The burden of HEV related acute liver failure in the developing world: a systematic review and meta-analysis

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Research Article

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Abstract

Background

Hepatitis E has the potential to progress into HEV related acute liver failure (HEV-ALF), but its burden in the developing world remains unclear. We systematically evaluated the burden of HEV-ALF in these regions regarding the frequency and mortality.

Methods

A systematic search of the literature was performed utilizing the databases of PubMed, the Cochrane Library, Medline, Embase and Web of Science. Studies in English or Chinese that reported on the burden of HEV-ALF in the developing world were included. Outcomes were pooled with meta-analysis utilizing R software. Estimates were calculated with random-effects models, subgroup analysis and sensitivity analysis were conducted to address heterogeneity. Egger's test and Begg's test were performed to assess the publication bias.

Results

A total of 20 eligible studies were included, the results indicated that the pooled proportion of HEV infection in etiology of acute liver failure was 39.0% (95% CI: 29.0–51.0) in non-pregnant individuals and 65.0% (95% CI: 60.0–71.0) in pregnant females. The incidence of HEV-ALF in HEV infected non-pregnant individuals was 24.0% (95% CI: 15.0–33.0), while in pregnant females, it was 34.0% (95% CI: 27.0–42.0). The mortality of HEV-ALF was 31.0% (95% CI: 20.0–43.0) and 63.0% (95% CI: 46.0–79.0) in non-pregnant individuals and pregnant females, respectively. It must be noted that there were differences across specific countries and population.

Conclusions

The burden of HEV-ALF in developing countries is heavy, prevention of HEV infection and early recognition of HEV-ALF in high risk regions and population is of great significance.

Introduction

Hepatitis E virus (HEV) is a positive-sense single-stranded RNA virus, which stands as one of the leading causes of acute viral hepatitis worldwide. A recent meta-analysis indicated that the prevalence of HEV infection was estimated to be 12.47% of the global population as of 2020, corresponding to approximately 939 million individuals who have experienced past HEV infection. The prevalence of HEV infection varies in different geographical regions, it is considered to be endemic in most regions of the
developing countries[2–3]. The manifestation of HEV infection ranges from clinically asymptomatic or self-limiting to liver failure[1–2], the specific host populations, geographical regions and HEV genotypes (GTs) infected differ markedly regarding to the clinical presentations of this disease[4]. Studies indicated that HEV is a major contributor to acute liver failure (ALF)[5], especially in pregnant females with HEV GT1-2 infection[4, 6], it could also lead to acute-on-chronic liver failure (ACLF) mainly in individuals who were with preexisting chronic hepatic diseases[4, 7], both HEV-ALF and HEV-ACLF cause significant mortality[4, 6–7]. High prevalence of HEV infection and the significant mortality caused by HEV-ALF and HEV-ACLF highlight the significant public health concern posed by HEV infection in the developing world[1–2].

HEV-ALF is considered to be an issue long time be underestimated, several previous studies indicated that it was often under-reported because HEV is not an etiology routinely be screened in ALF patients, and it is reported that a large proportion of HEV-ALF cases were misdiagnosed as drug induced liver injury (DILI) or ALF with etiologies other than HEV[8–10]. Studies have reported varying estimates of its incidence and mortality in the developing countries, probably because the specific geographical regions, HEV GTs and populations focused in these studies were not identical, thus the burden of HEV-ALF is not well understood to date. In addition, the mechanism of progressing to HEV-ALF remained not fully explained and treatment of it usually involves artificial liver support or liver transplantation, effective treatments were rarely reported[1, 10–11]. However, shedding light on the real story of HEV-ALF is the key to increasing the awareness of medical workers, promoting early diagnosis and treatment for these patients. Therefore, a systematic review and meta-analysis is necessary to comprehensively evaluate the burden of HEV-ALF in the developing world. Through analyzing eligible cohort studies and cross-sectional studies, our study aimed to provide a summary of the current available evidence on the proportion of HEV infection in etiologies of ALF and the incidence, mortality of HEV-ALF in pregnant and non-pregnant population from the developing world. The findings of this study may serve as a basis for future research on this issue.

Methods

This systematic review and meta-analysis was registered in PROSPERO (Registration ID: CRD42022382101), and it was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[12] (Supplementary Table 1).

2.1 Data sources and searches

A comprehensive search for studies on HEV-ALF in the developing countries was conducted in five databases, including PubMed, the Cochrane Library, Medline, Embase and Web of Science, from inception until 25/02/2023. The search was limited to studies published in English or Chinese language. The search strategy included the keywords “HEV”, “Hepatitis E”, “liver failure”, “liver injury”, “hepatic failure”. The detailed search strategies are provided in Supplementary Table 2. In addition, a snowball tracking method was used to identify potentially relevant studies that met our inclusion criteria. All literature
searches were conducted by trained postgraduate students (RD and CDC). We did not contact the authors of the original studies during our study period. All eligible studies were managed in Endnote 20.0 software.

2.2 Study selection

2.2.1 Inclusion criteria

Studies were included if they met the following criteria:

(1) Studies that reported data on HEV-ALF in pregnant and non-pregnant individuals with HEV infection or HEV infection as the etiology of acute liver failure or mortality of HEV-ALF in developing countries.

(2) Studies that provided explicit-enough data on HEV-ALF that could be extracted for analysis.

(3) Studies that stated the definition (or diagnostic criteria) of HEV infection and HEV-ALF.

(4) Studies reported data of HEV-ALF in human beings and focused on adults.

2.2.2 Exclusion criteria

Studies were excluded if they met the following criteria:

(1) Studies were reviews, meta-analyses, case reports, randomized controlled trials or abstracts.

(2) Non-human studies.

(4) Data in the studies were incomplete, insufficient or reused.

(5) Duplicate studies or full-article unavailable.

(6) Studies reported in neither English nor Chinese.

2.3 Data extraction

A pretested data extraction form was employed in this study. Two independent reviewers (RD and CDC) extracted the necessary data from eligible studies, which were then double-checked to ensure accuracy. The extracted data included the first author's name, year of publication, study period, study design, time of the studies, demography of HEV-ALF participants (age, gender, country/region), number of HEV-ALF individuals, number of HEV infected individuals (pregnant females and non-pregnant individuals), number of expired HEV-ALF individuals and diagnostic criteria or definition of HEV-ALF. Any discrepancies or disagreements between the reviewers were resolved through discussion.

2.4 Methodological quality assessment

Methodological quality assessment of eligible studies was performed with the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for prevalence studies which comprised 9 items in relation to risk of bias,
rigour and transparency\textsuperscript{[13]} (Supplementary Table 3A). The importance of each item was not weighted and each item was judged with “Yes”, “No”, “Unclear” and “Not applicable”. The number of positive items (“Yes”) a study received on a scale of nine was defined as the overall score it evaluated in the quality assessment session. Studies scored 1–3 were defined as low quality, 4–6 as moderate quality and 7–9 as high quality. The quality evaluation was conducted by two independent reviewers (RD and CDC), and any conflicts encountered were solved by the involvement of a third reviewer (JW).

2.5 Statistical analysis

Since the data of HEV-ALF in pregnant and non-pregnant individuals were markedly different, to estimate the proportion, incidence and mortality separately, we divided the eligible studies into pregnant group and non-pregnant group. Statistical analysis was performed with the “metaprop” module in R-4.0.4 statistical software package. Heterogeneity among included studies was initially assessed with the $I^2$ test and Cochran-Q test, in which $I^2$ was used to indicate the percentage of variation between the included studies that is due to heterogeneity rather than sampling errors, while the presence or absence of heterogeneity was illustrated with the Cochran Q statistics. A $P$-value less than 0.1 indicated the presence of heterogeneity, and the heterogeneity among studies was considered to be mild, moderate or severe if $I^2$ was < 50%, 50–75% and > 75%, respectively. Considering the expected heterogeneity, the estimates were calculated with the DerSimonian-Laird’s random effect models, and Freeman-Tukey double arcsine was applied before pooling data to minimize the effect of the size of study-specific estimates of rates on the overall estimate\textsuperscript{[14]}, the corresponding 95% confidence interval (95% CI) was estimated utilizing Wilson score method. Sensitivity analysis was conducted with “metainf” command in the random model to identify the effect of an individual eligible study on the pooled outcome and test the reliability of the results. In addition, subgroup analysis was performed trying to figure out the possible resource of heterogeneity. In addition, Begg’s test and Egger’s test were conducted with the command of “metabias” to assess the potential publication bias, $P > 0.05$ indicated that no statistically significant publication bias was found.

Results

3.1 Study Selection and Characteristics

A comprehensive search of five databases yielded 4948 results, of which 764 were from PubMed, 1211 were from Cochrane Library, 1068 were from Embase, 960 were from Web of Science and 945 were from Medline. Five additional candidate studies were added via the snowball tracking method. Deduplication conducted in Endnote 20.0 removed 1445 results, and 425 duplicate results were removed manually through screening their first author, titles and abstracts. Reviewing the titles and abstracts removed 2915 candidates which did not meet our inclusion criteria. A total of 168 candidates were subjected to full-text screening for further evaluation, resulting in 20 studies meeting the inclusion criteria and finally included in this systematic review and meta-analysis. The included studies were cited in supplementary material. The entire selection process was depicted in Fig. 1.
The detailed characteristics of included studies were summarized in Supplementary Table 4. Of the 20 eligible studies published from 2008 to 2022, studies conducted in India took the largest part (n = 12, 60.0%) followed by China (n = 6, 30.0%), the other two studies were from Bangladesh. All of the included studies declared that HEV infection were diagnosed by serum anti-HEV IgM positive and/or HEV RNA, and the definitions or diagnostic criteria for ALF were demonstrated in Supplementary Table 5. The data of HEV GTs were available in 7 eligible studies, but most of them only reported data for a limited subset of the study population. In terms of the quality assessment, 85.0% (n = 17) of the eligible studies were assessed as having moderate quality, while none of them were assessed as low quality. Detailed quality assessment information was presented in Supplementary Table 3B.

3.2 Meta-analysis

3.2.1 The proportion of HEV in etiology of ALF

A total of 11 studies (1527 non-pregnant participants) and 6 studies (750 pregnant participants) were pooled to estimate the proportion of HEV in various etiologies of ALF. The heterogeneity among the included studies was severe ($I^2 = 93.6\%, P < 0.01$) in non-pregnant group and moderate ($I^2 = 59.3\%, P = 0.03$) in pregnant group (Supplementary Fig. 1). Results demonstrated that the proportion of HEV-ALF in non-pregnant ALF individuals ranged from 11.00% (95% CI: 6.0–18.0) to 64.0% (95% CI: 52.0–76.0) with a combined overall rate of 39.0% (95% CI: 29.0–51.0), while the proportion of HEV-ALF in pregnant ALF females ranged from 58.00% (95% CI: 43.0–72.0) to 75.0% (95% CI: 62.0–86.0) with a combined overall rate of 65.0% (95% CI: 60.0–71.0).

3.2.2 The incidence of progressing to HEV-ALF in HEV infected individuals

A total of 10 studies (2470 non-pregnant participants) and 6 studies (1071 pregnant participants) were pooled to estimate the incidence of progressing to HEV-ALF in HEV infected individuals. The heterogeneity across the included studies was severe in both non-pregnant group ($I^2 = 96.7\%, P < 0.01$) and pregnant group ($I^2 = 79.9\%, P < 0.01$) (Supplementary Fig. 2). Results indicated that the incidence of HEV-ALF in non-pregnant individuals with HEV infection ranged from 4.00% (95% CI: 3.0–6.0) to 42.0% (95% CI: 36.0–48.0) with a combined overall rate of 24.0% (95% CI: 15.0–33.0), while the incidence of HEV-ALF in pregnant females with HEV infection ranged from 23.00% (95% CI: 19.0–27.0) to 46.0% (95% CI: 32.0–61.0) with a combined overall rate of 34.0% (95% CI: 27.0–42.0).

2.2.3 The mortality of HEV-ALF

A total of 9 studies (687 non-pregnant HEV-ALF participants) and 6 studies (415 pregnant HEV-ALF participants) were pooled to estimate the mortality of HEV-ALF individuals, the heterogeneity across the included studies was severe in both non-pregnant group ($I^2 = 85.4\%, P < 0.01$) and in pregnant group ($I^2 = 89.9\%, P < 0.01$) (Supplementary Fig. 3). Results indicated that the mortality of HEV-ALF in non-pregnant ranged from 10.00% (95% CI: 0.0–45.0) to 65.0% (95% CI: 49.0–79.0) with a combined overall rate of
31.0% (95% CI: 20.0–43.0), while the mortality of HEV-ALF in pregnant females with ranged from 33.00% (95% CI: 12.0–62.0) to 87.0% (95% CI: 79.0–93.0) with a combined overall rate of 63.0% (95% CI: 46.0–79.0).

### 2.3 Subgroup analysis

Pregnant status, geographical regions and HEV GTs are crucial factors that may heavily influence the severity of HEV infection and the prognosis of individuals with HEV-ALF. Although data of HEV GTs were rarely reported in original studies, dominated HEV GTs varied in different developing countries. Thus, on the basis of pregnancy status, we further stratified the included literature by subgroup of countries where studies were conducted. The heterogeneity decreased in most of the subgroups. Notably, the heterogeneity disappeared ($I^2 = 0.0\%$) in the subgroup of Bangladesh regarding the proportion of HEV-ALF in non-pregnant individuals with ALF. The heterogeneity was decreased from severe to moderate ($I^2 = 69.9\%$) in the subgroup of India regarding the mortality of HEV-ALF in non-pregnant individuals. This indicated that geographical region is one of the possible causes of heterogeneity. However, data of pregnant females were all from India, and due to the scarcity of available data, we did not conduct other meaningful subgroup analysis, such as age of the participants, different regions within one country, could be the possible sources as well.

In terms of the proportion of HEV infection in etiologies of ALF, results indicated that the HEV was involved in 40.0% (95% CI: 29.0–51.0), 21.0% (95% CI: 3.0–47.0) and 62.0% (95% CI: 52.0–72.0) of the etiologies of ALF in non-pregnant individuals in India, China and Bangladesh, respectively (Fig. 2a), while it was involved in 65.0% (95% CI: 60.0–71.0) of the etiologies of ALF in pregnant females in India (Fig. 2b). For the incidence of exacerbating to HEV-ALF in HEV infected individuals, results demonstrated that 28.0% (95% CI: 20.0–37.0), 10% (95% CI: 1.0–28.0) of the HEV infected non-pregnant individuals exacerbated to HEV-ALF in India and China, respectively, while 34.0% (95% CI: 27.0–42.0) of the HEV infected pregnant females progressed to HEV-ALF in India (Fig. 3). In addition, the mortality of HEV-ALF in non-pregnant individuals is 31.0% (95% CI: 19.0–44.0) and 23.0% (95% CI: 14.0–34.0) in India and China, respectively, while it was 63.0% (95% CI: 46.0–79.0) in HEV-ALF pregnant females in India (Fig. 4). Moreover, solely one included study reported the mortality data of HEV-ALF in non-pregnant individuals in Bangladesh, so quantitative synthesis in this subgroups was not feasible. Alam et al reported that, of 43 HEV-ALF non-pregnant individuals, 28 individuals were expired, in Bangladesh.

### 2.4 Sensitivity analyses and publication bias tests

Sensitivity analysis was administered in three outcomes of both non-pregnant group and pregnant group, the results illustrated that the pooled outcomes were not greatly changed when the studies were omitted one by one, which further indicated that the pooled results were stable (Supplementary Fig. 4–6). Moreover, no publication bias was found in both non-pregnant group and pregnant group of three major outcomes with Egger’s test and Begg’s test (Supplementary Table 6).

### Discussion

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To the best of our knowledge, this is the first systematic review and meta-analysis that explored the burden of HEV-ALF in the developing world. Our study reported three major findings: the pooled proportion of HEV infection in etiologies of ALF, the pooled incidence of progressing to HEV-ALF in HEV infected individuals and the mortality of HEV-ALF. These pooled results indicated that the burden of HEV-ALF in developing countries, both in terms of frequency and mortality, is heavy. However, it must be noted that there were clear differences across specific countries and population\[15\].

Current evidence indicated that HEV infection was involved in approximately 39.0% ALF cases in non-pregnant individuals in developing countries, with proportions of 40.0%, 21.0% and 62.0% in India, China and Bangladesh, respectively. This finding supported previous studies that suggested HEV is a leading cause of ALF in the developing countries, particularly in hyper-endemic areas, such as India and Bangladesh\[9, 15\]. This may be attributed to a combination of many factors, such as high prevalence of HEV infection, mainly HEV GT1-2 infection in these regions\[16\]. Pooled incidence also revealed that, in India, about 28.0% HEV infected non-pregnant individuals progressed to HEV-ALF, however, this incidence was about solely 10.0% in Chinese non-pregnant individuals. HEV GTs is one of the key influential factors regarding the burden of HEV-ALF, the manifestation of HEV infection varies remarkably in regard of different HEV GTs. Infection of HEV GT1-2 is usually associated with more severe clinical presentation, while in HEV GT3-4 dominated areas, manifestation of HEV infection is relatively milder and HEV-ALF is relatively rare to report in these areas\[17\]. HEV GT1 is reported to be prevalent in India and Bangladesh, while HEV GT3-4 are more frequently to be reported in China in recent years\[17–18\]. This is in line with the provided HEV GTs information in our included studies. Among seven included studies that reported the information of HEV GTs, five Indian studies reported HEV GT 1 infection, and two Chinese studies reported HEV GT 3–4 infection. High prevalence of HEV infection and the prevalent HEV GT1 provided one possible explanation of why HEV accounted for more etiology of ALF cases in India and Bangladesh and higher incidence of progressing to HEV-ALF in India when compared with them of China.

In pregnant females, high proportion of HEV in etiologies of ALF and high incidence of progressing to HEV-ALF are also particularly concerning. Our study found that HEV was the causative agent of ALF among about 65.0% of pregnant females in India, in contrast to 40.0% among non-pregnant individuals in the same country. Pregnancy is a unique situation, due to the alternation of immune system, hormone change (progesterone and oestrogen), pregnant females are more susceptible for progressing to HEV-ALF\[19–21\], especially in the 2nd and the 3rd trimester or when infection is blamed for HEV GT1\[22\]. Pooled incidence in our study also revealed that, in India, about 28.0% HEV infected non-pregnant individuals progressed to HEV-ALF, while this incidence was approximately 34.0% in pregnant individuals. Increased incidence of progressing to HEV-ALF during pregnancy and high prevalence of HEV infection and HEV GT1 dominated infection together possibly translated into such a high proportion of HEV infection in etiologies of ALF in Indian pregnant females.

Geographical regions, specific dominant HEV GTs and specific population may also be associated with the prognosis of HEV-ALF. Previous studies indicated that pregnancy and HEV GT1 infection have an
increased risk of mortality\cite{20}, results of our meta-analysis illustrated that the pooled mortality of HEV-ALF was 31.0% and 23.0% in Indian and Chinese non-pregnant individuals, respectively, with a combined mortality of 31.0%, while it was 63.0% in Indian pregnant HEV-ALF females. The pooled results revealed that the mortality in HEV-ALF non-pregnant individuals was higher in India compared with it of China, and it was almost doubled in pregnant females compared with non-pregnant individuals in India. However, the result of Bhatia et al provided a similar mortality rate between HEV-ALF pregnant and non-pregnant individuals in India. Immunity change and higher viral load during pregnancy may contributed to higher mortality rate\cite{15,17,20,24,19,23}, but the detailed mechanism remained unclear.

The pathological mechanism, diagnostic and prognostic markers/models and the targeting treatments for HEV-ALF still need to be further investigated\cite{23}. Luckily, many studies were trying to conquer these issues. Elevating inflammatory cytokines, alteration of innate and adaptive immunity in these patients indicated that host immune response, rather than HEV virus itself, is a key factor for the occurrence of HEV-ALF\cite{21}. Gut microbiota and its metabolites was recently found to be involved in the change of immune system, may participating in the development of HEV-ALF\cite{24}. Moreover, several studies also focused on the diagnostic and prognostic markers of HEV-ALF, which indicated that low platelets and dynamic changes of serum metabolites may associated with the severity of HEV infection and prognosis of HEV-ALF\cite{25–27}. Current treatment strategies for HEV-ALF usually involve fundamental supporting critical care, artificial liver support and liver transplantation, which often cause high medical expenditure and usually not available in resource limited regions\cite{1,10}. It is also reported that ribavirin probably could improve the symptoms and liver synthetic function, but mechanism and efficacy has still not been clarified yet\cite{28}. Apart from investigating new treatment, prevention of HEV infection and early recognition of HEV-ALF in high risk regions and population is of great significance\cite{20}.

However, the results should be treated with caution due to the limitations of our study. Firstly, heterogeneity ranged from moderate to severe among the studies remained not fully explained. The possible sources of heterogeneity may also include the age of the population, different regions in one country, minor difference between the diagnosis criteria of HEV-ALF. In an effort to minimize this problem, we conducted subgroup analysis which found that part of the heterogeneity was due to population and country-specific reasons. Sensitivity analysis was also conducted, results of which showed the pooled results were stable, estimates were without major changes. Secondly, despite that the burden of HEV-ALF was initially estimated in our study, studies on this issue remained scarce and the eligible studies were from limited countries or regions, which prevented us further investigating the burden of HEV-ALF in more developing countries and different regions within one country. Therefore, more research on this issue is needed, and future studies should provide more detailed and explicit data.

**Conclusion**

In conclusion, the burden of HEV-ALF in developing countries is substantial in terms of frequency and mortality, clear differences were found across specific countries and population. Prevention of HEV
infection and early recognition of HEV-ALF in high risk regions and population is of great significance.

Declarations

Author Contributions

RD, JW contributed to the conception and designing of the study. RD, CDC contributed to data collation, MTZ and QG contributed to quality assessment. RD, YC and CS contributed to the statistical analysis. RD, CDC, HZL wrote the manuscript. JW and PH critically revised this manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval

Ethical approval is not applied because this meta-analysis is based on published research and the original data are anonymous.

Data availability statement

The data presented in the study were included in the manuscript or supplementary materials. Further inquiries can be directed to the corresponding author.

Acknowledgments

We thank all members who participated in this work.

References


**Figures**
Figure 1

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### Figure 2

Legend not included with this version.

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Heterogeneity: \( \tau^2 = 0.02; \ \chi^2 = 88.28, \ df = 6 \ (P < 0.01); \ I^2 = 93.2\%

| **Country: China**      |        |       |                     |        |
| Liu, et al., 2008       | 18     | 53    | 0.34 [0.22; 0.48]   | 48.2%  |
| You, et al., 2013       | 12     | 114   | 0.11 [0.06; 0.18]   | 51.8%  |
| **Total (95% CI)**      | 167    |       | 0.21 [0.03; 0.47]   | 100.0% |

Heterogeneity: \( \tau^2 = 0.04; \ \chi^2 = 12.21, \ df = 1 \ (P < 0.01); \ I^2 = 91.81\%

| **Country: Bangladesh** |        |       |                     |        |
| Alam, et al., 2009      | 43     | 67    | 0.64 [0.52; 0.76]   | 54.5%  |
| Mahtab, et al., 2009    | 13     | 23    | 0.57 [0.34; 0.77]   | 45.5%  |
| **Total (95% CI)**      | 90     |       | 0.62 [0.52; 0.72]   | 100.0% |

Heterogeneity: \( \tau^2 = 0; \ \chi^2 = 0.43, \ df = 1 \ (P = 0.51); \ I^2 = 0\%

Heterogeneity: \( \tau^2 = 0.03; \ \chi^2 = 155.48, \ df = 10 \ (P < 0.01); \ I^2 = 93.57\%
### Figure 3

Legend not included with this version.
Supplementary Files

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