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TITLE:

HEPATITIS E VIRUS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW

Running Title:

HEV in HSCT recipients: a systematic review

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Highlights

- Hematopoietic stem cell transplant recipients are at high risk of HEV infection
- The overall prevalence of HEV infection differs according to the diagnostic method
- The overall anti-HEV IgM/IgG seroprevalance was 2.0% and 11.4%, respectively
- HEV RNA prevalence in HSCT recipients is 1.50%
- HEV infection in underestimated in HSCT recipients

Abstract: Background: In developed countries, Hepatitis E virus (HEV) infections, especially by HEV-3, are frequently associated with asymptomatic infection or self-limiting acute hepatitis, although it has been described as a cause of chronic infection, especially in immunocompromised hots. Hematopoietic stem cell transplant (HSCT) recipients have been recognized as an important risk group for HEV infection due to their prolonged immunosuppression state.
Objectives: We aimed to perform a systematic review of published data to evaluate HEV infection prevalence among HSCT recipients.
Study Design: Literature search was performed concerning published manuscripts regarding 'hepatitis E virus AND stem cell transplantation' following the Preferred Reporting of Systematic Reviews and MetaAnalyses (PRISMA) guidelines. Statistical analysis was performed using the MetaXL software to estimate the overall prevalence of HEV infection according to the different diagnostic approaches (HEV RNA and anti-HEV IgM and/or IgG detection).
Results: A total of 7 manuscripts were included for data analysis, with 6 studies performed in Europe and 1 study in China. Regarding HEV RNA detection, the overall HEV infection prevalence was 1.50% (95% CI: 0.70- 2.60). The overall anti-HEV IgM seroprevalence was 2.00% (95% CI: 0.30- 4.50), and anti-HEV IgG was 11.4% (95% CI: 1.80-26.3).
Conclusions: This systematic review reveals that the overall prevalence of HEV infection in HSCT patients differ according to the diagnostic, thus emphasizing the need of more studies to increase the data regarding prevalence and incidence in HSCT recipients.

Keywords: Hepatitis E virus; HEV; stem cell transplantation; HSCT; prevalence; systematic review.

BACKGROUND

Hepatitis E virus (HEV) was recently recognized as the most common cause of acute viral hepatitis worldwide, with the World Health Organization (WHO) estimating 20 million infections, >3 million acute cases, and >57,000 HEV-related deaths, annually[1,2]. In industrialized countries, hepatitis E was considered a rare disease until the discovery of the new HEV genotypes that turned this infection a concern of public health. In fact, four major HEV genotypes infect humans: genotypes 1 (HEV-1) and 2 (HEV-2), that are transmitted through the fecal-oral route via fecal contaminated water, being prevalent in areas of poor sanitation, such as in developing countries[3,4]; and genotypes 3 (HEV-3) and 4 (HEV-4) that are zoonotic viruses transmitted to humans mainly through undercooked pork and boar meat and contact with pigs[3–8], although, the transfusion of blood products has also been recently recognized as a risk factor[9–11]. HEV-3 is today recognized as the main cause of sporadic autochthonous cases in industrialized countries[3,4] and the numbers show that the incidence of reported cases has been increasing[12–17].

In Europe, HEV infections are mainly caused by HEV-3, a genotype that causes asymptomatic infection or self-limiting acute hepatitis in healthy individuals, although it can lead to chronic infection with rapidly progressive cirrhosis in immunosuppressed patients, such as individuals with HIV, hematological malignancies, or transplant-related patients[18–21]. Solid organ transplant (SOT) recipients and hematopoietic stem cell transplant (HSCT) recipients are an important group at risk for HEV infection due to their prolonged immunosuppression state, that increases the risk for developing chronic infection[19]. Patients undergoing allogeneic-HSCT (allo-HSCT) have in general a higher risk for viral infections and higher incidence of graft-versus-host disease (GVHD) than autologous-HSCT (auto-HSCT)[22,23]. In allo-HSCT recipients, progression to chronic infection may be favored by the severity of immunosuppression, which results in impaired immune reconstitution, including insufficient lymphocyte recovery, that are risk factors for post-transplantation infections[24–26].

Moreover, HSCT recipients have a high transfusion burden, which is a problem particularly in countries that have not introduced HEV screening in blood donations[22,27,28].

The evidence that most of the HEV-3 infections become chronic in immunocompromised hosts, especially those after transplantation, makes these patients an important group of study[29,30]. In SOT recipients, the reported acute HEV infection prevalence is 1-3%, with 47-83% of the patients developing chronic hepatitis[31–33], however, the prevalence and incidence of HEV in HSCT recipients is largely unknown.

OBJECTIVES

In the present study, we aim to summarize published data regarding HEV infections in HSCT recipients by performing a systematic review of the literature.

STUDY DESIGN

Literature search and study selection

Preferred Reporting of Systematic Reviews and MetaAnalyses (PRISMA) guidelines were followed in the preparation of this systematic review. Different queries, including MeSH terms, were tested and the literature search was performed with the query that obtained more representative manuscripts: **'**hepatitis E virus AND stem cell transplantation'. PubMed and Scopus databases were searched, independently by two of the authors (SC and CC), for published manuscripts on 31st January 2019 without restrictions on time period, sample size or population.

The eligibility criteria applied to studies were: 1) HEV infection (present or past) identified by the presence of HEV RNA and/or HEV-specific antibodies (IgM/IgG) in tested samples; 2) HSCT

recipients; 3) provide prevalence data. The exclusion criteria applied were: 1) duplicate data; 2) other types of manuscripts (reviews, case reports, comments or letters to the editor); 3) no access to abstracts and/or full texts; and 4) other languages rather than English, Spanish or Portuguese. Manuscript titles and abstracts were screened according to the eligibility criteria and selected manuscripts were fully reviewed for data extraction (author, publication date, country, population, age range, type of HSCT, HEV detection methods and the number of positive and negative cases). All manuscripts were reviewed independently by two of the authors (SC and CC) with disagreements mediated by the senior researcher (HS).

Statistical analysis

All data was inserted in a database that was used for prevalence analysis and comparison between studies. Prevalence analysis was performed using the *MetaXL* program version 5.3 (EpiGear International, Sunrise Beach, Queensland, Australia). The overall prevalence of HEV infection was estimated using the different approaches of diagnosis (HEV RNA or anti-HEV IgM/IgG detection) in HSCT recipients pooling the study data using the random effects model. The random effects model was used since a considerable heterogeneity among studies was expected, due largely to the different settings (populations, types of patients, age, gender, diagnostic methods) in which studies were conducted. The double arcsine transformation method was used for variance stabilization[34] considering a 95% confidence interval and a 5% statistical significance level (p<0.050).

RESULTS

Study selection and description

The literature search retrieved a total of 73 manuscripts from both databases, and after duplicates removal, a total of 54 records were screened (Figure 1). After applying inclusion/exclusion criteria, 41

records were excluded: language (n=1), reviews (n=18), other types of articles such as Case Reports and Letter to the Editor (n=9), and studies not related to HSCT patients or HEV detection (n=13). A total of 13 full-text articles were assessed for full-reading of which 6 were excluded: 1 review, 4 case reports and 1 was not performed in HSCT patients. The bibliography of the selected manuscripts was reviewed to identify any new publications and no other article was added to the analysis.

After the full revision process, we included 7 manuscripts for data analysis[18,21,35–39] (Table 1). Overall, these 7 studies included a total of 1178 HSCT patients from different countries: six studies were performed in Europe (United Kingdom, Netherlands, France, and Germany)[18,21,36–39] and one study in China[35]. These studies evaluated the prevalence of HEV infection based on the detection of HEV RNA (n=7) and/or the presence of anti-HEV IgM (n=3)/IgG (n=4). Phylogenetic analysis was performed in only three of these seven studies, revealing only HEV-3 genotype[21,37,39].

Here, we briefly resume the data from all included studies. In China, a study evaluated HEV infection in 177 haploidentical-HSCT recipients that presented unexplained elevated transaminases after transplant, identifying 7 patients with an acute/current HEV infection (2 positives for HEV RNA and 5 positives for anti-HEV IgM/IgG)[35]. In the United Kingdom, two studies identified a total of 4 recipients with an acute HEV infection based in the presence of HEV RNA: in one study, 259 HSCT recipients (111 allo-HSCT, 145 auto-HSCT, and 3 CD34 top-up procedures) were evaluated and only 1 HEV RNA positive patient was identified[39]; while the other study analyzed 144 allo-HSCT recipients and 3 patients were positive for HEV RNA[21]. In the Netherlands, two studies analysed HEV infection in HSCT: one study was performed in 130 allo-HSCT recipients with elevated alanine aminotransferase (ALT), identifying 5 HEV RNA positive patients[36]; the other study analyzed 328 allo-HSCT recipients transplanted over a 5-year period, identifying a total of 10 patients with a current infection (8 were positive for HEV RNA and 2 were positive for anti-HEV IgM) and 41 patients were seropositive for anti-HEV IgG[37]. In France, a study with 88 HSCT recipients (72 allo-HSCT and 16 auto-HSCT) revealed that none patient tested positive for HEV RNA, while 3 were positive for anti-

HEV IgM[18]. Interestingly, this study found a seroprevalence of anti-HEV IgG of 12,5% (11/88) and 36,4% (32/88) in the same group of HSCT recipients when using two different enzyme immunoassays (EIA) methods. In the study from Germany with 52 allo-HSCT recipients with elevated ALT, but without any specific cause of hepatitis, none of them tested positive for HEV RNA, while 3 were positive for anti-HEV IgG[38].

HEV infection prevalence analysis

We have performed an analysis of the prevalence of HEV infection in HSCT recipients according to the different approaches of diagnosis. The diagnosis of HEV positive cases is based on the identification of a patient with an HEV RNA positive sample (serum, plasma, blood or feces) or both anti-HEV IgM and IgG positive sample, nevertheless, the seroprevalence of the infection is referred to the detection of anti-HEV IgG only.

Considering the analysis of HEV RNA detection, a total of 1178 HSCT patients were studied and only 19 were positive, which gives an overall prevalence of 1.50% (95% CI: 0.70-2.60) with no significant difference observed between the different studies (p=0.090; Figure 2).

The analysis of anti-HEV IgM and IgG was performed separately: the detection of anti-HEV IgM as marker of acute infection was tested in a total of 593 HSCT patients with only 10 positive cases, giving an overall anti-HEV IgM prevalence of 2.00% (95% CI: 0.30-4.50; p=0.060; Figure 3); while the detection of anti-HEV IgG, a marker of past infection, was described in a total of 645 samples, 82 HSCT recipients were found positive to anti-HEV IgG giving an overall IgG seroprevalence of 11.4% (95% CI: 1.80-26.3), with statistically significant differences between the studies (p<0.001; Figure 4).

DISCUSSION

The evidence that most of the HEV-3 infections become chronic in immunocompromised hosts, especially those after transplantation, makes these patients an important group of study[29,30]. Since the prevalence and incidence of HEV in HSCT recipients is largely unknown, we have performed a systematic review to understand the burden of HEV infection in these group of immunocompromised patients.

We found that there is a wide variation in HEV infection definition in literature, although in accordance with a recent surveillance report by the *European Centre for Disease Prevention and Control* (ECDC), concerning hepatitis E virus in Europe, a positive case is considered in a patient with an HEV RNA positive sample (serum, plasma, blood or feces) or both anti-HEV IgM and IgG positive sample[12]. HEV RNA is detected usually between 2 and 8 weeks when viremia reaches its peak before strong declining, then, around 3 weeks after clinical symptoms, HEV RNA becomes undetectable, with the virus continuing to be shed in the stool for another 1 to 2 weeks. On the other hand, the anti-HEV IgM immune response remains detectable for 3–12 months and the IgG response reaches its peak four weeks later than IgM, remaining detectable for several years, although the exact duration of this response remains uncertain[20,30].

The fact that there is no standardized case definition, in addition to the heterogeneity in the analytical sensitivity of the commercial HEV assays, makes the comparison of studies more difficult. In this systematic review, all the seven studies performed the detection of HEV RNA, the most robust marker of acute/active infection[18,21,35–39], while four performed also the detection of anti-HEV IgM/IgG[18,35,37,38]. The studies that performed HEV RNA detection as the diagnostic method for HEV infection in HSCT recipients revealed similar results between them, with an overall prevalence of HEV infection of 1.5%. Furthermore, we found that the overall prevalence of anti-HEV IgM was of 2.0%, a comparable value to the reported by the detection of HEV RNA, which is expected since both are markers of acute infection.

The analysis of anti-HEV IgG showed an overall seroprevalence of 11.4% in HSCT patients, with significant differences between the results of the different studies, mainly due to the study from France which revealed a much higher prevalence when compared to the others studies[18]. These results are difficult to compare due to the differences in the sensitivities and specificities of anti-HEV IgG commercial immunoassays[40–43]. Moreover, seroprevalence is greatly influenced by food habits[5,43] and to differences in culinary practices between countries/regions[43]. Reported anti-HEV IgG seroprevalence not only varies between countries but also within countries, with significant variance between regional areas[43]. Indeed, even seroprevalences in Europe are very difficult to compare in consequence of these serology limitations and very different rates have been reported across the continent, ranging from 1.3-52%[44–46]. In Finland, anti-HEV IgG seroprevalence was found to be 27.6% in general population[47], while in Norway, Germany and Portugal reported seroprevalences were 11.4%, 16.8% and 16.3%, respectively[48–50]. Furthermore, several countries such as Netherlands, Spain, France, and Southwest England have performed these studies in healthy blood donors reporting an anti-HEV IgG prevalence ranging from 16.0 to 26.7%[51–54]. These facts contribute to the assumption that the anti-HEV IgG prevalence does not reflect the spread of HEV in the HSCT population, which reinforces the importance of better characterization in this group of patients.

HSCT recipients are at higher risk of HEV infection, that could lead to chronic infection, and the diagnosis of HEV infection is highly recommended. Over the last years, some attention has been given to this group of immunocompromised patients, but there is still a small number of studies in HSCT as demonstrated in the present systematic review. Therefore, more studies are needed to increase our understanding of the epidemiology of HEV in HSCT recipients.

Conflict Of Interest

The authors declare they have no conflict of interest.

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Author contributions:

SC, acquisition of data, analysis and interpretation of data, drafting the article, final approval; CC, acquisition of data, final approval; CC and AT final approval; RM, conception and design of the study, final approval; MSJN, interpretation of data, revising the article, final approval; HS, analysis and interpretation of data, conception and design of the study, revising the article, final approval.

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Figure 1 - PRISMA flow diagram.

Abbreviations: HEV, Hepatitis E Virus; HSCT, Hematopoietic stem cell transplantation

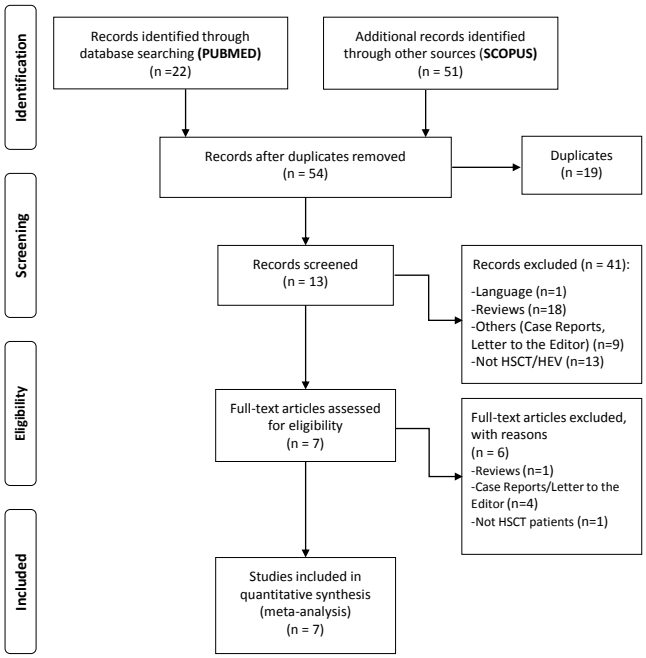

Figure 1 - PRISMA flow diagram applicable to the study.

Figure 2 - Forest plot of the overall prevalence based on the detection of HEV RNA.

Abbreviations: p, *p*-value; Prev (95%CI), Prevalence 95% Confidence Interval.

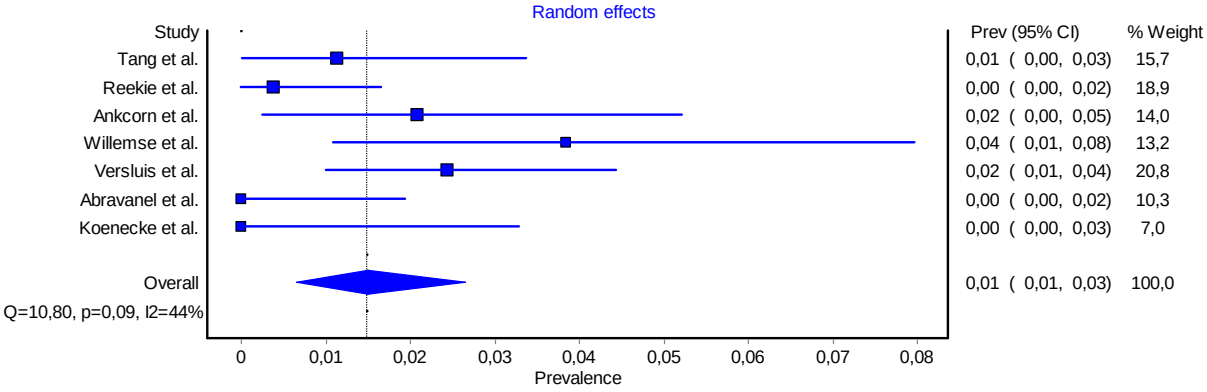

Figure 2 - Forest plot of the overall prevalence based on the detection of HEV RNA.

Abbreviations: p, *p*-value; Prev (95%CI), Prevalence 95% Confidence Interval.

Figure 3 - Forest plot of the overall prevalence based on the detection of IgM anti-HEV.

Abbreviations: p, *p*-value; Prev (95%CI), Prevalence 95% Confidence Interval.

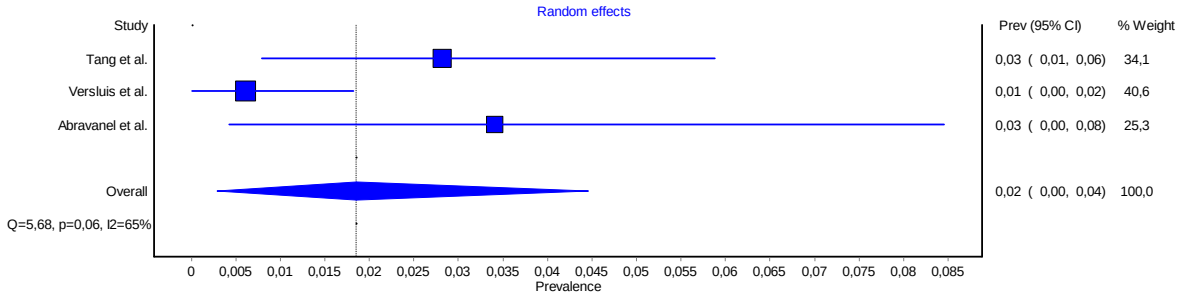

Figure 3 - Forest plot of the overall prevalence based on the detection of IgM anti-HEV.

Abbreviations: p, *p*-value; Prev (95%CI), Prevalence 95% Confidence Interval.

Figure 4 - Forest plot of the overall prevalence based on the detection of IgG anti-HEV.

Abbreviations: p, *p*-value; Prev (95%CI), Prevalence 95% Confidence Interval.

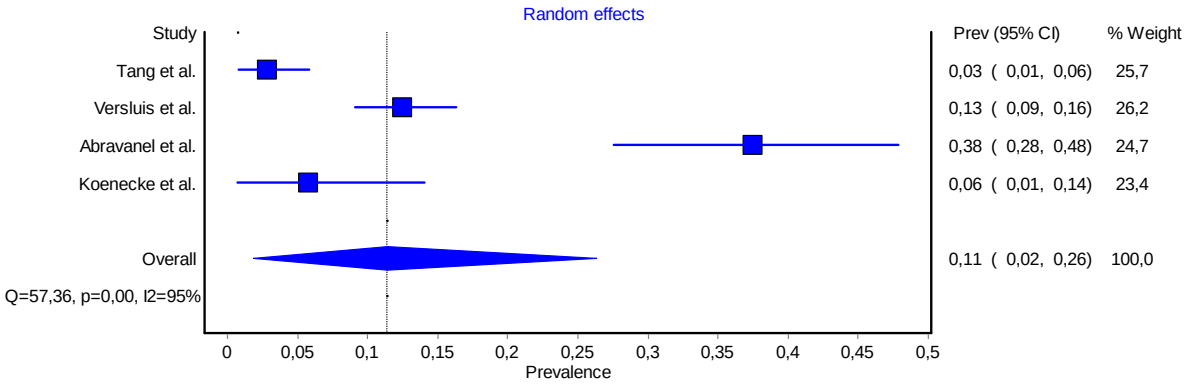

Figure 4 - Forest plot of the overall prevalence based on the detection of IgG anti-HEV.

Abbreviations: p, *p*-value; Prev (95%CI), Prevalence 95% Confidence Interval.

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Table 1 - Details of the studies reporting HEV infection in HSCT recipients used in data analysis.

Abbreviations: EIA, Enzyme Immunoassay; HEV, Hepatitis E Virus; HSCT, Hematopoietic stem cell transplantation; IgG, Immunoglobulin G; IgM, Immunoglobulin M; n, sample size; Nested RT-PCR, Nested Reverse Transcription-Polymerase Chain Reaction; RT-qPCR, Reverse Transcription-quantitative Polymerase Chain Reaction.

Table 1 - Details of the studies reporting HEV infection in HSCT recipients used in data analysis.

First author (country, year)	Patients, n	Type of HSCT	HEV Diagnostic Methods	Assay	Positive, n	Prevalence
Tang FF et al. (China, 2019)	177	Allo-HSCT	Anti-HEV IgM Anti-HEV IgG	EIA (MP Diagnostics ®)	5	2.82%
			HEV RNA	Commercial RT-qPCR	2	1.13%
Reekie I, et al. (England, 2018)	259	Allo/Auto-HSCT	HEV RNA	In-house RT-qPCR	1	0.39%
Ankcorn MJ, et al. (United Kingdom, 2018)	144	Allo-HSCT	HEV RNA	In-house RT-qPCR	3	2.08%
Willemse SB et al. (Netherlands, 2017)	130	Allo-HSCT	HEV RNA	Commercial RT-qPCR	5	3.85%
Verluis J, et al. (Netherlands, 2013)	328	Allo-HSCT	Anti-HEV IgM Anti-HEV IgG	EIA (Wantai ®)	2 41	0.61% 12.5%
			HEV RNA	In-house RT-qPCR	8	2.44%
Abravanel F, et al. (France, 2012)	88	Allo/Auto-HSCT	Anti-HEV IgM Anti-HEV IgG	EIA (Adaltis ®)	3 11	3.41% 12.5%
			Anti-HEV IgG	EIA (Wantai ®)	32	36.4%
			HEV RNA	In-house RT-qPCR	0	0.00%
Koenecke C, et al. (Germany, 2012)	52	Allo-HSCT	Anti-HEV IgG	EIA (Abbott ®)	3	5.77%
			HEV RNA	In-house Nested RT-PCR	0	0.00%

Abbreviations: EIA, Enzyme Immunoassay; HEV, Hepatitis E Virus; HSCT, Hematopoietic stem cell transplantation; IgG, Immunoglobulin G; IgM, Immunoglobulin M; n, sample size; Nested RT-PCR, Nested Reverse Transcription-Polymerase Chain Reaction; RT-qPCR, Reverse Transcription-quantitative Polymerase Chain Reaction.