Hepatitis E seroprevalence and viremia rate in immunocompromised patients: a systematic review and meta-analysis

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Background and Aims: Hepatitis E is an infectious disease of the liver caused by the hepatitis E virus (HEV). Immunocompromised patients present a particular risk group, as chronification of hepatitis E leading to life-threatening cirrhosis occurs when these patients are infected. Therefore, this study aims to estimate and compare the anti-HEV seroprevalence and the rate of HEV RNA positivity in transplant recipients and patients with human immunodeficiency virus (HIV).

Methods: This systematic review and meta-analysis involved a literature search (PubMed, Scopus; 1,138 studies) including 120 studies from 1996 to 2019, reporting anti-HEV seroprevalence and/or HEV-RNA positivity. Statistical analysis was performed using a linear mixed-effects meta regression model.

Results: Anti-HEV seroprevalence in 14,626 transplant recipients ranged from 6% (95% CI: 1.9-17.2) to 29.6% (95% CI: 21.6-39.4) in different commercially available assays and did not differ significantly compared to 20,825 HIV positive patients (range: 3.5% (95% CI: 0.9-12.8) – 19.4% (95% CI: 13.5-26.9)). In contrast, HEV-RNA positivity rate was significantly higher in transplant recipients than in HIV positive patients (1.2% (95% CI: 0.9-1.6) vs 0.39% (95% CI: 0.2-0.7); P-value = 0.0011).

Conclusion: Anti-HEV seroprevalence did not differ significantly between transplant recipients and HIV positive patients. Interestingly, rates of HEV-RNA positivity, indicating ongoing infection, were significantly higher in transplant recipients. These findings demonstrate that transplant patients have an elevated risk of chronic infection in comparison to HIV patients at comparable risk of HEV-exposure.

Keywords: Hepatitis E virus, HEV, Anti-HEV seroprevalence, immunocompromised patients, transplantation, Human immunodeficiency virus, HIV
Introduction

Hepatitis E is an infectious disease of the liver caused by the hepatitis E virus (HEV).\textsuperscript{1,2} Anti-HEV IgG positivity indicating previous HEV exposure is a common finding, with seroprevalence rates of up to 30% in Germany, France and the Netherlands.\textsuperscript{3} Risk of HEV exposure has elevated by almost double in the United States compared to neighbouring countries in Latin America.\textsuperscript{4} Although the vast majority of patients undergo an asymptomatic course, a minority develop clinically overt hepatitis.\textsuperscript{1,2} Hepatitis E may lead to acute-on-chronic liver failure (ACLF) in patients with underlying chronic liver disease, or it can cause chronic hepatitis in immunocompromised patients.\textsuperscript{2,5}

Chronic hepatitis E, which has been observed only in genotype (GT) 3 and 4 infections, may proceed to hepatic fibrosis and subsequent cirrhosis.\textsuperscript{6,7} It has been assumed that transplant recipients (TR) are at risk of chronification with rates up to 50%\textsuperscript{1,8} In addition to TR, chronic hepatitis E has been described in patients with HIV-1 infection.\textsuperscript{9-11} Notably, although HEV infection in HIV positive patients is assumed to be strongly associated with a reduced CD4 T cell count, chronic hepatitis E may persist even after the immune system has recovered under antiretroviral therapy.\textsuperscript{6,11} In addition to TR and HIV positive patients, chronic hepatitis E has been reported in rheumatological\textsuperscript{12-14} and haematological\textsuperscript{15-18} patients with chronification rates of up to 33%, in rheumatological patients respectively,\textsuperscript{19} in haematological patients ongoing hepatitis E with fatal outcome was observed in 16% of patients, as recently reported.\textsuperscript{20}

Despite the fact that chronicity of HEV infection is a topic of emerging relevance in transplant recipients and HIV positive patients, there is still no direct comparison of anti-HEV IgG and HEV-RNA positivity rates in these different groups of immunocompromised patients. Thus, we performed a systematic review and meta-analysis to estimate the anti-HEV seroprevalence and the rate of HEV RNA positivity in transplant recipients and HIV positive patients respectively.\textsuperscript{20} In line with previous meta-analyses,\textsuperscript{3,4} we focused on two different patient cohorts: transplant recipients and patients infected with HIV. TR were further categorized into subgroups because of the nature of transplantation (stem cell-, kidney-, liver-, heart-, lung-, multiple organ transplantation). Studies reporting anti-HEV seroprevalence or rates of HEV RNA in patients with elevated liver enzymes were analysed separately.

Methods

2.1 Search Strategy and Selection Criteria

The literature search was performed using two different databases: Scopus and PubMed. A literature search in both databases was performed by using terms “hepatitis E” or “HEV” in combination with the terms “transplant”, “transplantation” or “HIV”, “AIDS” or “immunocompromised”. 2289 articles were identified and checked for duplicates, subsequent 1160 duplicates were removed. Data search was restricted to publications between 01/1990 and 06/2019. Published articles were assessed in detail for possible inclusion. Only articles written in English were included for final analysis. This analysis is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).\textsuperscript{21}

2.2 Data extraction

Data were stratified by author, journal, year of publication, country, diagnostic assay, number of patients, anti-HEV seroprevalence and HEV RNA positivity. In line with previous meta-analyses,\textsuperscript{3,4} we focused on two different patient cohorts: transplant recipients and patients infected with HIV. TR were further categorized into subgroups because of the nature of transplantation (stem cell-, kidney-, liver-, heart-, lung-, multiple organ transplantation). Studies reporting anti-HEV seroprevalence or rates of HEV RNA in patients with elevated liver enzymes were analysed separately.

2.3 Study quality

The articles identified were examined for their study quality according to a fixed scheme. The criteria applied were as follows: identification of the employed assay (ELISA or PCR) and confirmation of use according to the manufacturer’s instructions; absence of age restriction in the study cohort (e.g. studies reporting on children and/or adolescents < 18 years were excluded) and population-based analysis. Studies that did not meet the study quality criteria were excluded from further analysis. Data were assessed based on their methodological quality according to the Joanna Briggs Institute’s well-established critical appraisal tool for prevalence studies.\textsuperscript{22,23} Studies were assessed by G.B. and discussed with T.H. accordingly. Any disagreements were resolved by discussing with a third investigator (S.P.).

2.4 Statistical analysis

The prevalence of anti-HEV was estimated by pooling the study data separately for HIV and transplant patients with a linear mixed effects regression analysis. We included the assay employed, year of publication and methodological quality score as moderators with an interaction term for assay and year. The interaction term was used to account for the use of different assays over time. For the analysis
of HEV-RNA positivity rate between HIV and transplant patients, we also used a linear mixed effects regression analysis, but only included the methodological quality score as a moderator. A restricted maximum likelihood estimator (REML) with logit transformation was used for prevalence estimation. Heterogeneity was checked via the quantity $I^2$ and publication bias was checked via a funnel plot. Analysis was conducted using R (version 3.5.1) and the `metafor` package.

### 3 | Results

Of 1,138 articles, 120 (10.5%) were included in the final analysis as shown in the study flow chart (Fig. 1). Detailed information on the studies included and their characteristics are provided as supplementary tables (Table S2-S4).

#### 3.1 | Overall anti-HEV Seroprevalence in immunocompromised patients

121 data sets from 96 studies reporting the anti-HEV seroprevalence of 35,451 patients were included in the analysis. Depending on the assay applied, estimated anti-HEV seroprevalence ranged from 6% (95% CI: 1.95-17.23) for Abbott to 29.6% (95% CI: 21.6-39.1) for Wantai in 14,626 TR, and from 3.5% (95% CI: 0.9-12.8) for Abbott to 19.4% (95% CI 13.5-26.9) for Wantai in 20,852 HIV positive patients (Fig. 2). Highest estimated anti-HEV seroprevalence in both cohorts was observed for the Wantai assay (40/121 data sets). Overall, anti-HEV seroprevalence, tested with commercially available assays, did not differ significantly between TR and HIV positive patients independently of the assay, methodological quality and study year (Table S1). Using inhouse assays, anti-HEV seroprevalence differed significantly (Table S1) in between TR (6.32%, 95% CI: 2.43-15.43) and HIV positive patients (25.74% (95% CI: 15.55-39.48); OR (95% CI): 0.19 (0.05-0.68; $P$-value = 0.0011). Age of tested individuals was available in 83 studies. However, we did not observe relevant effects on estimated prevalence rates in an age adjusted subgroup analysis (see "age adjusted anti-HEV IgG Seroprevalence" illustrated in Fig S1).

#### 3.2 | HEV RNA positivity rates

Additionally, 76 data sets from 56 studies reporting HEV RNA positivity rates of 25,708 patients were analysed. HEV RNA positivity in 18,064 TR was 1.2% (95%-CI 0.9-1.6), which was significantly higher in comparison to the rate of HEV RNA positivity in 7,644 HIV positive patients with 0.39% (95%-CI 0.2-0.7; $P$-value = .0011, OR 3.10; 95%-CI 1.57-6.12; Fig. 3).

#### 3.3 | Subgroup analysis of TR

Data on TR was further stratified according to the type of transplantation. We observed highest rates of anti-HEV seroprevalence in heart transplant recipients (36.5%), followed by lung transplant and...
recipients (32.5%), and the lowest was observed in recipients of multiple organs (23.44%) based on the Wantai assay. In contrast, the highest rates of HEV RNA positivity were observed in lung transplant recipients (2.1%), followed by multiple organ and heart transplant recipients (1.46%) and lowest in liver transplant recipients (0.95%). Detailed data are shown in Table 1.

3.4 | Immunocompromised patients with elevated liver enzymes

Studies reporting HEV RNA in immunocompromised patients with elevated liver enzymes were analysed separately (Fig. S2). In a subgroup of 566 TR, the rate of HEV RNA positivity was significantly higher in comparison to 1,268 HIV positive patients (5.21%, 95% CI 2.35-11.14 vs 0.37%, 95% CI 0.1-1.33; OR 95% CI 14.97 (2.86-78.51); P-value = .0014).

3.5 | Time trends of articles related to HEV and immunocompromised patients

The articles included were sorted by date of publication (Fig. S3). The number of articles related to anti-HEV seroprevalence in TR and HIV positive patients increased markedly until 2015 and decreased slightly until 2019. In contrast, the number of published articles related to HEV RNA positivity in TR increased clearly from 2012 on, whereas we observed a constantly lower number of publications reporting HEV RNA positivity in HIV positive patients.

4 | Discussion

Chronic HEV infection in immunocompromised patients including transplant recipients, HIV positive patients or patients with haematological malignancy has been considered increasingly relevant in recent years (Fig. S3).24 Regarding chronic HEV infection, we have yet to thoroughly understand its potential risk factors, long-term sequelae and management. Rapid disease progression to cirrhosis, a feared and potential life threatening complication, has frequently been observed in immunocompromised patients with chronic HEV infection.7 Even though relevance of HEV infection in the transplant setting has been acknowledged by the international scientific community, there are still conflicting standpoints on the overall anti-HEV seroprevalence and rate of chronic HEV infection in immunocompromised patients.8

To address this, we performed this systematic review and meta-analysis to compare anti-HEV seroprevalence and HEV viremia in
two cohorts of immunocompromised patients. We initially hypothesized that transplant recipients have higher rates of exposure than HIV positive patients because of possible HEV exposure as a result of blood transfusions.

The present study confirms high rates of anti-HEV seroprevalence up to 30% in the special cohorts of transplant recipients and HIV positive individuals (Fig. 2). These rates are far higher than previously described anti-HEV seroprevalence rates in the general population (2% to 17%), as reported in two recent systematic reviews and meta-analyses on anti-HEV seroprevalence in Europe and the Americas.\(^3,4\)

The highest anti-HEV seroprevalence rates were observed in heart transplant recipients. This is in line with Pischke et al., who found the highest anti-HEV seroprevalence in heart transplant recipients compared to non-transplant patients undergoing cardiac surgery and healthy controls. Thus, heart transplant recipients, frequently receiving blood products, seem to present a particular risk group for HEV exposure. This is remarkable, as heart transplant recipients are strongly immunosuppressed and therefore, a lack of sensitivity concerning serological testing is anticipated. However, anti-HEV IgG rates observed in this single centre study were much lower in comparison to the present study.\(^25\)

A known difficulty of seroprevalence studies is the large variety of commercially available assays and in particular, their different levels of sensitivity and specificity.\(^3\) Unlike what was initially hypothesized, anti-HEV seroprevalence in transplant recipients was not significantly higher than in HIV positive patients tested using commercially available assays. Overall, these findings support the assumption that in immunocompromised patients, prevalence could be underestimated because of undetectable anti-HEV antibodies. Interestingly, significantly lower anti-HEV seroprevalence in transplant recipients was observed in the subgroup tested with non-standardized inhouse assays. This observation seems to be mainly a result of the high level of heterogeneity of inconsistent inhouse assays in this subgroup. In addition, this might also be explained as an effect of time because inhouse assays are less frequently used because of the availability of highly sensitive commercial tests. Prevalence and risk factors for HEV among HIV positive patients have been discussed controversially. Several studies have evaluated anti-HEV IgG in HIV positive patients, with prevalence rates ranging from 1% up to 45% in a Ghanaian study.\(^26,27\) Crum-Cianflone et al. found HEV infections as a reason for liver enzyme elevation in 4% and an overall anti-HEV seroprevalence of 6% among HIV-infected patients.\(^28\) Nevertheless, Keane et al. reported similar anti-HEV seroprevalence rates between HIV positive persons and controls.\(^29\) A recent study from Shinohara et al. found increased anti-HEV seroprevalence rates only in a young subgroup (age 16-29) of HIV positive men engaging in sexual activity with men.\(^30\) However, affection of the immune system such as a reduction of CD4 count has been associated with increased anti-HEV seroprevalence rates and potential risk for chronification.\(^26\) In this study, we observed comparable HEV exposure rates in HIV positive patients and transplant recipients.

In addition, we aimed to assess rates of HEV RNA positivity in two cohorts of immunocompromised patients. Importantly, detecting HEV RNA via PCR is recommended in immunocompromised patients.\(^31,32\) In immunocompetent patients detectable viremia is assumed to last up to six weeks, whereas immunocompromised patients are at risk of developing chronic hepatitis E, which is defined as HEV RNA presence for at least three months.\(^33\)

In the present study, we found a high rate of HEV RNA positivity of 1.2% in the cohort of transplant recipients. In a sub-group of immunocompromised patients with elevated liver enzymes, HEV-RNA positivity increased even to 5.2%. Both rates where significantly higher in comparison to HIV positive patients. Thus, meticulous testing for HEV RNA is of central relevance for detecting HEV infection in transplant recipients, in particular in those with elevated liver enzymes. In the cohort of HIV positive patients, viremia was observed less frequently (HEV RNA positivity rate 0.4%). These observations indicate that persistent HEV infection in HIV positive patients seems to be rare, possibly because of a presumably improved immune status under antiretroviral therapy (ART).

The present study provides novel insights on the nature of HEV infection in immunocompromised patients. However, our investigation has some limitations. First, findings depend on the quality of the studies included for review. However, in order to prevent potential bias, data were assessed by experienced scientists according to the Joanna Briggs Institutes’ critical appraisal tool, well-established for prevalence studies.\(^22\) The statistical analyses and the interpretation of the data were performed by a well-experienced experts. Second, the studies did not provide clinical data such as serum total IgG levels to interpret the immunological conditions. In particular, the HIV positive patient cohort is presumably undergoing standard ART treatment and thus potentially does not have a substantially

### TABLE 1 Subgroup analyses of transplant recipients: Anti-HEV seroprevalence rates and HEV RNA are shown in percent with 95% confidence interval (CI)

| Tx          | anti-HEV Seroprevalence (data sets/patients) | HEV-RNA (data sets/patients) | anti-HEV seroprevalence in % (Wantai, 95% CI) | HEV RNA positivity in % (95% CI) |
|-------------|-----------------------------------------------|------------------------------|-----------------------------------------------|----------------------------------|
| Kidney      | 27/ 7,604                                     | 19/ 8,220                    | 33.94 (23.97, 45.56)                          | 1.17 (0.68, 2.00)                |
| Liver       | 16/ 4,915                                     | 18/ 5,821                    | 27.41 (18.33, 38.86)                          | 0.95 (0.56, 1.63)                |
| Heart       | 5/ 955                                        | 6/ 1,252                     | 36.53 (20.24, 56.63)                          | 1.30 (0.52, 3.23)                |
| Stem cell   | 4/ 556                                        | 5/ 871                       | 25.63 (13.18, 43.90)                          | 1.28 (0.44, 3.62)                |
| Lung        | 2/ 157                                        | 4/ 678                       | 32.49 (11.84, 63.30)                          | 2.08 (0.69, 6.08)                |
| Multiple    | 3/ 439                                        | 3/ 1,222                     | 23.44 (11.32, 42.34)                          | 1.46 (0.46, 4.56)                |
impairment of the immune system. Even though spontaneous HEV clearance is very unlikely in transplant recipients and can be interpreted as a persistent infection, a positive HEV RNA finding does not necessarily represent a chronic infection.34

In conclusion, in this systematic review and meta-analysis we compared anti-HEV seroprevalence and rates of HEV RNA positivity in a large cohort of transplant recipients and HIV positive patients. Anti-HEV seroprevalence did not differ significantly between these cohorts of immunocompromised patients. Of note, the rate of HEV-RNA positivity, indicating ongoing infection, was significantly higher in transplant recipients. These findings support the assumption that transplant recipients have an elevated risk of chronic HEV infection in comparison to HIV positive patients at comparable exposure rates.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest regarding this study.

AUTHOR CONTRIBUTIONS
Study concept and design: Buescher, Ozga, Pischke, Horvatits. Literature search, acquisition of data, analysis or interpretation of data: Buescher, Ozga, Lorenz, Horvatits. Drafting of the manuscript: Buescher, Pischke, Horvatits. Critical revision of the manuscript for important intellectual content: Addo, Pischke, Lorenz, May. Statistical analysis: Ozga.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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