Seroepidemiology of Hepatitis E Virus Infection in Patients Undergoing Maintenance Hemodialysis: A Systematic Review and Meta-Analysis

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Abstract

**Background:** Hepatitis E virus (HEV) infection is an important emerging health issue in patients on hemodialysis (HD). To date, numerous studies have reported controversial findings regarding the seroprevalence of HEV among this high-risk group around the world. The aim of the present study was to estimate the overall seroprevalence of HEV in HD patients.

**Methods:** A systematic literature search was carried out using PubMed, Web of Science, Scopus, Embase, and Google scholar from inception to January 10, 2020 with standard keywords. Pooled seroprevalence estimates with 95% confidence intervals (CI) were calculated using a random intercept logistic regression model.

**Results:** A total of 56 studies met the inclusion criteria compromising 9483 HD patients. The pooled seroprevalence of HEV was estimated 9.31% (95%CI: 6.83%-12.57%). The seroprevalence of HEV was increased from 6.6% between the years of 1994 and 2000 to 11.13% from the year of 2016 to 2020. Blood transfusion was associated with a nearly two-fold increase in the rate of HEV seropositivity (OR=1.99; 95%CI: 1.50-2.63, P value < 0.0001, I²=6.5%).

**Conclusions:** Our results indicated an increased exposure of HD patients with HEV infection over the last decade. We concluded that blood transfusion, age and duration of HD are considerable risk factors for acquiring HEV infection among HD patients.

**Background**

Hepatitis E, which is due to infection with 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 a 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 results in large-scale outbreaks [2, 3]. In industrialized countries, transmission usually occurs via alternative routes, like the consumption of undercooked pork as a foodborne zoonosis, which likely contribute 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 have also been demonstrated, especially in developed countries [2, 5].

Chronic kidney disease and resulting End-Stage Renal Disease (ESRD) have become recognized as serious challenges in the global public health, and hemodialysis (HD) continues to be the predominant therapeutic approach for treatment of ESRD patients in most countries. Peritoneal dialysis and renal transplantation are two other major types of renal replacement therapies for ESRD patients, provide 20% of overall dialysis treatment [6, 7]. It is well known that patients on hemodialysis 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 blood-borne viruses [8]. In previous studies, it has 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 anti-HEV antibodies among HD patients throughout the world.

Methods

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 the 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. Full details of the search strategy for each database are in Table 1. Bibliographies section 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, USA) for further evaluation.
**Table 1.** The details of search terms for each database

| Databases     | Search criteria                                                                                                                                 |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| PubMed        | ("Renal Dialysis"[Mesh Terms] OR Dialyses, Renal OR Ren Hemodialysis OR Hemodialyses OR Dialysis, Extracorporeal Dialyses OR Extracorporeal Dialysis) AND ("Hep virus"[Mesh Terms] OR Hepatitis, Water-Borne OR Hepatitisides, V OR Water-Borne Hepatitisides OR Water-Borne Hepatitis OR ET-NB, Enterically-Transmitted OR Enterically-Transmitted Non-Transmitted 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 'hepatitis e' OR 'hepatitis e virus'/exp OR 'hev (hepatitis)' OR 'e') AND ('hemodialysis'/exp OR 'blood dialysis' OR 'chronic hae OR 'chronic intermittent haemodialysis' OR 'chronic intermittent dialysis, blood' OR 'extracorporeal blood cleansing' OR 'extracor 'haemodialysis center' OR 'haemodialysis centre' OR 'haemodi unit' OR 'haemodialysis units, hospital' OR 'hemodialyse' OR 'h OR 'hemodialysis department' OR 'hemodialysis unit' OR 'hemorenodialysis' OR 'hemotrialysate' OR 'intermittent chronic hemodialysis' OR 'intermittent haemodialysis' OR 'i dialysis') |
| Scopus        | TITLE-ABS-KEY ( ( "hepatitis e" OR "enterically transmitted non a non b hepatitis" OR "hepatitis e" OR "hepatitis e virus" OR "hepatitis virus e" ) AND ( "hemodialysis" OR "chronic haemodialysis" OR "chronic hemodialysis" OR "chronic intermittent hemodialysis" OR "dialysis ce extracorporeal blood cleansing" OR "extracorporeal dialysis hemodialysis center" OR "haemodialysis centre" OR "haemodialysis unit" OR "haemodialysis units, hospital" OR "hemodialysis units, hospital" OR "hemorenodialysis" OR "chronic haemodialysis" OR "intermittent chronic hemodialysis" OR "intermittent hemodialysis" OR "renal dialysis" ) ) |
| Web of Science| TS= ( ( "hepatitis e" OR "enterically transmitted non a non b hepatitis" OR "hepatitis e" OR "hepatitis e virus" OR "i" OR "hepatitis virus e" ) AND ( "hemodialysis" OR "chronic hemodialysis" OR "chronic intermittent hemodialysis" OR "dialysis center" OR "dialysis cleansing" OR "extracorporeal dialysis" OR "haemodialysis: hemodialysis centre" OR "haemodialysis department" "haemodialysis units, hospital" OR "hemodialyse" OR "hemodialysis department" OR "hemodialysis unit" OR "hemorenodialysis" OR "hemotrialysate" OR "intermittent chronic hemodialysis" OR "intermittent hemodialysis" OR "renal dialysis" ) ) |

**Selection criteria**

The inclusion criteria were as follows: 1) studies reporting the seroprevalence rate of anti-HEV IgG among HD patients across the world; 2) conference abstracts, letters to editor, short communications, and English abstracts with sufficient data; 3) studies performed by enzyme-linked immunosorbent
assay (ELISA) and western blot. Studies meeting one of the following criteria were excluded: 1) reviews and case reports; 2) studies investigating the seroprevalence rate of anti-HEV IgM among HD patients; 3) studies investigating the molecular prevalence of HEV in HD patients; 4) studies on patients under other types of dialysis such as peritoneal dialysis; 5) studies assessing the incidence of HEV among patients undergoing hemodialysis, like prospective studies.

**Data extraction**

Titles and abstracts were screened by two blinded reviewers, and studies which were obviously not relevant to the study were excluded. Then, the full-texts of all potentially eligible studies were obtained and further evaluated by two independent reviewers, and any disagreements were resolved by consultation with a third reviewer. For each 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, USA).

**Statistical methods**

To estimate the pooled HEV seroprevalence among HD patients, a random intercept logistic regression model was implemented [13]. 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 [14]. A standard continuity correction of 0.5 was added to the studies with prevalence of zero [15]. In order 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 [16]. All statistical tests and time-trend graph production were performed using R package Meta [17] (version 4.9.9, R Foundation for Statistical
Computing, Vienna, Austria), and P values of less than 0.05 were considered statistically significant.

Results

**Literature search**

In the initial search, 615 articles were identified from five electronic international 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 by the full-text review. After full-text screening, 28 articles were excluded due to the following: 12 articles were not relevant to the subject, 10 articles were included duplicated data, four articles had no full-text available, one article was determined the incidence of HEV among HD patients, and one article was not presented 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.

**Study characteristics**

In this meta-analysis, a total of 56 studies, including a total of 9483 patients from 20 countries were included. Publication date of articles was ranged from 1994 to 2020. The characteristics of eligible studies in this systematic review and meta-analysis are summarized in Table 2. The largest study [18] included 420 and the smallest [19] 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’ sex, 7 studies provided information on patients’ sex, 4 had information on duration of HD, and 6 studies presented data on history of blood transfusion. In total, 53.5% of the studies (n=30) were performed before 2010, and 46.5% of the studies (n=26) were performed after 2010.

**Table 2.** Characteristics of studies included in the systematic review and meta-analysis

| Author (Ref.) | Year | Study Location | Sample size | Mean age (year) | Detection method        |
|--------------|------|----------------|-------------|-----------------|-------------------------|
| Halfon [23]  | 1994 | France         | 147         | 62.3            | ELISA/Western blot      |
| Knödler [24] | 1994 | Germany        | 150         | -               | ELISA/Western blot      |
| Buti [25]    | 1995 | Spain          | 50          | -               | ELISA/Western blot      |
| Cengiz [26]  | 1996 | Turkey         | 72          | 45.5            | ELISA                   |
| Author                | Year | Country     | Value | Reference |
|-----------------------|------|-------------|-------|-----------|
| Fabrizi [27]          | 1996 | Italy       | 204   | ELISA     |
| Gessoni [28]          | 1996 | Italy       | 193   | 59.5      | ELISA     |
| Guiserix [29]         | 1996 | France      | 62    | -         | ELISA     |
| Psychogiu [18]        | 1996 | Greece      | 420   | 57.3      | ELISA     |
| Fabrizi [30]          | 1997 | Italy       | 204   | 61.1      | ELISA     |
| Parana [22]           | 1997 | Brazil      | 392   | -         | ELISA     |
| Abdel Hady [31]       | 1998 | Egypt       | 96    | -         | ELISA     |
| Arinsoy [32]          | 1998 | Turkey      | 52    | -         | ELISA     |
| Gessoni [33]          | 1998 | Italy       | 247   | -         | ELISA     |
| Dalekos [34]          | 1998 | Greece      | 211   | -         | ELISA/Western blot |
| Sylvan [35]           | 1998 | Sweden      | 182   | -         | ELISA     |
| Agarwal [36]          | 1999 | India       | 64    | 38        | ELISA     |
| Kilic [37]            | 1999 | Turkey      | 70    | -         | ELISA     |
| Mateos [38]           | 1999 | Spain       | 63    | -         | ELISA/Western blot |
| Trinta [39]           | 2001 | Brazil      | 65    | 65.1      | ELISA     |
| Irshad [40]           | 2002 | India       | 58    | -         | ELISA     |
| Ayoola [41]           | 2002 | Saudi Arabia| 83    | 39        | ELISA     |
| Kiesslich [42]        | 2002 | Brazil      | 192   | -         | ELISA     |
| Ding [43]             | 2003 | Japan       | 60    | 46.2      | ELISA     |
| Mitsui [44]           | 2004 | Japan       | 416   | 60.1      | ELISA     |
| Stefanidis [45]       | 2004 | Greece      | 351   | 60        | ELISA     |
| Lee [46]              | 2005 | Taiwan      | 400   | 57        | ELISA     |
| Taremi [47]           | 2005 | Iran        | 324   | 53.5      | ELISA     |
| Kikuchi [48]          | 2006 | Japan       | 300   | 60.1      | ELISA     |
| Pourahmad [49]        | 2009 | Iran        | 43    | 59.3      | ELISA     |
| Uçar [50]             | 2009 | Turkey      | 92    | 55        | ELISA     |
| Mina [51]             | 2010 | Greece      | 366   | 60.5      | ELISA     |
| Khameneh [52]         | 2011 | Iran        | 65    | -         | ELISA     |
| El Sayed Zaki [19]    | 2013 | Egypt       | 30    | -         | ELISA     |
| Harrison [53]         | 2013 | United Kingdom | 76 | -     | ELISA     |
| Mobain [54]           | 2013 | Iran        | 93    | 57        | ELISA     |
| Scotto [55]           | 2013 | Italy       | 104   | 65.1      | ELISA/Western blot |
| Zekavat [56]          | 2013 | Iran        | 80    | 55.69     | ELISA     |
| Ben-Ayed [57]         | 2014 | Tunisia     | 286   | 54.86     | ELISA     |
| Kelishadi [21]        | 2014 | Iran        | 149   | 56        | ELISA     |
| Mousavi [58]          | 2014 | Iran        | 47    | 55.27     | ELISA     |
| Alavian [59]          | 2015 | Iran        | 274   | 59.9      | ELISA     |
| El Sayed Zaki [60]    | 2015 | Egypt       | 96    | 46.6      | ELISA     |
| Eini [61]             | 2015 | Iran        | 153   | -         | ELISA     |
| Scotto [62]           | 2015 | Italy       | 231   | -         | ELISA/Western blot |
| Debes [63]            | 2016 | Argentina   | 81    | -         | ELISA     |
| Hajiahmadi [64]       | 2016 | Iran        | 149   | 55.09     | ELISA     |
| Pisano [65]           | 2016 | Argentina   | 82    | 60        | ELISA     |
| Naziri [66]           | 2016 | Iran        | 300   | 54        | ELISA     |
| Ricco [67]            | 2016 | Italy       | 88    | 74.3      | ELISA     |
| Yilmaz [68]           | 2017 | Turkey      | 66    | -         | ELISA     |
| Sheng [20]            | 2017 | China       | 170   | -         | ELISA     |
| Altuğlu [69]          | 2018 | Turkey      | 68    | 49.2      | ELISA     |
| de Oliveira [70]      | 2018 | Brazil      | 310   | -         | ELISA/Western blot |
| Kuznetsova [71]       | 2018 | Estonia     | 176   | 50.9      | ELISA/Western blot |
| Lemos [72]            | 2019 | Brazil      | 286   | -         | ELISA     |
| Mrzljak [73]          | 2020 | Croatia     | 394   | 70.5      | ELISA     |
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] of 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 for pooling the data. The highest and lowest seroprevalence 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, subgroup analysis was conducted. This analysis showed that 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 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 ($P=0.3$). 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 hemodialysis duration more than 60 months was significantly higher than those with hemodialysis duration less than 60 months (27.69%, 95%CI: 20.69%-35.99% vs 15.78%, 95%CI: 8.85%-26.57%, respectively) ($P=0.06$). 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) ($P=0.7$). 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 seroprevalences 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 ($P=0.005$). Table 3 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 two-fold increase in the
rate of HEV seropositivity (OR=1.99; 95%CI: 1.50-2.63, P value < 0.0001, I²=6.5%) (Figure 3).

**Table 3.** Subgroup analysis of the seroprevalence of HEV infection in HD patients

| Subgroup Analysis | NA: Not applicable; ELISA: enzyme-linked immunosorbent assay; |
|-------------------|---------------------------------------------------------------|
| † Statistical significant | }
### Characteristics

| Categories                              | No. of Studies | Pooled prevalence (%) (95% CI) | Heterogeneity test |
|-----------------------------------------|----------------|--------------------------------|--------------------|
| **Overall**                             | 56             | 9.31 (6.83-12.57)              | 9%                 |
| **Diagnostic method**                   |                |                                |                    |
| ELISA                                   | 47             | 10.37 (7.30-14.54)             | 9%                 |
| ELISA/Western blot                      | 9              | 5.14 (3.62-7.25)               | 5%                 |
| **Duration of HD (Month)**              |                |                                |                    |
| 60<                                     | 4              | 15.78 (8.85-26.57)             | 87%                |
| 60>                                     | 2              | 27.69 (20.69-35.99)            |                    |
| **Age (Year)**                          |                |                                |                    |
| 40<                                     | 6              | 4.91 (1.76-12.97)              | 52%                |
| 40>                                     | 7              | 12.19 (6.42-21.93)             | 94%                |
| **Gender**                              |                |                                |                    |
| Male                                    | 17             | 10.86 (6.66-17.20)             | 94%                |
| Female                                  | 17             | 9.54 (5.62-15.74)              | 91%                |
| **Study year**                          |                |                                |                    |
| 1994-2000                               | 18             | 6.60 (3.82-11.16)              | 92%                |
| 2001-2005                               | 9              | 9.81 (4.54-19.93)              | 9%                 |
| 2006-2010                               | 4              | 10.77 (5.16-21.12)             | 8%                 |
| 2011-2015                               | 13             | 11.70 (6.15-21.15)             | 9%                 |
| 2016-2020                               | 12             | 11.13 (5.59-20.94)             | 9%                 |
| **Study location**                      |                |                                |                    |
| Argentina                               | 2              | 9.82 (6.10-15.42)              |                    |
| Brazil                                  | 5              | 1.77 (0.23-12.31)              | 9%                 |
| China                                   | 1              | 48.24 (40.82-55.73)            |                    |
| Croatia                                 | 1              | 27.92 (23.71-32.55)            |                    |
| Egypt                                   | 3              | 12.78 (1.54-57.82)             | 9%                 |
| Estonia                                 | 1              | 3.98 (1.91-8.11)               |                    |
| France                                  | 2              | 7.63 (3.29-16.72)              | 2%                 |
| Germany                                 | 1              | 3.33 (1.39-7.76)               |                    |
| Greece                                  | 4              | 4.90 (3.86-6.19)               |                    |
| India                                   | 2              | 38.52 (30.32-47.43)            |                    |
| Iran                                    | 11             | 9.11 (4.53-17.49)              | 9%                 |
| Italy                                   | 7              | 7.52 (4.39-12.58)              | 8%                 |
| Japan                                   | 3              | 17.26 (9.87-28.44)             | 8%                 |
| Saudi Arabia                            | 1              | 7.23 (3.28-15.17)              |                    |
| Spain                                   | 2              | 6.19 (2.98-12.43)              |                    |
| Sweden                                  | 1              | 6.04 (3.38-10.58)              |                    |
| Taiwan                                  | 1              | 31.00 (26.66-35.70)            |                    |
| Tunisia                                 | 1              | 10.14 (7.14-14.21)             |                    |
| Turkey                                  | 6              | 12.92 (5.65-26.87)             | 8%                 |
| United Kingdom                          | 1              | 36.84 (26.79-48.18)            |                    |

(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 the years of 1994 and 2000. Since 2001 until 2020, the number of HEV-seropositive cases among HD patients dramatically was increased, and the seroprevalence was 11.13% (95% CI: 5.59%-20.94%) between the years of 2016 and 2020 (Table 3). Discussion

The present study for the first time estimated the seroprevalence of HEV in HD patients in order to 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 [74]. After cardiovascular complications, infections are the second major leading cause of death in HD patients [75]. Among the different blood-borne viral infections, hepatitis and human immunodeficiency viruses are the most common problems in HD units as well as general population [76]. Hepatitis E is generally considered as 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 especially in immunocompromised individuals such as HD patients [77]. A recent meta-analysis performed on the association between HEV seroprevalence and hemodialysis showed that the seroprevalence is more prevalent in patients undergoing HD than non-HD control [78]. One of the most important finding of our study is that the overall seroprevalence of HEV infection in patients on HD is increasing during the last years around the world, which should be considered as 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. It is interesting that 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 [79]. It should be noted that HEV G3 is more associated with the establishment of persistent infection in immunocompromised patients, leading to the development of chronic hepatitis and serious liver complications [80]. Our analysis suggested that the seroprevalence of HEV in HD units varies throughout the world. In the
past, it was thought that HEV infection was limited to developing countries with poor hygiene and sanitary conditions. Nowadays, this assumption has been challenged, because the 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 the wide variety of the HEV prevalence. In developed countries, transmission of HEV to humans occurs mainly via consumption of raw pork products, particularly pork liver [81]. It was documented that zoonotic HEV G3 strains mostly circulate between humans, swine and wild boar in Europe [82].

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 an only recombinant HEV vaccine approved in China since 2011 which exhibited a high effectiveness to prevent HEV infection in the general population in China [83]. Therefore, vaccination schedule in HD patients can play an effective role to reduce HEV prevalence. Another suggestion for preventing hepatitis E transmission is taking preventive measures at the level of the community (e.g., water decontamination, improved hygiene and sanitation) and the personal (e.g., 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 consider as the best strategies for decreasing the prevalence rate. On the other hand, it should be noted that our estimation can be affected by some limitation such as small number and low geographical coverage of the studies. Until now, there is 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.

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 as an emerging public health issue. We also demonstrated that blood transfusion is significantly associated with increased rate of HEV seropositivity. There are no data regarding the seroprevalence of HEV in HD patients in some countries, and therefore, it is highly recommended to perform screening tests for HEV in HD patients in other regions of the world to have more reliable estimates of overall seroprevalence of HEV.

**Abbreviations**

HEV: Hepatitis E virus; HD: hemodialysis; CI: confidence interval; ESRD: End-Stage Renal Disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ELISA: enzyme-linked immunosorbent assay.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

All data generated or analyzed during this study are included in this article.

**Competing interests**

The authors have no conflict of interest.

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**Authors ‘contributions**

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

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Figures
Figure 1

Flowchart presenting the steps of literature search and selection
| Study            | Events | Total | Proportion | 95%-CI    |
|------------------|--------|-------|------------|-----------|
| < 2010           |        |       |            |           |
| Knodler 1994     | 5      | 150   | 0.03       | [0.01; 0.08] |
| Halton 1994      | 16     | 147   | 0.11       | [0.06; 0.17] |
| Buti 1995        | 3      | 50    | 0.06       | [0.01; 0.17] |
| Psichogiou 1996  | 27     | 420   | 0.06       | [0.04; 0.09] |
| Guiserix 1996    | 2      | 62    | 0.03       | [0.00; 0.11] |
| Gessoni 1996     | 18     | 193   | 0.09       | [0.06; 0.14] |
| Fabrizi 1996     | 6      | 204   | 0.03       | [0.01; 0.06] |
| Cengiz 1996      | 10     | 72    | 0.14       | [0.07; 0.24] |
| Parana 1997      | 0      | 392   | 0.00       | [0.00; 0.01] |
| Fabrizi 1997     | 6      | 204   | 0.03       | [0.01; 0.06] |
| Sylvan 1998      | 11     | 182   | 0.06       | [0.03; 0.11] |
| Dalekos 1998     | 7      | 211   | 0.03       | [0.01; 0.07] |
| Gessoni 1998     | 23     | 247   | 0.09       | [0.06; 0.14] |
| Arinsoy 1998     | 9      | 52    | 0.17       | [0.08; 0.30] |
| Abdel Hady 1998  | 38     | 96    | 0.40       | [0.30; 0.50] |
| Mateos 1999      | 4      | 63    | 0.06       | [0.02; 0.15] |
| Del 1999         | 4      | 70    | 0.06       | [0.02; 0.14] |
Figure 2

Forest plot of the seroprevalence of HEV infection among HD patients, according to the random effect model, stratified by study year (before and after 2010)
Figure 3
Forest plot of the association between blood transfusion and HEV seropositivity, according to the random effect model

Figure 4
Time trend in the seroprevalence of HEV among HD patients