Continues)