adulthood can happen between 6 to 12 months from the onset of acute infection; meanwhile, they also stated that CHB was defined as the persistence of HBsAg or HBV DNA positivity for at least 6 months. In this case, whether patients involved in the cited paper were in acute or chronic state puzzles us. Now that the infected patients with persistent HBsAg positivity for more than 6 months from onset should be diagnosed as chronic HBV infection, in spite of HBsAg loss at any time after 6 months, the cases included in our study could be considered as patients with chronic infection because treatment also takes time (clearance of HBsAg takes time). Details can been seen in Table 1 in our manuscript, such as age of diagnosis (not age of onset), age of commencing treatment, and so on. Actually, it may be more complex. Moreover, HBV infection in infants displays unique characteristics. There is no comparability between results from the adult population and outcomes from infants and children. Regarding patient enrollment, it should be noted that infantile-onset hepatitis B is an unusual condition and such cases are not commonly encountered. In our study, patients attending the clinic who satisfied the inclusion criteria were enrolled.

Finally, as stated in our manuscript, further trials with larger cohorts are needed to support our results.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.031.

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Burden of hepatitis E infection and associated healthcare resource utilization among hematological malignancy-related hospitalizations: A national perspective in the United States, 2007–2014

To the Editor:

We read the paper recently published by von Felden *et al.* with great interest.[1] The authors have commendably presented multicenter data concerning the burden and impact of HEV infection among patients with hematological malignancies. The findings are important in that the occurrence of HEV infection can alter the course of hematological malignancy, even in patients with stable disease. In addition, the authors also reported that the presence of HEV significantly increases the risk of liver failure and related mortality among these patients. The findings hint towards possible worse prognosis in patients with hematologic malignancies, despite the prevailing notion of HEV infection being a merely benign and self-limiting condition (Table 1).

Keywords: Hepatitis E; Hematologic malignancy; Viral hepatitis; Hospitalizations; Inpatients; Hematologic neoplasms; Non-Hodgkin Lymphoma.

As the study only collected data from European nations and there is lack of reported epidemiologic data on the incidence of HEV infections among the United States (US) inpatient population, we provide additional evidence from the US inpatient cohort. In this retrospective nationwide analysis from January 2007 to December 2014, we queried the National Inpatient Sample (NIS) database which is representative of nationwide US hospitalizations.[2] The NIS comprehends a stratified sample of 20% non-federal US community hospitals and collected data infers findings generalizable to over 95% of the US population when weighted (~35 million annual hospital records). HEV-related hospitalizations were identified using the ICD-9 CM codes 070.43 (HEV infection with hepatic coma) and 070.53 (HEV infection without hepatic coma). Categorical variables and frequencies between the groups were assessed using the Pearson's Chi-square test. A 2-sided p value <0.05 was considered a threshold for statistical significance.

Table 1. Baseline characteristics of study population with HEV infection with *vs.* without hematologic malignancy.

Variable	HEV without hematologic malignancy (n = 1,001)	HEV with hematologic malignancy (n = 55)	Overall (n = 1,056)	*p* value
Age (years) at admission				0.362
Median [IQR]	52 [37–61]	51 [35–62]	51 [37–61]	0.736
18–44	34.2%	36.8%	34.3%	
45–64	49.5%	54.1%	49.8%	
≥65	16.3%	<11*	15.9%	
Sex				<0.001
Male	48.5%	72.2%	49.8%	
Female	51.5%	27.8%	50.2%	
White	45.9%	65.1%	47.0%	0.011
Non-elective admission	88.9%	92.0%	89.1%	0.376
Survived to discharge	95.5%	91.8%	95.3%	0.118
Routine discharge	68.2%	44.6%	67.0%	<0.001
Length of stay (days), median [IQR]	4 [2–10] days	6 [3–15] days	4 [2–10] days	0.031
Total hospital charges, median [IQR]	$31,450 [$15,314–$64,423]	$47,523 [$21,008–$103,050]	$32,418 [$16,307–$64,459]	0.005

p values <0.05 indicate statistical significance.

In our analysis, the burden of HEV infection among US hospitalizations was 0.42/100,000 (n = 1,056) hospitalizations, with an exponential increase between 2007 and 2014 (0.27 in 2007 to 0.75 in 2014 per 100,000 hospitalizations) (p <0.001). Among 1,056 HEV-related nationwide hospitalizations over 8 years, 55 patients (5.2%) had co-existing hematological malignancy. Interestingly, Cangin *et al.,* using data from the National Health and Nutrition Examination Survey (NHANES), reported that HEV seropositivity increased from 4.5% in 2013–2014 to 8.1% in 2015–2016.[3] Our study cohort of patients with HEV and hematological malignancy were mostly males (72.2%). Correspondingly, studies have suggested higher male predilection towards HEV infection.[3,4] Similar to findings from the study by von Felden *et al.*, we found that non-Hodgkin lymphoma (60%) was the most frequent hematologic malignancy associated with HEV infection. The highest burden of HEV infection among admissions related to hematologic malignancy was noted in non-Hodgkin's' disease (1.73 per 100,000), followed by leukemia (0.86 per 100,000) and myeloproliferative disorders (0.56 per 100,000), which were significantly higher than the prevalence observed among the general inpatient cohort over the study period (0.42 per 100,000) (p <0.0001). The HEV cohort associated with hematological malignancies had lower survival to discharge (91.8%) compared to those without hematological malignancies (95.5%). However, it was higher than the survival rates reported by Felden and colleagues (84%).[1] The higher survival rate reported in our study compared to the study by von Felden *et al.* could be due to variations in the patient demographics, risk factors for liver failure, and cancer staging at the time of diagnosis of HEV.[1] Due to privacy restrictions set forth by Healthcare Cost and Utilization Project (HCUP) regarding smaller sample sizes (<11), we could not report the prevalence of liver failure or other acute events in both the groups; however, we observed that HEV infection among patients with hematological malignancy was associated with prolonged length of hospitalization and higher hospital charges in comparison to the patients without hematological malignancy. Therefore, we believe that the US inpatient data reported in this study indicate a relatively high burden of HEV among patients with hematologic malignancies as reported by von Felden *et al.* from European centers. Our findings warrant a global collaborative effort to report clinical data on high-risk patient populations with HEV infection to facilitate and systematize multidisciplinary clinical and policy perspectives for optimal management.

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Authors' contributions

Concept and design: DZ & HG, Analysis: RD, writing of article RD, SS & PB, Final approval: all authors.

Supplementary data

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Reply to: "Burden of hepatitis E infection and associated healthcare resource utilization among hematological malignancy-related hospitalizations: A national perspective in the United States, 2007–2014"

HEV disparities between the United States and Europe: meaningful or not?

To the Editor:

We read the letter to the editor by Dr. Desai and colleagues on the burden of hepatitis E in the United States (U.S.) between 2007–2014[1] with great interest. The authors queried the National Inpatient Sample database representing nationwide hospitalizations in the U.S. and found higher rates of HEV infection in patients with hematological malignancy compared to the overall U.S. population. Specifically, their observation of high rates of HEV infection in patients with non-Hodgkin lymphoma and leukemia is consistent with our findings[2] and further supports the notion that rituximab-exposed patients are at risk of hepatitis E, including severe complications.[3]

Large scale data on the clinical relevance of hepatitis E in the U.S. is lacking and the study by Dr. Desai and colleagues represents the first of its kind. In contrast to the vast amount of clinically significant HEV infections reported in Europe, there are only limited data available from the U.S. An explanation could be the lack of FDA-approved diagnostic tests for HEV infections in the U.S. Despite an increase in HEV seroprevalence in the general U.S. population from 4.5% in 2013–2014 to 8.1% in 2015–2016, HEV seroprevalence still appears much lower compared to European countries where it reaches 8–32% depending on the assay and region.[4–6] Another explanation could be the predominance of HEV genotype 3a in the U.S., which differs from most European countries, where genotype 3e, 3f, or 3 g are most common.[2,7–9] Interestingly, chronic hepatitis E in solid organ transplant recipients in Japan has been reported to be lower compared to European countries,[10] suggesting genotype 3a, which is also the most prevalent genotype in Japan, might cause less severe courses of HEV infection with a lower risk for chronicity. In addition to the commonly discussed reporting bias, these data might suggest a different biology of the disease in the U.S. compared to Europe (Fig. 1).

Due to the study design, Dr. Desai and colleagues could not investigate the modes of transmission of HEV in their cohort. In our study, blood-borne transmission of HEV contributed to the burden and was associated with mortality.[2] Interestingly, the prevalence of HEV RNA positive blood donations appears to be lower in the U.S. (0.002%) compared to Germany (0.12%), when comparing studies using the same PCR assay (Cobas TaqMan™, Roche).[8,9] However, the high rates of clinically significant hepatitis E among patients with hematological malignancies in the U.S.[1] suggest blood-borne transmission to be likely in these patients in whom transfusion of blood products is common. But specific studies to support this hypothesis for U.S. patients are needed.

Dr. Desai and colleagues report a high burden of hepatitis E in their cohort based on longer hospital stay and higher costs compared to hematological patients without hepatitis E.[1] Our study did not assess these socio-economic parameters, but given the severity of the disease in terms of liver-related complications among our patients, we believe that an economic burden of hepatitis E in our cohort likely coexists. As outlined by the authors themselves, Dr. Desai and colleagues were not able to delineate the clinical burden of hepatitis E, including chronic hepatitis E, extrahepatic manifestations and liver failure, which clearly represents a missing piece required to further understand potential disparities in the course of hepatitis E between both continents. Further, it remains unclear whether hepatitis E patients in the U.S. National Inpatient Sample database were identified by serology or PCR. In our study, we specifically limited the inclusion to patients with PCR positive HEV infections and elevated aminotransferases to highlight the clinical impact of hepatitis E on hematological patients.[2] These differences might account for the lower survival rates in our cohort compared to patients with hepatitis E and hematological malignancy reported by Dr. Desai and colleagues (84% *vs.* 91.8%).[1,2]

In conclusion, the letter by Dr. Desai and colleagues represents the first large scale data on HEV in hematological patients in the U.S., and underscores the burden of this disease among this special patient population despite a potentially less aggressive HEV genotype and lower prevalence in the general U.S. population compared to European populations. Nevertheless, data on liver morbidity and liver-related mortality in patients with hematological malignancy and other immunocompromised cohorts in the U.S. are urgently needed to better understand potential disparities in the clinical course of the disease