

CASE REPORT

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# The question of screening organ donors for hepatitis e virus: a case report of transmission by kidney transplantation in France and a review of the literature

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## Abstract

**Background** Hepatitis E is a potentially serious infection in organ recipients, with an estimated two-thirds of cases becoming chronic, and with a subsequent risk of cirrhosis and death. In Europe, transmission occurs most often through the consumption of raw or undercooked pork, more rarely through blood transfusion, but also after solid organ transplantation. Here we describe a case of Hepatitis E virus (HEV) infection transmitted following kidney transplantation and review the literature describing cases of HEV infection transmitted by solid organ transplantation.

**Case presentation** Three weeks after kidney transplantation, the patient presented with an isolated minimal increase in GGT and hepatic cytolysis 6 months later, leading to the diagnosis of genotype 3c hepatitis E, with a plasma viral load of 6.5 log<sub>10</sub>IU/mL. In retrospect, HEV RNA was detected in the patient's serum from the onset of hepatitis, and in the donor's serum on the day of donation, with 100% identity between the viral sequences, confirming donor-derived HEV infection. Hepatitis E had a chronic course, was treated by ribavirin, and relapsed 10 months after the end of treatment.

**Discussion** Seven cases of transmission of HEV by solid organ transplantation have been described since 2012 without systematic screening for donors, all diagnosed at the chronic infection stage; two patients died. HEV organ donor transmission may be underestimated and there is insufficient focus on immunocompromised patients in whom mild liver function test impairment is potentially related to hepatitis E. However, since HEV infection is potentially severe in these patients, and as evidence accumulates, we believe that systematic screening of organ donors should be implemented for deceased and living donors regardless of liver function abnormalities, as is already the case in the UK and Spain. In January 2024, the French regulatory agency of transplantation has implemented mandatory screening of organ donors for HEV RNA.

**Keywords** Hepatitis E, Hepatitis E Virus, Organ transplantation, Chronic hepatitis, Donor screening, Donor-derived infection, Transplant-related infection, Donor-derived transmission

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## Introduction

Awareness of hepatitis E virus (HEV) has increased considerably over the past 15 years. Autochthonous hepatitis E in developed countries has been increasingly recognized as a significant public health concern [1, 2]. Seroprevalence studies in Europe have shown substantial differences between geographical areas, which can at least in part rely on tested populations and serological tests. In France, for example, seroprevalence has been reported to range from 8.0% to 86.4% in the general population, and from 21.9% to 71.3% in blood donors with a higher endemicity level in southern France [3, 4].

HEV is a small quasi-enveloped (since not enveloped when excreted in stools) RNA virus [5, 6]. Eight genotypes have been identified in the *Paslahepevirus balayani* species in the family *Hepeviridae* and subfamily *Orthohepevirinae*, of which types HEV-1, HEV-2, HEV-3, HEV-4, and HEV-7 are known to infect humans [7]. Recent studies have reported that another species, *Rocahepevirus rattii*, may also infect humans [8, 9].

HEV-1 and HEV-2 have a strictly human reservoir, while that for HEV-3, HEV-4 and HEV-7 is animal [5]. In Europe, pigs and wild boars are the main reservoirs for HEV-3 and HEV-4. Camels are a reservoir for HEV-7 [10]. Very recently, the animal reservoir of human HEV infections has been supplemented by rats, for *Rocahepevirus rattii* [11].

HEV-1 and HEV-2 are responsible for epidemics in developing countries through fecal–oral transmission. In contrast, zoonotic transmission through close contact or – primarily – through consumption of raw or insufficiently cooked food is responsible for HEV infections, especially in developed countries for HEV-3 and HEV-4 genotypes (anecdotally for the HEV-7 genotype in the United Arab Emirates [10]).

Hepatitis E is a potentially serious infectious disease in specific populations. Most often asymptomatic, HEV infection can lead to acute hepatitis, more rarely to death, while HEV-3, HEV-4, HEV-7 and *Rocahepevirus rattii* can lead to chronic infection (defined as viral RNA positivity in the blood and disturbance of liver function tests for more than 3–6 months) in immunocompromised individuals [12–15]. Since 2008, HEV-3 and HEV-4 infections have been recognized as a cause of progression to cirrhosis in these patients, especially in solid organ transplantation recipients (SOTRs) [16–19]. More recently, in 2016, HEV-7 was associated with a chronic infection in a liver transplant recipient from the United Arab Emirates [10]. A first chronic infection by *Rocahepevirus rattii* has been described in 2018 in a liver transplant recipient who lived in a rat-infested housing estate in Hong Kong [20]. Although different studies show a variation in the rate of developing chronicity, overall, HEV infections

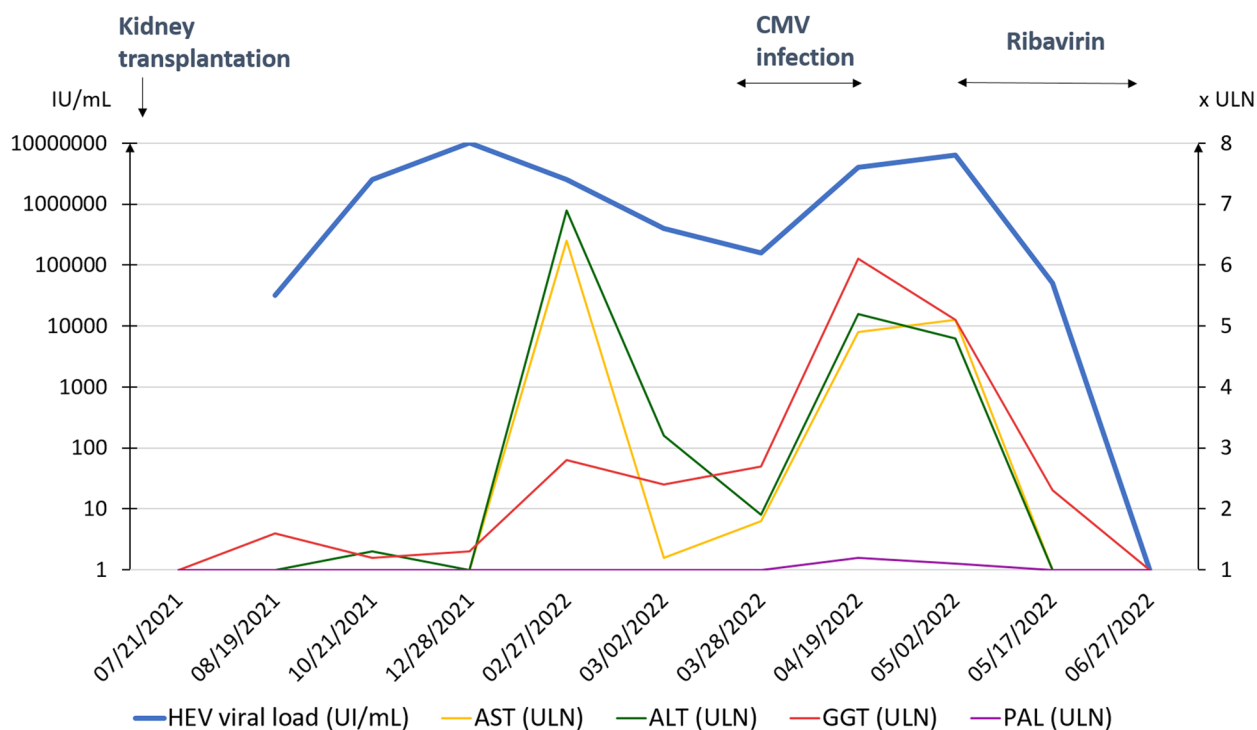
of *Paslahepevirus balayani* species become chronic in about two-thirds of SOTRs based on large cohort studies and meta-analyses, including in our geographical area [21–24]. Regarding the *Rocahepevirus rattii* species, only one small series of immunocompromised patients has been reported, with a seemingly similar chronicity rate (7/9 patients developed a chronic form) [9].

In addition to the modes of transmission described above, HEV transmission can be iatrogenic. Several studies of blood banks in Europe have shown a prevalence of HEV RNA positivity ranging from 0.02 to 0.14% in blood donors [13], and transfusion-transmitted hepatitis E has been described [25]. Because HEV viremic donors can be asymptomatic, HEV RNA screening is the only option to control transmission (anti-HEV antibodies can be absent in the presence of HEV RNA in cases of very recent infection), and several European countries, including France, have implemented mandatory screening of blood donors for HEV RNA [26]. Moreover, solid organ donation has also been shown to be a possible source of HEV [27–29]. Here, we describe a case of hepatitis E transmission from a kidney transplant donor in France and we discuss the relevance of systematic screening prior to organ donation.

## Case report

A woman in her 50s with polycystic kidney and hepatic disease underwent kidney transplantation on 21 July 2021. She received immunosuppressive therapy with anti-thymocyte globulins, tacrolimus, mycophenolate mofetil, and corticosteroids. She presented a negative cytomegalovirus (CMV) serology whereas donor serology was positive. Kidney graft function was stabilized at 98  $\mu\text{mol/L}$  of creatinine 3 months after transplantation, but the patient developed post-transplant diabetes, and two episodes of acute graft pyelonephritis in January and February 2022. On 27 February 2022, she was hospitalized for isolated fever while still being treated with ertapenem for her second episode of acute graft pyelonephritis. Levels of the gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were increased to 109, 243, and 225 IU/L, respectively. Alkaline phosphatase (ALP) and bilirubin levels were within reference range. There was no sign of hepatocellular deficiency. The patient had no background of alcohol intake or illicit drug use. The abdominal ultrasonography was normal. HEV RNA detection was positive using a real-time reverse transcription Polymerase Chain Reaction (qPCR) assay, as previously described [23], viral load was 6.5  $\log_{10}$  IU/mL, and IgM and IgG serologies were negative (Fig. 1).

HEV was determined to be of genotype 3c using the Hepatitis E Virus Genotyping Tool v.1.0 (<https://www.rivm.nl/mpf/typingtool/hev/>) and by phylogeny



**Fig. 1** Evolution of HEV viral load (blue curve, Log<sub>10</sub>IU/mL) of AST (times ULN), of ALT (times ULN), of GGT (times ULN) and ALP (times ULN) in the first year post-kidney transplantation. ULN of laboratory was 35 IU/L for AST and ALT, 40 IU/L for GGT and 105 IU/L for ALP. A result of liver function tests below the ULN has been reported as 1 time ULN in this graph. HEV: hepatitis E virus. AST: aspartate transaminase. ALT: alanine transaminase. CMV: cytomegalovirus. GGT: gamma-glutamyltransferase. ALP: alkaline phosphatase. ULN: upper limit of normal

(Supplementary Figure S1). No other infectious agents were identified. We then tried to define the mode and time of infection. Questioning did not find evidence for foodborne transmission of HEV during the 10 previous weeks. There was no history of transfusion.

Retrospective examination of biological data revealed that liver function abnormalities dated from August 2021, i.e. during the first month after kidney transplantation. Indeed, we noticed an increase in the GGT level on 10 August 2021. An increase of ALT was subsequently detected on 7 October 2021. Liver function tests were normal before the graft. Additional retrospective analyses performed on available sera detected HEV RNA by qPCR on 19 August 2021 at a titer of 4.5 log<sub>10</sub>IU/mL, while qPCR was negative the day of the transplantation (Fig. 1). In addition, abnormality of liver tests and the presence of HEV RNA in the serum for more than 6 months led us to conclude that it was a case of chronic hepatitis E. Besides, HEV infection occurrence so close to the transplantation raised suspicion of transmission from the donor.

The donor was a man in his 50s admitted to the Intensive Care Unit (ICU) for a cardiac arrest following a severe trauma. He died after Maastricht category III circulatory arrest. The two kidneys and tissues, including bones and cardiac valves, were recovered whereas the

liver was not because of suspicion of an ischemic cholangitis. Indeed, liver tests were abnormal on admission to the ICU (ALT 52 IU/L, AST 107 IU/L, GGT 84 IU/L, ALP 61 IU/L). The donor received two packed red blood cells and one pack of platelets before organ procurement.

We retrospectively detected HEV RNA by qPCR in the donor's serum while HEV IgG and IgM were negative. Viral load was 4.9 log<sub>10</sub>copies/mL. Retrospective qPCR showed that stored health and safety samples of the three blood products received by the organ donor were free of HEV RNA. Based on these findings and their timing, and the 100% identity between HEV sequences obtained from the organ donor and the kidney transplant recipient, in addition to phylogenetic analysis including these sequences (Supplementary Figure S1), we retained the diagnosis of nosocomial HEV transmission through the kidney transplant.

HEV RNA viral load in the transplant recipient was 5.6 log<sub>10</sub>IU/mL on 3 March 2022 and 5.3 log<sub>10</sub>IU/mL on 28 March 2022 (Fig. 1). She was hospitalized on 28 March 2022 for CMV disease with digestive, pulmonary, and hematological involvement. She was treated with ganciclovir from 29 March to 19 April 2022 associated with the decrease of immunosuppressive therapy (reduction of the mycophenolate mofetil dosage by a factor of 4).

On 19 April 2022, HEV RNA load had increased to 6.8  $\log_{10}$  IU/mL. CMV PCR was negative. The patient was thus treated with ribavirin at 800 mg/day from 2 May 2022 for 3 months. On 27 June 2022, liver function tests were normal, and HEV qPCR was negative. Although HEV seroconversion was not observed in August 2022 it was apparent in April 2023 for both IgM and IgG anti-HEV antibodies. HEV RNA tested retrospectively using the Altona RT-PCR assay (Altona Diagnostics, Hamburg, Germany) on a stored stool sample collected as on April 2023 was undetectable. Despite seroconversion, she developed new HEV viremia on June 16 2023, 10 months after ribavirin treatment had ended. Phylogenetic analysis indicated that the strain was the same (Supplementary Figure S1). Her liver function test and fibroscan were normal. Because HEV viremia persisted for 3 months, Ribavirin was reintroduced from October 2023 to January 2024, resulting in HEV viremia clearance. HEV qPCR in the stools was negative in January 2024 (Altona RT-PCR assay).

We conducted an investigation to identify other infected recipients from the same donor. The two kidneys and tissues – as bones and cardiac valves – were transplanted. Mild GGT level increase was observed 9 days after the kidney transplant in the other kidney recipient, but not secondary to HEV infection since blood samples retrospectively tested negative for anti-HEV IgM and HEV RNA just before the transplant as well as 3 and 9 months post-transplant. A left knee medial tibia plateau was grafted 2 months after procurement for the repair of a complex knee fracture in a 25-year-old woman. Anti-HEV IgM and IgG were negative 7.5 months post-osseous graft. In conclusion, HEV transmission occurred in only one of two kidney recipients. Recipients of donor tissues appear to have remained free of infection, subject to missing data.

## Discussion

Here we describe a case of HEV-3 infection transmitted by a kidney transplant donor. This case is distinguished by the mode of HEV transmission that is classically zoonotic in Europe, mostly foodborne, with pigs and wild boars as the main reservoir.

While HEV transplant transmission had not been documented until 2012 [2], several cases have been described since then. The first case of liver transplant transmission was described in 2012 in Germany [27]. Liver cirrhosis developed within 15 months and the patient died of septic shock. A second case of liver transplant transmission was described in 2018 in China which was part of an outbreak that affected five organ transplant recipients who shared the same donor and were all diagnosed at the stage of chronic hepatitis E [29]. The

liver transplant recipient developed severe hepatitis with progressive portal hypertension. Regarding HEV kidney transplant transmission, four cases had been reported: two in France in 2017 and two in China in 2018 [28, 29]. In these four cases, HEV sequences from the transplant recipients were identical with each other and with that of the common donor, indicating donor-derived infection [27, 28]. HEV was of genotype 3 for the European cases and of genotype 4 for the Chinese cases. A case of HEV infection presumed to have been acquired through lung transplantation, was described in the USA in 2017 [30]. Supporting evidence included the positive anti-HEV IgG and IgM testing of the donor's serum and the patient's persistent transaminitis that began after transplantation, even though the donor was negative for HEV RNA. HEV infection was diagnosed in the lung transplant recipient at the cirrhosis stage, simultaneously to HEV meningoencephalitis, 11 years post-transplantation. Finally, a recent publication by Ushiro-Lumb et al., has further documented transmission by organ donation diagnosed through the UK's systematic donor screening policy [31]. Between 2017 and 2022, 9500 deceased potential organ donors were screened with nine confirmed viraemic cases identified (incidence of 0.94 per 1000). Among the 20 organ recipients from the 8 proceeding donors, 14 cases of infection were diagnosed: in 5 liver transplant recipients and 9 kidney transplant recipients. As evidence of HEV organ donor transmission accumulates, it is possible that organ donor-derived HEV infections are underestimated in endemic areas, since acute and chronic hepatitis E in immunocompromised patients remain underdiagnosed [19, 21].

Secondary HEV transmission between humans is rare [5] and the scarcity of this event might be notably explained by dose-dependence and a high infectious dose [32, 33]. The organ donor-derived HEV infections raise the question of infectious dose. As liver is the target and the main reservoir of HEV during hepatitis, HEV transmission by liver transplantation is not surprising. In the German study by Schlosser et al., antibody screening and RT-PCR were negative in the donor but HEV RNA was reported to be “in high concentration” in the liver [27]. In the Chinese study by Sridhar and colleagues, HEV was also detected in the donor liver and viral load was 288 copies/reaction [29]. In the English series by Ushiro-Lumb et al., all liver transplant recipients from a donor with HEV viremia, even very low at 100 IU/mL, had an infection (except for one recipient who presented a transient viremia in the context of liver graft withdrawal on day 5) [31]. In the cases of HEV transmission by kidney, lung, and heart transplants, it can be hypothesized that HEV was transmitted by the blood remaining in the different organs after washout. The

risk of transfusion-transmitted HEV infection has been found to be closely related to the plasma volume of blood components [34, 35]. In a study performed in southeast England, Tedder et al. reported that the HEV-infected blood donations associated with transmission exhibited a median viral titer of  $4.53 \log_{10}$  IU/ml and a lowest titer leading to infection of  $2.61 \log_{10}$  IU/ml [36]. Significant viremia was retrospectively detected on archived serum from each organ donor collected on the organ retrieval day and exceeded the minimum infectious titer seen in blood products, being  $6.5 \log_{10}$  IU/mL for the French kidney donor,  $5.3 \log_{10}$  IU/mL for the Chinese organ donor, and  $4.9 \log_{10}$  IU/mL for our donor. Among the fourteen patients receiving kidney transplant from HEV positive English donors, five developed no infection, and their donors had a viral load of less than 500 IU/mL. Nevertheless, five developed HEV infections and their donor's viral load ranged significantly, from 111 IU/mL to  $4.9 \log$  IU/mL, suggesting the importance of transmission factors other than viral load [31]. Infectious HEV circulates in peripheral blood as enveloped particles that appear to be the major type of HEV in blood and therefore the primary cause of blood-transmitted HEV infections, while non-enveloped particles excreted in stools are the most infectious [37]. In the case presented here, tested recipients of tissues remained free of infection. In addition, a recent literature review found no case of HEV infection transmitted through cell and tissue allografts [38].

Considering the clinical presentation of the nine cases of organ donor-derived HEV infections without systematic screening published in the literature and found in our case, HEV infection was diagnosed at the chronic hepatitis stage in all patients, at post-mortem for two ([27, 29], present case) and after a mean of 211 days after transplantation for seven ([28, 29], present case). HEV RNA positivity determined retrospectively has been reported after a mean time of 57 days and as soon as 21 days after transplantation on available sera for four patients ([27, 29], present case). Two cases developed liver cirrhosis [27, 30], and one presented severe hepatitis with progressive portal hypertension [29]. Although the rate of progression to chronicity varied between the different studies, HEV infections overall became chronic in about two-thirds of SOTRs [21, 22, 24], while almost all the cases of organ donor-transmitted HEV infection in SOTRs are described as having become chronic. Furthermore, we observed a relapse of chronic hepatitis despite ribavirin treatment and sero-conversion in our case.

Organ donor-transmitted HEV infection in SOTRs is characterized by an infection on the day of transplantation, probably at the worst juncture for achieving an immune response against HEV. In fact, in previous studies in SOTRs, there was no trend for an association

between initial viral load and chronic HEV infection [19, 21]. Such an observation, however, largely depends on the clinical samples available for testing. It is possible that the temporality between HEV infection and organ transplantation and the introduction of immunosuppressive treatment in organ donor-transmitted HEV infection challenges this result. There have been studies on the implications of immunosuppressive drugs (apart from anti-T polyclonal antibodies) for treatment in chronic hepatitis E [39, 40]. Immunosuppressive induction treatment led as expected to the quasi-complete depletion of lymphocytes in our patient (total lymphocyte count of 0.97 G/L before and 0.06 G/L several hours after transplant). This highlights an inadequate defense against HEV provided by innate immunity. It should be noted that clinical presentation as mild hepatitis then moderate chronic hepatitis looks like the HEV infection of athymic nude rats, resulting in mild alterations of liver enzyme levels, lack of hepatic injury, and persistent hepatitis, as reported by Debing et al. [41].

All the cases of organ donor-transmitted HEV infection have been diagnosed at the chronic hepatitis stage. If this evolution was undoubtedly favored by immunosuppression, the lack of attention to mild or moderate liver function test impairment at the beginning of the hepatitis course should also be highlighted, because it is typical of E hepatitis in SOTRs compared to immunocompetent patients, and has been associated with chronic HEV infection development [19, 21, 42]. Two French SOTR cohorts estimated that 6 to 8% of patients with biological liver abnormalities had hepatitis E, which reflects the high HEV endemicity level in France [16, 43]. In view of the potential severity of liver damage, any biological liver abnormalities in SOTRs should be investigated for HEV by qPCR, the diagnostic method of preference for on-going HEV infection [19, 21, 43]. Furthermore, in the absence of any abnormal liver function tests, we recommend systematic annual screening for hepatitis E in SOTRs, because we showed that HEV monitoring in KTRs is clinically relevant especially in high endemic regions [44]. Moreover, this has been estimated to be cost-effective in a UK study, expecting to avoiding 7 cases of cirrhosis and 3.5 cases of cirrhosis-related death per 1000 screened patients [45]. When considering the time to diagnosis, any diagnosis of HEV infection in SOTRs within the first year of transplantation should raise the possibility of transmission from the organ donor.

The hope for a better prevention of HEV infection in immunocompromised patients may notably depend on the availability of safe and effective vaccines. The only approved vaccine (Hecolin) was licensed in China in 2011 [5]. Because neutralizing anti-HEV antibodies produced in response to a natural infection mainly target the capsid

protein, it has been suggested that neither pre-exposure to HEV nor ORF2-based HEV vaccines such as Hecolin confer protection against enveloped HEV virions [37]. However, vaccination with Hecolin in rabbits prior to administration of immunosuppressants fully protected them against HEV genotype 3 and 4 infections, whereas only partial protection was achieved when the animals were already receiving immunosuppressants [46]. These data could argue in favor of preferentially vaccinating patients on the waiting list for organ transplantation [39]. As HEV vaccines are not commercialized worldwide, as evidence of HEV organ donor transmission accumulates in endemic areas, and as mild liver function test impairment potentially related to hepatitis E in immunocompromised are insufficiently considered, we think that systematic screening of organ donors – at least in HEV hyperendemic areas such as ours [47] – should be implemented independently of liver function abnormalities. This would be in line with screening already performed in the UK and Spain for deceased and living donors, regardless of HEV incidence [44, 48, 49]. Recommendations from The British Transplantation Society and the UK Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO), in place since 2017, state that all organ donors must be screened for hepatitis E viremia using HEV-Nucleic Acid Amplification Testing.

In France, a similar policy has been implemented no later than January 2024. The timing of HEV systematic screening depends on the type of donor. In the case of a living kidney donor, screening will be carried out the week before the kidney donation according to new French recommendation. If it is positive, the transplant will be cancelled. In Marseille, we also screen HEV RNA during the initial assessment of donors. In the case of a deceased donor, screening will be carried out emergency prior to the kidney donation, with the constraint that the screening result may not be available at the time of donation: the donor's HEV status will be determined by qPCR within 48 h. When assessing the risk–benefit balance for transplantation, the donor's liver function must be carefully evaluated. In this context, the detection of viremia is unlikely to be an absolute contra-indication to use of an organ from a donor but will certainly inform clinical management decisions post-transplant.

## Conclusion

Documented cases of HEV infection derived from organ donation should not be overlooked. Given the potential severity of HEV infection in immunocompromised patients, the initial presentation as moderate hepatitis, and the potential delay in diagnosis, we believe that systematic screening of organ donors is valuable for both deceased and living donors.

## Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
CMV	Cytomegalovirus
GGT	Gamma-glutamyltransferase
HEV	Hepatitis E virus
ICU	Intensive Care Unit
qPCR	Real-time Polymerase Chain Reaction
SOTRs	Solid organ transplant recipients
ULN	Upper limit of normal

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12985-024-02401-2>.

Additional file 1: Supplementary Figure S1. Phylogeny reconstruction based on a fragment of the ORF2 gene.

## Authors' contributions

JS, TL, PB, VM were in charge of the patient. CB, AM, SA, PC performed virological analyses. VP, VF, MFA provided information about other recipients of organs from the same donor. JS drafted the manuscript and produced the figures. PC and VM participated in writing the manuscript. VM supervised the work. All authors revised the manuscript critically and approved the final version.

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## Availability of data and materials

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

NA.

### Consent for publication

The patient has given her written consent for the publication of this article.

### Competing interests

The authors declare no competing interests.

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