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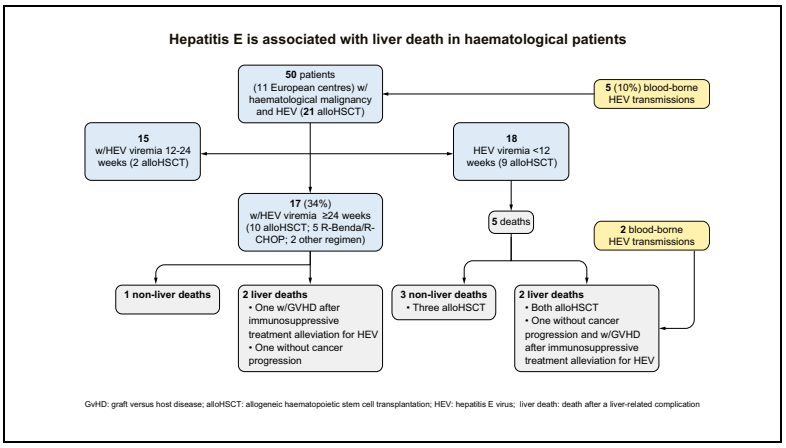
The burden of hepatitis E among patients with haematological malignancies: A retrospective European cohort study

Graphical abstract



Highlights

- Hepatitis E is associated with liver failure and mortality in haematological malignancy.
- Blood-borne transmission contributes to the burden.
- Alleviation of immunosuppressive treatment for hepatitis E requires caution.
- Ribavirin is effective and should be initiated early.

Authors

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Lay summary

Little is known about the burden of hepatitis E among patients with haematological malignancy. We conducted a retrospective European cohort study among 50 patients with haematological malignancy, including haematopoietic stem cell transplant recipients, with clinically significant HEV infection and found that hepatitis E is associated with hepatic and extrahepatic mortality, including among patients with indolent disease or among stem cell transplant recipients in complete remission. Hepatitis E virus infection evolved to chronic hepatitis in 5 (45.5%) patients exposed to a rituximab-containing regimen and 10 (47.6%) stem cell transplant recipients. Reducing immunosuppressive therapy because of hepatitis E was associated with mortality, while early ribavirin treatment was safe and effective.

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The burden of hepatitis E among patients with haematological malignancies: A retrospective European cohort study

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Background & Aims: The burden of hepatitis E virus (HEV) infection among patients with haematological malignancy has only been scarcely reported. Therefore, we aimed to describe this burden in patients with haematological malignancies, including those receiving allogeneic haematopoietic stem cell transplantation.

Methods: We conducted a retrospective, multicentre cohort study across 11 European centres and collected clinical characteristics of 50 patients with haematological malignancy and RNA-positive, clinically overt hepatitis E between April 2014 and March 2017. The primary endpoint was HEV-associated mortality; the secondary endpoint was HEV-associated liver-related morbidity.

Results: The most frequent underlying haematological malignancies were aggressive non-Hodgkin lymphoma (NHL) (34%), indolent NHL (iNHL) (24%), and acute leukaemia (36%). Twenty-one (42%) patients had received allogeneic haematopoietic stem cell transplantation (alloHSCT). Death with ongoing hepatitis E occurred in 8 (16%) patients, including 1 patient with iNHL and 1 patient >100 days after alloHSCT in complete remission, and was associated with male sex ($p = 0.040$), cirrhosis ($p = 0.006$) and alloHSCT ($p = 0.056$). Blood-borne transmission of hepatitis E was demonstrated in 5 (10%) patients, and associated with liver-related mortality in 2 patients. Hepatitis E progressed to chronic hepatitis in 17 (34%) patients overall, and in 10 (47.6%) and 6 (50%) alloHSCT and iNHL patients, respectively. Hepatitis E was associated with acute or acute-on-chronic liver failure in 4 (8%) patients with 75% mortality. Ribavirin was administered to 24 (48%) patients, with an HEV clearance rate of 79.2%. Ribavirin treatment was associated with lower mortality ($p = 0.037$) and by trend with lower rates of chronicity ($p = 0.407$) when initiated <24 and <12 weeks after diagnosis of hepatitis E, respectively. Immunosuppressive treatment reductions were associated with mortality in 2 patients (28.6%).

Conclusion: Hepatitis E is associated with mortality and liver-related morbidity in patients with haematological malignancy. Blood-borne transmission contributes to the burden. Ribavirin should be initiated early, whereas reduction of immunosuppressive treatment requires caution.

Lay summary: Little is known about the burden of hepatitis E among patients with haematological malignancy. We conducted a retrospective European cohort study among 50 patients with haematological malignancy, including haematopoietic stem cell transplant recipients, with clinically significant HEV infection and found that hepatitis E is associated with hepatic and extra-hepatic mortality, including among patients with indolent disease or among stem cell transplant recipients in complete remission. Hepatitis E virus infection evolved to chronic hepatitis in 5 (45.5%) patients exposed to a rituximab-containing regimen and 10 (47.6%) stem cell transplant recipients. Reducing immunosuppressive therapy because of hepatitis E was associated with mortality, while early ribavirin treatment was safe and effective.

Keywords: Hepatitis E virus; Blood transfusion; Immunocompromised host; Haematopoietic stem cell transplantation; Outcome; Ribavirin.

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Introduction

The hepatitis E virus (HEV), the causative agent of hepatitis E, is a member of the *Hepeviridae* family that includes enterically-transmitted, small, non-enveloped positive-sense RNA viruses that can infect mammals (*Orthohepevirus* A, C and D), birds (*Orthohepevirus* B) and trout (*Piscihepevirus*). There are 4 major HEV genotypes (HEV-1 to HEV-4) that can infect humans.[1] HEV is predominately transmitted by contaminated water in low-income countries (mostly HEV-1 and HEV-2) and by contaminated meat and offal that originate from HEV-infected animals (HEV-3 and HEV-4) in high-income countries.[2,3] Blood-borne transmission of HEV via red blood cells, platelets and plasma has also been reported worldwide.[4–7] HEV is pandemic globally, including in industrialised countries.[5]

In the absence of comorbidity, HEV infection is usually a self-limiting illness lasting 1 to 3 months with spontaneous resolution. However, fulminant courses leading to life-threatening liver failure are possible and chronic hepatitis E can occur in immunocompromised hosts, including transplant recipients and lymphopenic hosts.[8–10] In the setting of chronic hepatitis E following transplantation, reduction of immunosuppressive drugs has been recommended as initial treatment, whereas ribavirin treatment serves as second line.[11,12] Yet, these recommendations are based on low grade of evidence, in particular for patients with haematological malignancy.[12–14]

The course of HEV infection among patients with haematological malignancy has been scarcely reported. HEV infection occurred in 8 (2.4%) patients in a retrospective cohort of 328 adult allogeneic haematopoietic stem cell transplant recipients from Rotterdam, the Netherlands, of whom 5 (62.5%) had HEV replication for more than 6 months and 4 (50%) died with ongoing HEV infection without a liver-related complication.[8] In an observational cohort of 26 haematological patients with HEV infection from Toulouse, France, 5 (37.5%) patients had HEV replication for more than 3 months, and 1 patient with non-alcoholic steatohepatitis developed a liver-related complication.[15] Otherwise, cases of liver failure and liver-related death have been reported occasionally in patients with haematological malignancy.[16–19]

The inconclusive evidence on the association between hepatitis E and the outcome of patients with haematological malignancy prompted us to conduct a retrospective, multicentre, European cohort study to describe the burden of hepatitis E among these patients, including allogeneic haematopoietic stem cell transplant recipients.

Patients and methods

Patients

We conducted a retrospective study across 11 European centres [France: Paris, 3 centres (n = 12), Toulouse (n = 6); Germany: Bonn (n = 2), Freiburg (n = 1), Hamburg (n = 11), Heidelberg (n = 1); Italy: Vicenza (n = 1); the Netherlands: Rotterdam (n = 20); Scotland: Glasgow (n = 2)] and collected data on patients with haematological malignancy, including allogeneic haematopoietic stem cell transplant recipients, who were diagnosed with clinically overt HEV infection between April 2014 and March 2017. Clinically overt hepatitis E was defined as HEV viraemia in the presence of abnormal liver enzyme tests, including elevated alanine aminotransferase (ALT) levels above the upper limit of normal (ULN) in respect to locally accepted thresholds. Patients with HEV viraemia but otherwise normal liver enzyme or liver function tests were not included. We excluded 6 (10.7%) patients with HEV infection, who had insufficient details on haematological diagnosis (n = 1) or turned out to have non-malignant haematological diseases (n = 5), *e.g.* acquired haemophilia, aplastic anaemia, idiopathic thrombocytopenic purpura, mastocytosis. The haematological disease was categorised into lymphoid neoplasms, including aggressive lymphoma (*e.g.* diffuse large B-cell lymphoma, mantle cell lymphoma, aggressive T-cell lymphoma, and Hodgkin's lymphoma), indolent lymphoma (*e.g.* chronic lymphocytic leukaemia, follicular lymphoma, and other low-grade B-cell non-Hodgkin lymphomas), and multiple myeloma, and myeloid neoplasms, including acute leukaemia, myeloproliferative neoplasms (*e.g.* polycytheaemia vera) and myelodysplastic syndrome. The study was approved by the institutional review board of Cochin University Hospital, Paris, France (CLEP decision AAA-2017-06010). At each centre, an investigator collected patients' data from medical records. All the authors vouch for the completeness and accuracy of the data presented. Seven patients were previously reported in small case series or single case reports.[6,8,20,21]

Virological assessment

Hepatitis E was diagnosed by means of detection of HEV RNA in the serum (nucleic acid testing [NAT]). For some patients, the time of infection was determined by using frozen serum of prior blood draws, if available. Otherwise, the duration of hepatitis E infection was estimated from the first elevation of ALT in the context of HEV RNA positivity to HEV RNA negativity. Centres in Rotterdam, Hamburg, and Paris, which contributed the majority of patients (n = 40), tested for HEV RNA by means of an internally controlled quantitative real-time reverse transcription PCR (RT-qPCR). The RT-qPCR has a lower limit of detection (95% hit rate) of 143 IU/ml, as determined by the first World Health Organization standard for HEV RNA nucleic acid amplification testing-based assays.[22] In the remaining centres (n = 10 patients), HCV RNA was tested with semi-quantitative RT-PCR assays. If available, blood products were tested retrospectively for HEV RNA to identify blood-borne transmission. To confirm transfusion-transmitted HEV infection, the following criteria were required: (1) evidence of infection in the recipient due to a component from a donor with confirmed viraemia, and (2) nucleotide sequence identity between the viruses present in the recipient and the donor.

Treatment for HEV infection

In this retrospective study, the decision to treat hepatitis E with reduction of immunosuppressive treatment or with ribavirin was made individually based on the physician's choice. Dosage and duration of ribavirin treatment was not standardised. Sustained virological response (SVR) to ribavirin treatment and spontaneous clearance without antiviral therapy were defined as repeatedly undetectable HEV RNA in the serum for at least 12 weeks.

Outcome measures

The primary endpoint was HEV-associated mortality, defined as death with ongoing hepatitis E. More specifically, we assessed liver death as death with decompensated liver disease or following acute or acute-on-chronic liver failure. Acute liver failure (ALF) was defined as an acute increase in aminotransferase levels in an individual without underlying chronic liver disease,

associated with jaundice (total bilirubin >2 times the ULN) or coagulopathy (international normalized ratio >1.5).[23] Acute-on-chronic liver failure (ACLF) was defined as acute decompensation of cirrhosis associated with or without extrahepatic organ failure.[24]

The secondary endpoint was HEV-associated morbidity, including ALF or ACLF, and chronic hepatitis E, defined as persistence of HEV viraemia for at least 24 weeks, irrespective of survival outcome. Cirrhosis was diagnosed through biopsy or clinical assessment, including liver stiffness >12.5 kPa according to transient elastography (FibroScan®, Echosens, Paris, France).

Statistical analysis

For descriptive statistics, continuous variables were displayed as median and ranges and categorical variables as counts and percentages. Variables were compared with the use of Student's *t* test, Pearson's chi-square or Fisher's exact test. All statistical analyses were performed with SPSS version 24 (IBM Corporation, New York, NY). A *p* value below 0.05 was considered statistically significant.

Results

Characteristics of the cohort

A total of 50 patients were included across 11 centres from 5 European countries between April 2014 and March 2017. A summary of the cohort is depicted in Table 1 (for detailed characteristics of each patient see Table S1). Overall, median (range) age was 54.0 (16 to 83) years and 66% of the patients were male. Lymphoid neoplasms were present in 32 (64%) patients, of whom 17 (53.1%) and 12 (37.5%) patients had aggressive and indolent lymphoma, respectively. Myeloid neoplasms were present in 18 (36%) patients, of whom 11 (61.1%) patients had acute leukaemia. Significantly fewer patients had received allogeneic haematopoietic stem cell transplantation (patients number 30 to 50) (n = 21, 42%) compared to those who had not (patients number 1 to 29) (n = 29, 58%) ($p = 0.036$). Among allogeneic haematopoietic stem cell transplant recipients, 16 (66.7%) patients were treated with calcineurin inhibitors (cyclosporine A in 14 patients, of whom 4 received a combination with mycophenolate mofetil, and tacrolimus in 2 patients).

Diagnosis of haematological malignancy preceded diagnosis of hepatitis E in all cases. Median time (range) between allogeneic haematopoietic stem cell transplantation and diagnosis of hepatitis E was 210 (20–4,835) days and 16 (76.2%) patients developed hepatitis E more than 100 days after allogeneic haematopoietic stem cell transplantation. The most frequent (n = 11, 22%) systemic chemotherapy protocol among patients who did not receive an allogeneic haematopoietic stem cell transplantation was a rituximab-containing regimen with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) or with bendamustine (R-Benda), respectively.

Cirrhosis was present in 6 (12%) patients; it was diagnosed with a liver biopsy in 5 patients and with transient elastography in 1 patient (liver stiffness of 36 kPa). Of those, alcohol use disorders were present in 2 patients; the other 4 patients had no risk factor of chronic liver disease.

Transmission of HEV

All HEV infections were autochthonous and the route of transmission remained unclear in most patients, although blood-borne transmission was demonstrated in 5 (10%) patients (patients number 6, 32, 44, and 49 from Germany, and patient number 10 from France), and food-borne transmission was suspected by the treating physicians in 14 (28%) patients. HEV genotyping was performed in a subset of 34 (68%) patients, which revealed genotype 3 in all of them. Data on subtypes was available for 32 patients with genotype 3c, 3f, 3h, and 3i in 7 (21.8%), 10 (31.3%), 1 (3.2%), and 14 (43.8%) patients, respectively. Subtypes clustered in geographical regions: genotype 3c and 3f were prevalent in France (6 out of 7 and 7 out of 10 cases, respectively) and 3i in the Netherlands (13 out of 14 cases). One case with subtype 3 h occurred in Italy.

Course of HEV infection

Hepatitis E was associated with mortality in 8 (16%) patients (Table 2). Liver death occurred in 4 patients (patients number 29, 32, 44, and 47), including 3 allogeneic haematopoietic stem

Table 1. Characteristics of patients.

	Overall (n = 50)	With a liver-related complication (n = 20)	Without a liver-related complication (n = 30)	*p* value*
Age, years	54.0 (16–83)	54.0 (32–81)	54.5 (16–83)	0.893
Male	33 (66%)	13 (65%)	20 (66.7%)	0.903
Blood-borne transmission	5 (10%)	3 (15%)	2 (6.7%)	0.336
Underlying disease				
Lymphoid neoplasm	32 (64%)	14 (70%)	18 (60%)	0.470
Aggressive lymphoma	17 (34%)	8 (40%)	9 (30%)	0.464
Indolent lymphoma	12 (24%)	6 (30%)	6 (20%)	0.417
Multiple myeloma	3 (6%)	0	3 (10%)	0.433
Myeloid neoplasm	18 (36%)	6 (30%)	12 (40%)	0.470
Acute leukaemia	11 (22%)	3 (15%)	8 (26.7%)	0.329
MPN	3 (6%)	2 (10%)	1 (3.3%)	0.331
MDS	4 (8%)	1 (5%)	3 (10%)	0.523
alloHSCT	21 (42%)	12 (60%)	9 (30%)	0.035
Calcineurin inhibitors	16 (32%)	9 (45%)	7 (23%)	0.107
Cyclosporin A (+/− MMF)	14 (28%)	7 (35%)	7 (23%)	0.368
No immunosuppressive drugs	2 (4%)	1 (5%)	1 (3%)	0.768
Death	8 (16%)	5 (25%)	3 (10%)	0.156

* Computed for with liver-related complications *vs.* without liver-related complications. Continuous variables are displayed as medians and ranges, and categorical variables as counts and percentages. *p* values are calculated comparing groups with and without liver-related complications with Student's *t* test or Pearson's chi-square for continuous or categorical variables, respectively. ALT, alanine amino transferase; HEV, hepatitis E virus; alloHSCT, allogeneic haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MPN, myeloproliferative neoplasm.

Table 2. Characteristics of 8 patients with haematological malignancy who died with ongoing HEV infection.

Pt #	Age, sex	Diagnosis	alloHSCT recipient	Chemotherapy or IS	Time alloHSCT to HEV [d]	Duration HEV infection [wk]	Blood-borne transmission	RBV (mg/kg body-weight)	Max ALT	Liver-disease progression	Cancer progression
24	41, male	HL	None	BEAM + autoHSCT	N/A	42	None	8	444	Chronic hepatitis E	Yes
29	74, male	FL	None	R-Benda	N/A	>24	None	10	219	Chronic hepatitis E with decompensated cirrhosis	None
30	44, male	B-NHL	Yes	None	790	<1	None	None	72	None documented	Yes
31	67, male	AML	Yes	CSA, MMF	201	<1	None	None	78	None documented	Yes
32	57, male	AML	Yes	CSA	78	1	Yes	None	556	ACLF (underlying liver cirrhosis)	Yes
44	47, male	MCL	Yes	Steroids	1000	6	Yes	10	242	Fulminant hepatic GvHD with ALF after reduction of IS	None
45	38, male	FL	Yes	CSA, MMF	368	8	None	10	1441	None documented	Yes
47	59, male	ALL	Yes	Tac	210	25	None	Yes	N/A	ACLF (underlying liver cirrhosis), Chronic hepatitis E, GvHD after reduction of IS	Yes

Characteristics and presence of liver-related complications of patients who died with ongoing HEV infection in the cohort. alloHSCT, allogeneic haematopoietic stem cell transplantation; ACLF, acute-on-chronic liver failure; ALL, acute lymphatic leukaemia; ALT, alanine amino transferase; AML, acute myeloid leukaemia; BEAM, carmustine, etoposide, cytarabine and melphalan; CSA, Ciclosporin A; FL, follicular lymphoma; GvHD, graft versus host disease; HEV, hepatitis E virus; HL, Hodgkin's lymphoma; IS, immunosuppression; MCL, mantle cell lymphoma; MMF, mycophenolate mofetil; NHL, non-Hodgkin lymphoma; Pt., patient; R-Benda, rituximab and bendamustine; RBV, ribavirin; Tac, Tacrolimus.

cell transplant recipients 78, 210, and 1,000 days after transplantation (patients number 32, 44, and 47). Cirrhosis and ACLF after reduction of immunosuppressive therapy contributed to liver death in 2 of them (patients number 32 and 47). A 74-year-old male patient (patient number 29) with indolent follicular lymphoma and a 47-year-old male patient (patient number 44) with mantle cell lymphoma died in complete remission of their haematological disease more than 2 years after allogeneic haematopoietic stem cell transplantation; the first with decompensated cirrhosis, the latter with ALF without any underlying liver disease after immunosuppressive treatment reduction for transfusion-transmitted hepatitis E. In total, blood-borne hepatitis E contributed to liver death in 2 (40%) cases (patients number 32 and 44). Another 4 patients died with cancer progression and ongoing hepatitis E, including 3 without liver-related complications (patients number 30, 31, and 45) and 1 with chronic hepatitis E after autologous stem cell transplantation (patient number 24). Risk factors for hepatitis E-associated mortality were male sex ($p = 0.040$), underlying cirrhosis ($p = 0.006$), and allogeneic haematopoietic stem cell transplantation ($p = 0.056$). Median (range) time between allogeneic haematopoietic stem cell transplantation and death with hepatitis E was 289 (78 to 1,000) days. Median peak ALT elevation (range) was 5.4 (1.6 to 32.0) times the ULN and 18.0 (1.9 to 68.7) times the ULN among patients with and without hepatitis E-associated mortality ($p = 0.028$), respectively (Fig. 2A).

Hepatitis E infection lasting for at least 12 and 24 weeks was observed in 32 (64%) and 17 (34%) patients, respectively. Hepatitis E infection lasting for more than 24 weeks was observed in 10 (47.6%) and 7 (24.1%) patients with and without allogeneic haematopoietic stem cell transplantation ($p = 0.083$), respectively, and in 5 (45.5%) patients exposed to a rituximab-containing chemotherapy regimen, including the association with rituximab and bendamustin. Excluding patients who died within 24 weeks after hepatitis E diagnosis, the median (range) ALT peak value was 22.5 (1.9–68.7) and 9.1 (3.1–43.1) times the ULN among patients who did or did not resolve hepatitis E within 24 weeks ($p = 0.038$) (Fig. 2B).

One out of 4 (25%) patients survived after hepatitis E-associated acute (n = 2) or acute-on-chronic (n = 2) liver failure. The survivor was a 42-year-old female with recurrent diffuse large B-cell non-Hodgkin lymphoma without underlying liver disease who developed ALF with hepatic encephalopathy (grade 3 according to West Haven Classification) 4 weeks after autologous stem cell transplantation (patient number 22). Serum ALT and bilirubin levels peaked at 45 and 19 times the ULN, respectively, with a peak international normalized ratio of 1.6. Hepatitis E was diagnosed with NAT and serum viral load was 1.8×10^8 copies/ml, whereas other hepatotropic viruses tested NAT-negative. Retrospective assessment of earlier blood samples revealed HEV viraemia with a viral load of 4.4×10^6 copies/ml within 4 weeks prior to autologous stem cell transplantation, which corresponded to a 1.4 log-fold increase of viral load. Ribavirin treatment (20 mg/kg/d) was initiated for 21 weeks and was associated with an SVR and a recovery of liver function.

Treatment for HEV infection

A detailed overview of patients with and without ribavirin treatment and their respective outcome is displayed in Fig. 1. In our cohort, the use of ribavirin was more frequent among female patients ($p = 0.022$) and among patients with a diagnosis

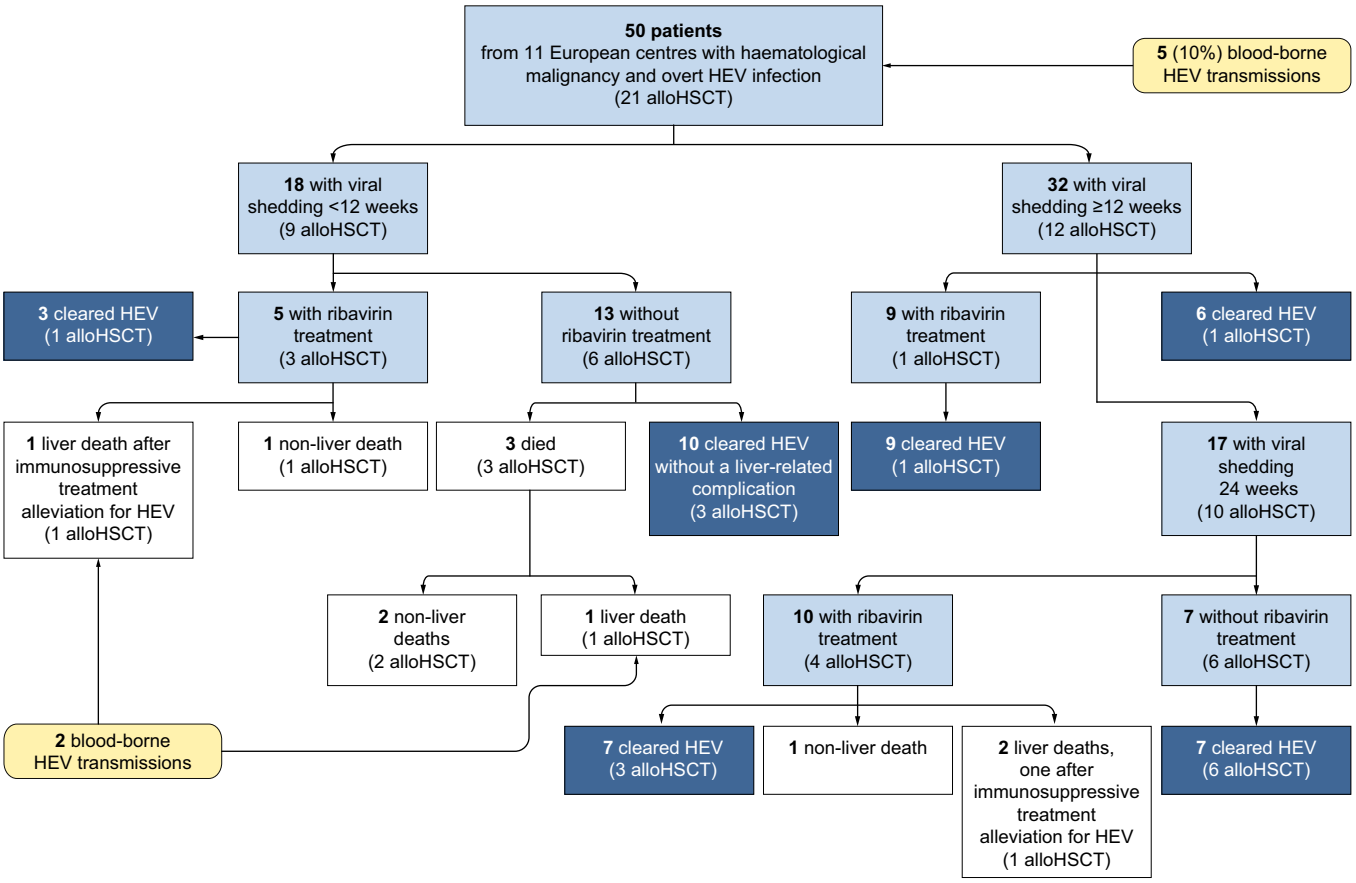

Fig. 1. Flow chart of cohort containing 50 patients with overt HEV infection and haematological malignancy according to duration of hepatitis E. Administration of ribavirin was not randomised. HEV, hepatitis E virus; HSCT, haematopoietic stem cell transplantation. (This figure appears in colour on the web.)

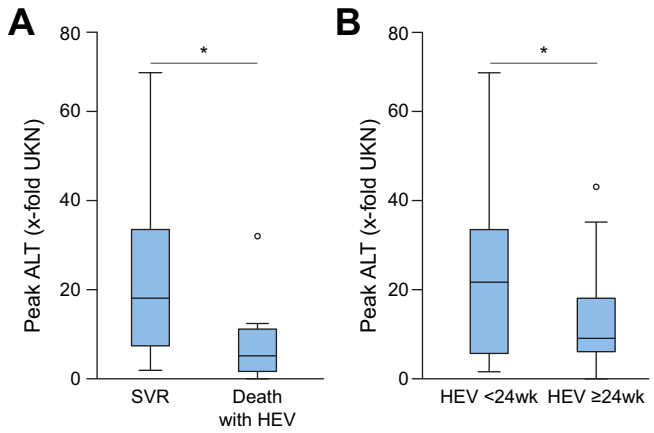

Fig. 2. Association of peak ALT elevation and outcome. A, patients who cured HEV (SVR) *vs.* patients who died with ongoing HEV infection (*$p = 0.028$, Student's *t* test). B, patients with HEV <24 weeks *vs.* ≥24 weeks (*$p = 0.038$, Student's *t* test). ALT, alanine aminotransferase; HEV, hepatitis E virus; SVR, sustained virological response.

of aggressive lymphoma ($p = 0.090$) and less frequent among patients with acute leukaemia ($p = 0.025$). Other baseline characteristics did not differ between patients who did and did not receive ribavirin (Table 3).

Ribavirin treatment was given to 24 (48%) patients at a median (range) starting dose of 10.0 (5.0 to 22.0) mg/kg per day for a median (range) duration of 12.0 (1.0 to 32.0) weeks. Dose reduction of ribavirin was necessary in 10 (45.5%, missing information for n = 2) patients because of anaemia or pancytopenia. Ribavirin treatment was associated with HEV clearance in 19 (79.2%) patients, including 7 (70%) and 12 (85.7%) patients with and without HEV replication for more than 24 weeks, respectively ($p = 0.35$). Initiation of ribavirin therapy <24 weeks after hepatitis E diagnosis was associated with lower mortality and higher SVR rates compared to later initiation (14.3% *vs.* 66.7%, $p = 0.037$, and 85.7% *vs.* 33.3%, $p = 0.037$, respectively). Furthermore, initiation of ribavirin <12 weeks after diagnosis was associated by trend with lower rates of chronicity compared to initiation >12 weeks after diagnosis (33.3% *vs.* 50%, $p = 0.407$).

Immunosuppressive drugs were reduced in 7 (33.3%) haematopoietic stem cell transplant recipients because of hepatitis E, which was associated with mortality in 2 (28.6%) patients. A total of 6 (12%) patients had cancer treatment plan modification because of hepatitis E, including a delay of intended haematopoietic stem cell transplantation in 3 (14.2%) patients.

Discussion

In a large multicentre and retrospective cohort of patients with haematological malignancy, hepatitis E was associated with liver-related mortality, including patients with indolent non-Hodgkin lymphoma, patients who survived 100 days after allogeneic haematopoietic stem cell transplantation, and patients in complete remission of their haematological disease. Blood-borne hepatitis E contributed to the burden and was associated

Table 3. Characteristics of patients according to ribavirin treatment.

	Overall (n = 50)	Ribavirin (n = 24)	No Ribavirin (n = 26)	*p* value*
Age, years	54.0 (16–83)	53.0 (28–81)	55.5 (16–83)	0.922
Male	33 (66%)	12 (50%)	21 (80.8%)	0.022
Blood-borne transmission	5 (10%)	2 (8.3%)	3 (11.5%)	0.706
Underlying disease				
Lymphoid neoplasm	32 (64%)	19 (79.2%)	13 (50%)	0.031
Aggressive lymphoma	17 (34%)	11 (45.8%)	6 (23.1%)	0.090
Indolent lymphoma	12 (24%)	7 (29.2%)	5 (19.2%)	0.411
Multiple myeloma	3 (6%)	2 (8.3%)	1 (3.8%)	0.504
Myeloid neoplasm	18 (36%)	5 (20.8%)	13 (50%)	0.032
Acute leukaemia	11 (22%)	2 (8.3%)	9 (34.6%)	0.025
MPN	3 (6%)	1 (4.2%)	2 (7.7%)	0.600
MDS	4 (8%)	2 (8.3%)	2 (7.7%)	0.933
alloHSCT	21 (42%)	8 (33.3%)	13 (50%)	0.233
Time between alloHSCT and HEV	210 (20–4,835)	196 (50–1000)	250 (20–4,835)	0.218
Presence of cirrhosis	6 (12%)	3 (13%)	3 (12%)	0.917
Peak Bilirubin, mg/dl	1.5 (0.1–39.4)	1.8 (0.1–39.4)	1.5 (0.3–18.5)	0.087
Peak INR	1.1 (0.9–2.2)	1.0 (0.9–1.5)	1.1 (0.9–2.2)	0.136
Peak ALT, U/L	748 (66–3090)	444 (66–1,995)	811 (72–3,090)	0.284
HEV infection, weeks	14 (1–187)	20.5 (4–82)	10.5 (1–187)	0.554
Chronic HEV infection	17 (34%)	10 (41.7%)	7 (26.9%)	0.272
Viral load, copies/ml	10^6 (n.q.-2.3 × 10^9)	4.4 × 10^6 (1.8 × 10^4-2.3 × 10^9)	2.4 × 10^5 (n.q.-2. × 10^7)	0.295
ALF	2 (4%)	2 (8.3%)	0	–
ACLF	2 (4%)	1 (4.2%)	1 (3.8%)	0.954
SVR	42 (84%)	19 (79.2%)	23 (88.5%)	0.370
Death	8 (16%)	5 (20.8%)	3 (11.5%)	0.370

* Computed for ribavirin *vs.* no ribavirin groups. Continuous variables are displayed as medians and ranges, and categorical variables as counts and percentages. *p* values are calculated comparing groups with and without ribavirin with Student's *t* test or Pearson's chi-square for continuous or categorical variables, respectively. ALF/ACLF, acute/(on-chronic) liver failure; ALT, alanine amino transferase; HEV, hepatitis E virus; alloHSCT, allogeneic haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; n.q., not quantifiable; SVR, sustained virological response.

with death in 2 (40%) patients. Ribavirin treatment led to viral eradication in about 80% of patients, whereas immunosuppressive treatment reduction for hepatitis E was associated with mortality in 2 patients (28.6% of patients with immunosuppressive drug reduction for HEV and 9.5% of all haematopoietic stem cell transplant recipients). In addition, Hepatitis E was associated with cancer treatment plan modification, including delays to intended stem cell transplantation. Hepatitis E progressed to chronic hepatitis in 17 (34%) patients, particularly in haematopoietic stem cell transplant recipients and patients with indolent non-Hodgkin lymphoma treated with rituximab-containing chemotherapy regimens. Death with hepatitis E was associated with male sex, cirrhosis, and allogeneic haematopoietic stem cell transplantation.

The 5-year cumulative relative survival rates in large European registry studies range from ∼43% to ∼93% for aggressive and indolent lymphomas,[25] and ∼17% to ∼63% for acute myeloid leukaemia and myeloproliferative neoplasms,[26] respectively. However, survival rates are greatly variable even within the same disease category (*e.g.* aggressive lymphoma) depending on molecular subtypes, prognostic factors of patient and disease subtype, and treatment decisions.[27] Given the retrospective and heterogeneous nature of our cohort, it is difficult to directly compare our findings of HEV-associated mortality to reported survival rates. However, our study demonstrates that HEV infection can alter cancer treatment plans, including delaying haematopoietic stem cell transplantation, and decreasing cancer-free mortality. Generally speaking, infections are a potentially life-threatening hazard for patients with haematological malignancy receiving myeloablative treatments, including allogeneic haematopoietic stem cell transplantation.[28,29]

The epidemiology of HEV in Europe is complex and incompletely understood. HEV is circulating and there is good evidence that the domestic pig is the main reservoir.[30] Anti-HEV-seroprevalence varies among European adults, ranging from 7.5% to 32% and increases with age.[31] The presence of HEV RNA among European blood donors also varies and reported rates range from 1:14,520 in Scotland to 1:611 in the Netherlands.[32,33] Therefore, infection pressure is different across and within European countries.[5] In Germany, a mesoendemic area for HEV,[34] a total of 417,242 new seroconversions occur every year.[35] Regional variations in dietary preferences and in viraemic blood products probably accounted for the different HEV attack rates in our participating centres, which ranged from 1 (Vicenza, Italy) to 19 cases (Rotterdam, the Netherlands).[7] Differences in HEV awareness and screening modalities could have also accounted for this discrepancy. We could not identify all risk factors of HEV transmission, although food-borne transmission was suspected to be the main mechanism as for solid-organ transplant recipients.[36] Besides blood-borne transmission of HEV, which has been reported consistently,[4,7] reactivation of previously acquired HEV infections (with low levels of HEV replication) after myelosuppressive chemotherapy may also play a role, as suggested by our data (patient number 22) and previous reports.[37]

Our observations suggest that hepatitis E can alter the course of haematological malignancy, including in patients in complete remission. Chronic hepatitis E, ACLF, ALF and graft versus host disease contributed to the burden, and underlying cirrhosis increased the hazard of death, as reported for non-haematological patients.[38] In our cohort, patients with indolent non-Hodgkin lymphoma were at high risk of chronic hepatitis E (50%), including those treated with the combination of rituximab and bendamustine.[10,15] The rate of chronic hepatitis E among patients with allogeneic haematopoietic stem cell transplantation (47.6%) was consistent with other cohorts.[8,39] Our

data further confirmed prior reports in solid-organ transplant recipients that chronicity is associated with lower peak ALT values during the infection.[40] In fact, elevated ALT levels might be a surrogate for effective immune activation against the virus as reported in immunocompetent hosts.[41]

Ribavirin treatment was given at the physician's discretion and the HEV clearance rate with ribavirin treatment was consistent with previous retrospective studies in haematological and solid-organ transplant recipients.[14,15] Whether ribavirin treatment altered the course of ALF or ACLF remained unclear although it was suggested in 1 patient with HEV-associated ALF. Current recommendations on the management of HEV infection in patients with prior allogeneic haematopoietic stem cell transplantation, or transplantation in general, suggest a reduction of immunosuppressive therapy as first choice.[11,12] We report 2 cases in which alleviation of immunosuppressive drugs for hepatitis E led to fulminant graft versus host disease and death. Therefore, we think that ribavirin should be considered as first-line therapy in patients with a predisposition or manifest liver-related complication associated with hepatitis E. Our observations also suggest that ribavirin should be given early to cancer patients, to reduce the risk of fatal outcomes, including liver disease progression, cancer treatment plan modifications and chronic hepatitis.[15]

Our study has limitations due to its retrospective and uncontrolled design. Ribavirin efficacy could not be compared with immunosuppressive treatment alleviation. Baseline characteristics differed between patients who did and did not receive ribavirin, however, it remains speculative, why the treated group was enriched for aggressive lymphoma and female gender. Also, we could not assess the incidence of HEV infection in our participating centres.

In summary, our data indicate that hepatitis E can alter the course of patients with haematological malignancy, including those with stable disease and indolent non-Hodgkin lymphoma. The prevailing view that hepatitis E is a rather benign and self-limiting disease is challenged by our data. Our results strongly suggest the transfusion of HEV-free blood products in this high-risk population. Currently Ireland, the UK, and the Netherlands have universal blood donor screening, with a number of other countries opting for selective screening policies.[42] Additionally, patients with haematological malignancies should be informed about the risk of HEV infection. With respect to previously published data, our results further encourage modifying guidelines for patients with haematological malignancies,[37] in order to administrate ribavirin early after the diagnosis of hepatitis E. HEV infection is often overlooked and mistaken for drug-induced liver injury or other viral infections. Screening for HEV RNA should therefore be carried out with NAT for all haematological patients with acute or chronic hepatitis, including patients more than 100 days after allogeneic haematopoietic stem cell transplantation. Future studies should focus on new prevention strategies, including vaccination and routine NAT screening, to reduce the burden of hepatitis E in patients with haematological malignancy.

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Conflict of interest

Dr. Alric reports grants, personal fees and non-financial support from Abbvie, BMS, Gilead, Janssen, and MSD, all outside the submitted work. Dr. Pischke reports personal fees from Abbvie, Falk Foundation, MSD Pharma, and Roche Diagnostics, all outside the submitted work. Dr. Schlabe reports grants from DZIF Clinical Leave Stipend, non-financial support from Abbvie, Gilead, InfectoPharm, and Janssen for Educational Events, all outside the submitted work. Dr. Mallet reports grants, personal fees and non-financial support from Abbvie, personal fees and non-financial support from Gilead Science, all outside the submitted work. The remaining authors have nothing to declare regarding the submitted work.

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

Authors' contributions

Conception and design: JvF, SP, VM. Acquisition of patients and/or clinical data: JvF, SP, LA, JJC, CA, SS, US, MTG, PS, DB, RT, AX, MB, FA, AWL, JMP, RAdM, VM. Analysis and interpretation of the data: JvF, SP, VM. Drafting of the article: JvF, SP, VM. All authors critically revised the draft and gave their approval to the final version of the article.

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Supplementary data

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Author names in bold designate shared co-first authorship

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