Hepatitis E virus infection in hematopoietic stem cell transplant recipients: a systematic review and meta-analysis

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ABSTRACT

Although most patients with hepatitis E virus (HEV) infection are asymptomatic or have mild symptoms, its infection is generally underdiagnosed and overlooked. In immunocompromised patients, HEV infection can lead to acute liver failure and death. However, the clinical evidence of HEV infection in hematopoietic stem cell transplant (HSCT) recipients is scarce; thus, we conducted this systematic review and meta-analysis to assess the prevalence of HEV infection in this population. We searched MEDLINE, EMBASE, and the Cochrane Library databases from inception through October 2020 to identify studies that reported the prevalence of HEV infection among HSCT recipients. HEV infections were confirmed by HEV-IgG/IgM or HEV-RNA assay. A total of 1977 patients from nine studies with a follow-up time up to 40 months were included in the final analysis. The pooled prevalence of positive HEV-RNA was 3.0% (95% CI 2.3% to 4.0%). The pooled prevalence of positive HEV-IgG was 10.3% (95% CI 4.5% to 21.8%). The pooled prevalence of de novo HEV infection was 2.9% (95% CI 1.8% to 4.5%). Age and male gender were not associated with HEV-RNA or HEV-IgG positivity in the meta-regression analysis. In conclusion, the prevalence of HEV-IgG in HSCT recipients was about 10%, while the prevalence of HEV-RNA was only 3%. However, further studies that focus on the clinical outcomes in this population are warranted.

INTRODUCTION

Hepatitis E virus (HEV) is endemic and one of the most common causes of acute hepatitis in many developing countries.[1–3] However, the number of HEV infections has been rising in developed countries over the last decade.[4–6] HEV is transmitted primarily by fecal-oral route, usually via contaminated water and food (raw or undercooked meat).[7–9] However, the transmission of HEV can also occur through contaminated blood products, either via transfusion or stem cell products in hematopoietic stem cell transplant (HSCT).[10–13] The clinical course of HEV infection is usually asymptomatic or self-limited, without leading to chronic infection in the general population.[14] Nevertheless, HEV infection may result in fulminant hepatic failure, with high mortality rates, and can also evolve to chronicity in pregnant women, patients with chronic liver disease, and immunocompromised patients.[15–21]

The clinical outcomes of HEV infection in transplant recipients are mostly available in patients with solid organ transplant. HEV infection has been reported to cause graft cirrhosis and liver failure in liver transplant recipients.[22] A recent meta-analysis showed that the prevalence of HEV infection was highest in liver transplant and lowest in lung transplant.[23] Subgroup analyses also showed that the prevalence of HEV infection was significantly higher in middle-income countries compared with high-income countries. However, data on HEV infection in HSCT recipients are limited. Available data suggest that HSCT recipients had a wide range of HEV infection prevalence from less than 1% to 4% and an HEV-IgG seroprevalence as high as 30%.[24–26] Nevertheless, each cohort was limited by a small sample size and the nature of being a single-center study. Most importantly, evidence supporting the adverse outcomes in HSCT population infected with HEV is still lacking. Thus, we conducted this systematic review and meta-analysis to assess the prevalence of HEV infection in HSCT recipients. The results of this study would emphasize the burden of HEV infection in HSCT recipients, leading to further investigations on its association with patient and graft outcomes.

METHODS

Search strategy

We recently reported the prevalence of HEV infection in solid organ transplant recipients.[23] Thus, the search strategy in the current study was similar to our recent publication. Additionally, the methodology of this systematic review partially resembled our previous original article.[27] The current manuscript complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[28] statement as well as the Meta-Analysis of Observational Studies in Epidemiology[29] guidelines. We conducted the systematic search through Ovid MEDLINE, EMBASE, and the Cochrane Library from database inception to October 2020 using the

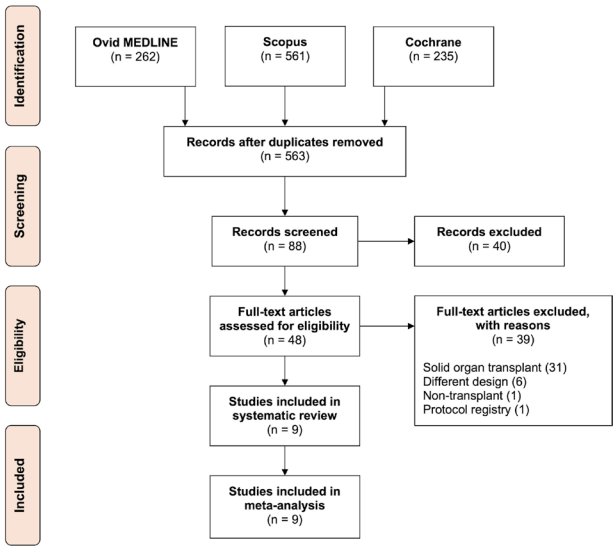

Figure 1 PRISMA flow diagram illustrating the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

following search terms: ("hepatitis E" OR "HEV") AND ("transplant" OR "transplantation") AND ("outcome*" OR "mortality" OR "incidence" OR "death"), without language restrictions. The complete search strategy for each database is available in online supplemental document 1.

Inclusion criteria

The eligibility of each study was determined by the following inclusion criteria: (1) the nature of the study is observational or conference abstract; (2) the study population is HSCT recipients; and (3) the prevalence of HEV infection was reported as one of the outcomes of interest. Case reports, case series, review articles, or articles concerning pediatric patients were excluded. Solid organ transplant recipients were excluded. Study eligibility was independently evaluated by two investigators (PH and AT). Any disagreements were resolved by mutual consensus among all authors. The quality of each study was assessed in compliance with the Newcastle-Ottawa Scale,[30] which is composed of six matrices, namely (1) representativeness of the subjects; (2) ascertainment of the exposure; (3) demonstration of the outcome of interest not present at the start of the study; (4) assessment of outcome; (5) follow-up duration period long enough for the outcome to occur; and (6) adequate follow-up duration.

Review process and data extraction

The titles and abstracts of all references were screened (PH and AT). The full text of the remaining articles was reviewed to determine their eligibility to be included in the systematic review and meta-analysis. We used our standardized data collection form to extract the following information from the included studies: first author's name, year of publication, country of origin, study design, subject(s), sample size, age, male sex, prevalence of HEV, laboratory test used to diagnose HEV infection, death, other reported outcomes, and follow-up duration. De novo HEV infection is defined by post-transplant HEV infection in patients with negative pretransplant HEV-IgG, HEV-IgM, or HEV-RNA.

Measurements

The prevalence of HEV infection and de novo HEV infection was meta-analyzed and the results were reported in percentage along with 95% CI. The forest plot of each analysis is presented. Descriptive statistics are presented in percentage for categorical data and in mean±SD or median (IQR) for continuous data.

Statistical analysis

All statistical analyses were performed by the Comprehensive Meta-Analysis V.3 software (Englewood, New Jersey, USA) and SPSS V.23.0. Statistical heterogeneity of studies was assessed using Cochran's Q-test, which was supplemented by I^2 statistics. An I^2 value of ≤25% represents insignificant heterogeneity, 25%–50% represents low heterogeneity, 50%–75% represents moderate heterogeneity, and >75% represents high heterogeneity.[31] For analyses with I^2 >50%, the results were analyzed by random-effects model to minimize heterogeneity and external variance.[32] A p value less than 0.05 represents statistical significance.

Subgroup analysis, meta-regression analysis, and publication bias

Subgroup analyses were conducted by categorizing the included studies based on study year and sample size. Mixed-effect model of analysis was used in the subgroup analyses. Meta-regression analysis was performed to determine the association between age and male sex with HEV-RNA positivity and HEV-IgG positivity. Publication bias was evaluated by Egger's regression intercept. An intercept p value less than 0.05 is considered significant for potential publication bias.

RESULTS

Literature search and study characteristics

A total of nine studies from 2012 to 2020 were included in this meta-analysis and systematic review. Seven studies were retrospective, one study was prospective, and one study was cross-sectional. Figure 1 provides a flow chart of the literature search and study selection for this meta-analysis. The final analysis included a total of 1977 patients with a follow-up duration up to 40 months. The baseline characteristics of the included studies are shown in table 1.

Meta-analysis results

Prevalence of positive HEV-RNA

A total of nine studies were included in the analysis for the outcome regarding the prevalence of positive HEV-RNA. The pooled prevalence of positive HEV-RNA was 3.0% (95% CI 2.3% to 4.0%; I^2=6.7%). The forest plot is shown in figure 2A. When three studies that included subjects with elevated hepatic enzymes were excluded, the pooled prevalence of positive HEV-RNA was 2.8% (95% CI 2.1% to 3.8%; I^2=26.8%). Similarly, when only studies that originated from Europe were analyzed (n=8), the pooled prevalence of positive HEV-RNA was 2.9% (95% CI 2.2% to 3.9%; I^2=13.0%). These findings were meta-analyzed using fixed-effects model.

Table 1 Baseline characteristics of included studies

Author, year	Country	Study type	Population	Sample size	Age (years)	% male	Follow-up (months)	Confirmatory test	Year of testing	% positive HEV-IgG	% positive HEV-RNA	Serology assay used
Abravanel *et al*, 2012[25]	France	Retrospective	Allo-HSCT and auto-HSCT candidates	88	51	65.9	6 months after transplant	Positive IgG/IgM/RNA	2009–2010	36.4	0	Adaltis/Wantai
Ankcorn *et al*, 2018[47]	UK	Prospective	Allo-HSCT candidates	144	N/A	N/A	4–18	HEV-RNA/Ag	2016	N/A	2.08	N/A
Furfaro *et al* 2020[24]	Italy	Retrospective	Allo-HSCT and auto-HSCT candidates	563	48	56.5	N/A	Positive IgG/RNA	2010–2015, 2017–2019	6.04	3.4	Wantai/Ultra
Koenecke *et al*, 2012[26]	Germany	Retrospective	Allo-HSCT with elevated ALT	52	41	62	N/A	Positive IgG/RNA	1998–2004	5.8	0	Abbott
Reekie *et al*, 2018[48]	UK	Cross-sectional	Allo-HSCT and auto-HSCT	259	N/A	N/A	N/A	HEV-RNA	2013–2015	N/A	0.39	N/A
Swartling *et al*, 2020[49]	Sweden	Retrospective	Allo-HSCT candidates	236	N/A	N/A	25	Positive IgG/IgM/RNA	2008–2015	4.7	3.4	Diapro
Tang *et al*, 2019[50]	China	Retrospective	Haploidentical allo-HSCT with elevated ALT	177	26	63.3	36.9	Positive IgG/IgM/RNA	2014–2017	N/A	3.9	MP Diagnostics
Versluis *et al*, 2013[20]	The Netherlands	Retrospective	Allo-HSCT candidates	328	50.4	54	40.9	Positive IgG/IgM/RNA	2006–2011	12.9	2.4	Wantai
Willemse *et al*, 2017[51]	The Netherlands	Retrospective	Allo-HSCT with elevated ALT	130	N/A	53.8	N/A	HEV-RNA	2005–2015	N/A	4	N/A

Ag, antigen; Allo-HSCT, allogeneic hematopoietic stem cell transplant; ALT, alanine transaminase; HEV, hepatitis E virus; N/A, not available.

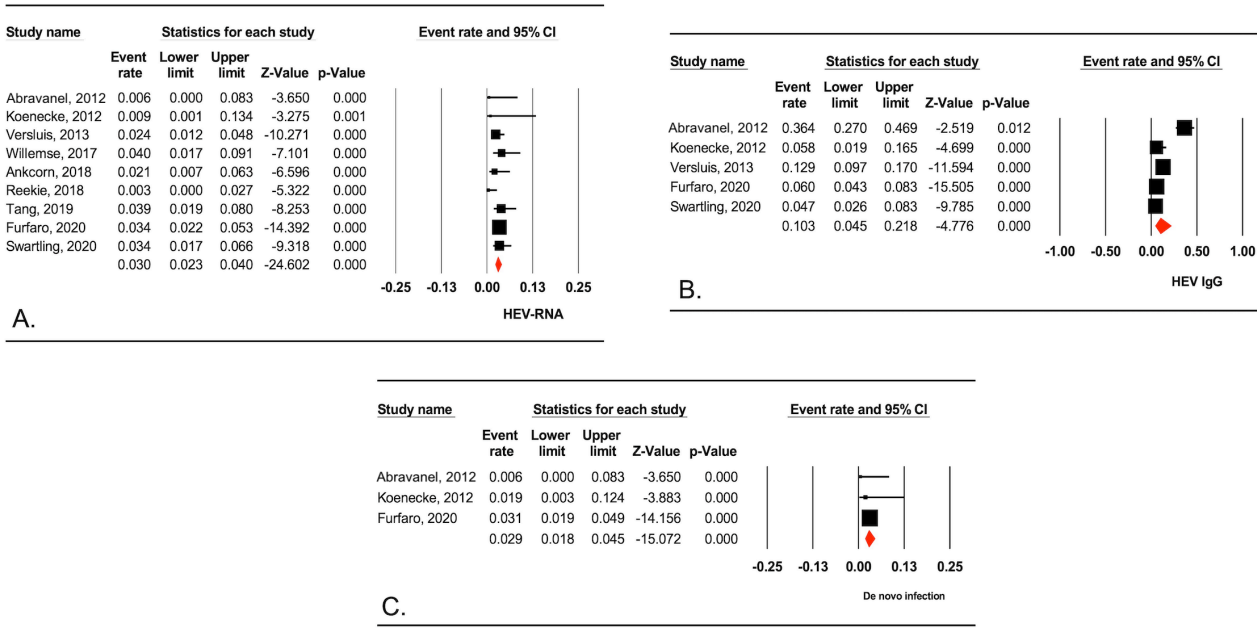

Figure 2 Forest plot for pooled prevalence of (A) positive HEV-RNA, (B) positive HEV-IgG, and (C) de novo HEV infection. HEV, hepatitis E virus.

Prevalence of positive HEV-IgG

A total of five studies were included in the meta-analysis for the outcome regarding the prevalence of positive HEV-IgG. The pooled prevalence of positive HEV-IgG was 10.3% (95% CI 4.5% to 21.8%; I^2=94.5%). The forest plot is shown in figure 2B. When three studies that included subjects with elevated hepatic enzymes were excluded, the pooled prevalence of positive HEV-IgG was 11.4% (95% CI 4.6% to 25.7%; I^2=95.8%). These findings were meta-analyzed using random-effects model.

Prevalence of de novo HEV infection after HSCT

A total of three studies were included in the meta-analysis for the outcome regarding the prevalence of de novo HEV infection. The pooled prevalence of de novo HEV infection was 2.9% (95% CI 1.8% to 4.5%; I^2=0). The forest plot is shown in figure 2C.

Subgroup analysis

The results of the subgroup analysis are shown in table 2. We analyzed the pooled estimated prevalence of positive HEV-RNA based on study characteristics by using mixed-effects model to minimize interstudy variance. We found that the estimated positive HEV-RNA prevalence was no different after adjustment for study year (prior to 2015 vs after 2015) and sample size (<200 vs >200).

Meta-regression analysis

The results of the meta-regression analysis are shown in table 3. In brief, age and male sex were not associated with HEV-RNA positivity and HEV-IgG positivity.

Publication bias

Egger's regression intercept for the prevalence of HEV-RNA, HEV-IgG, and de novo HEV infection was 0.013, 1.000, and 0.296, respectively. This indicated that the analysis of HEV-RNA prevalence could be subjected to publication bias. Publication bias analysis by funnel plot and Begg's test cannot be performed given the number of included studies is less than 10.[33 34]

DISCUSSION

Our systematic review and meta-analysis showed that the pooled prevalence of positive HEV-RNA, HEV-IgG, and de novo HEV infection after HSCT was 3%, 10.3%, and 2.9% respectively. The recent meta-analysis by Li *et al*,[35] including 419 studies, showed that the global prevalence

Table 2 Subgroup analysis

Subgroup	Results, % (95% CI)	Statistics
Year		
Prior to 2015	2.1 (1.1 to 4.0)	
After 2015	3.3 (2.4 to 4.4)	Q=1.342, p=0.247
Sample size		
Less than 200	3.1 (1.9 to 5.1)	
More than 200	3.0 (2.2 to 4.1)	Q=141, p=0.707

Table 3 Meta-regression analysis of clinical variables

Variable	n	Coefficient	Statistics
HEV-RNA positivity			
Age	5	−0.0138	Q=0.53, p=0.4292
Male gender	5	0.9675	Q=0.03, p=0.8582
HEV-IgG positivity			
Age	4	0.1708	Q=2.08, p=0.1490
Male gender	4	11.1997	Q=1.29, p=0.2555

HEV, hepatitis E virus.

of HEV-IgG and HEV-RNA in the general population was 12.5% (95% CI 10.4 to 14.7) and 0.2% (95% CI 0.15 to 0.5), respectively. Although our study did not compare our findings with the general population, it is suggestive that the pooled prevalence of HEV-IgG positivity in our study was similar to the meta-analysis by Li *et al*.[35] Interestingly, the pooled prevalence of HEV-RNA positivity in our meta-analysis was higher than the global prevalence in the general population. These findings indicate that the prevalence of acute HEV infection (defined by positive HEV-RNA) was higher in HSCT recipients.

Even though the major route of transmission is the fecal-oral route from contaminated water and food, HEV infection can be transmitted by contaminated blood products.[10–13] Patients with hematological malignancies and HSCT are likely to have frequent blood transfusions given the nature of their disease and treatment. Although HEV-RNA universal screening of blood transfusion has been introduced in some countries, such as UK, Japan, and the Netherlands, HEV is not routinely screened in many other countries.[36 37] In the UK, the prevalence of HEV viremia was reported at 1 in 3830 donations, with similar prevalence in other European countries.[38] Moreover, eight European Union countries implemented HEV screening strategies among blood donors in 2012.[39 40] In our study, an increase in HEV-RNA positivity could be explained by the year of testing ranging from 1998 to 2019—before universal testing for HEV has been implemented in Europe. With this time frame, it is speculated that the prevalence of HEV infection would decrease over time in the next decades if most of acute HEV infections are transmitted through blood products.

Immunosuppressants given to prevent graft-versus-host disease in HSCT recipients may be another factor contributing to HEV infection. The study by Kamar *et al*[41] found that tacrolimus use was one of the independent predictive factors associated with chronic HEV infection. Carré *et al*[42] also reported an allogeneic HSCT patient receiving ciclosporin/mycophenolate mofetil who developed fulminant hepatitis E. Similarly, Tavitian *et al*[43] reported a case with persistent HEV infection in a patient with vincristine/adriamycin/dexamethasone. One hypothesis linking the use of immunosuppressants and HEV infection is via impairment of T cell response, which is the primary immune response against HEV. This hypothesis was supported by Suneetha *et al*,[44] in which HEV-specific T cell response was decreased in transplant patients who developed chronic hepatitis E.

Compared with solid organ transplant recipients, the prevalence of HEV infection in HSCT recipients is lower. The recent meta-analysis by Hansrivijit *et al*[23] showed that the prevalence of HEV infection in solid organ transplant recipients was 20.1%. Also, the pooled prevalence of de novo HEV infection in solid organ transplant recipients was higher than HSCT recipients (5.1% vs 2.1%). Majority of the patients in that meta-analysis were patients with liver transplants. Interestingly, in a previous cohort by Riveiro-Barciela *et al*[45] it was found that liver transplant was one of the risk factors for HEV infection.

Our meta-analysis found that age and male gender are not independent factors for positive HEV-RNA or HEV-IgG. This finding was different from the previous study by Furfaro *et al*,[24] which showed that age was an independent factor for positive HEV-IgG. This discrepancy was limited by the fact that not all studies were included in the meta-regression analysis. To increase validity, more studies reporting baseline patient characteristics and their seroprevalence of HEV-IgG as well as the prevalence of HEV-RNA are required.

We acknowledge some limitations. First, all included studies were observational studies, which carry a risk of potential bias. Second, the prevalence of HEV can be affected by the type of assay used, which was not elucidated in our study due to the inhomogeneous use of serological assays. However, all studies used the standardized kit for HEV-RNA analysis. Third, it remains unclear how HEV infection affects the clinical outcomes given that the outcomes of HEV infection were not reported in the original studies. Nonetheless, despite the aforementioned limitations, our current study is the first meta-analysis reporting the pooled estimated prevalence of HEV infection in HSCT. Fourth, the serological assays for HEV-IgG were not uniform across studies. A few previous studies showed that the prevalence of seropositive IgG against HEV was higher in the Wantai assay.[23 35 46] More studies aiming to determine the clinical impact of HEV infection, especially among HSCT recipients, are recommended. It is also noteworthy that the analysis of HEV-RNA prevalence was subjected to publication bias.

In conclusion, the pooled prevalence of HEV-IgG positivity in HSCT recipients was 10.3% and the prevalence of HEV-RNA positivity was 3.0%. Age and male gender were not associated with HEV-IgG or HEV-RNA positivity.

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