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INTRA-ABDOMINAL INFECTIONS, HEPATITIS AND GASTROENTERITIS (T STEINER, SECTION EDITOR)

The Role of Emerging and Neglected Viruses in the Etiology of Hepatitis

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Abstract

Purpose of Review In this review, we present the overview of emerging and neglected viruses associated with liver involvement.

Recent Findings Hepatitis E virus (HEV) emerged in the last two decades, causing hepatitis in many parts of the world. Moreover, liver involvement was also described in some emerging arboviral infections. Many reports showed dengue-associated liver injury; however, chikungunya, West Nile, tick-borne encephalitis, and Zika virus are rarely associated with clinically manifest liver disease. In addition, some neglected highly prevalent viruses such as adenoviruses and parvovirus B19 are capable of causing hepatitis in specific population groups. Anelloviruses (torque teno virus/torque teno mini virus/torque teno midi virus, SEN virus), human bocavirus, pegiviruses, and lymphocytic choriomeningitis virus have shown a little potential for causing hepatitis, but their role in the etiology of liver disease remains to be determined.

Summary In addition to the well-known hepatotropic viruses, many emerging and neglected viruses have been associated with liver diseases. The number of emerging zoonotic viruses has been increasingly recognized. While zoonotic potential of HEV is well documented, the recent identification of new hepatitis-related animal viruses such as HEV strains from rabbits and camels, non-primate hepaciviruses in domestic dogs and horses, as well as equine and porcine pegivirus highlights the possible zoonotic transmission in the context of "One Health." However, zoonotic potential and hepatotropism of animal hepatitis viruses remain to be determined.

Keywords Hepatotropic viruses · Hepatitis E virus · Arboviruses · Adenoviruses · Parvovirus B19 · Anelloviruses · Human bocavirus · Pegiviruses · Arenaviruses

Introduction

Hepatotropic viruses are a group of viruses that share a common ability to cause inflammation of the liver. Spectrum of liver diseases caused by hepatotropic viruses ranges from asymptomatic, acute, and/or fulminant to chronic infection and liver cirrhosis with its complications such as portal hypertension and hepatocellular carcinoma. While the majority of hepatotropic viruses commonly cause acute form of liver disease, some of them such as hepatitis E virus (HEV) have been

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associated with the chronicity in specific populations [1]. In addition to well-known hepatotropic viruses [1–3], liver involvement was also described in some emerging arboviral infections [4–13]. Furthermore, some highly prevalent but neglected viruses are capable of causing hepatitis in specific population groups, such as immunocompromised persons [14–16] and children [17].

This review focuses on emerging and neglected viruses associated with liver involvement. The most common emerging and neglected hepatotropic viruses and their liver-related morbidity are presented in Table 1 and Fig. 1.

Hepatitis E Virus

HEV is a non-enveloped, single-stranded, positive-sense RNA virus that belongs to the family *Hepeviridae*, genus *Orthohepevirus*. The virus has at least eight different genotypes (G1–G8). Genotypes 1 and 2 are restricted to humans while genotypes 3 to 8 are zoonotic and infect humans and different animal species [45, 46]. Waterborne transmission is the most commonly recognized route of transmission in developing countries, and this route lately has gained attention in industrialized countries as well [47]. In developed countries, zoonotic and foodborne transmissions are most common, primarily due to consumption of raw and undercooked meat of domestic pigs, wild boar, and deer [47]. Additionally, occupational exposure in animal-related professions is associated with higher HEV IgG seroprevalence [48]. Less common routes include parenteral transmission via blood products as HEV RNA is found in asymptomatic blood donors [49] and transmission via liver and non-hepatic grafts after solid organ transplantations [50]. Hepatitis E virus infection typically manifests as an acute self-limited hepatitis. In developing countries, young men are most commonly affected (male-to-female ratio 2–5:1) [18]. Mortality rates are high in pregnant women (up to 25%), who usually develop fulminant hepatitis, in patients with preexisting liver diseases and in young children [19–21]. In developed countries, mostly older men are affected, presenting as an acute, self-limiting illness [22]. Patients with preexisting liver disease are at risk of acute-on-chronic liver failure [23]. Chronic HEV infection may develop in immunocompromised patients, mainly in solid organ transplant recipients, HIV-positive patients, and patients with hematological malignancies [24–26]. The majority of cases are asymptomatic, with mild but persistent liver test abnormalities. More than half of solid organ transplant recipients who develop acute HEV hepatitis will progress to a chronic infection [27], which may lead to rapid progression of liver fibrosis, liver decompensation, and death [24]. Most cases of acute HEV infection are self-limiting and require no treatment. In transplant population with chronic HEV infection, the first step is to reduce the immunosuppressive therapy. In order to achieve viral clearance, several treatment regimens have been used, including interferon-α and ribavirin as monotherapy or in combination [27]. HEV vaccine has been licensed, but so far, its use has been limited [1, 27].

Dengue Virus

Dengue virus (DENV) is a mosquito-borne flavivirus. There are four DENV serotypes (1–4) which circulate in endemic areas. Although many DENV infections are asymptomatic, dengue may present as dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Dengue is one of the most widely distributed arboviral infections with an estimated annual incidence of 100 million cases of DF with another 250,000 cases of DHF and mortality rate of 24,000–25,000 per year [51]. There are many reports on liver injury associated with DENV infection. All four serotypes have been associated with dengue-related hepatitis, but DENV-1 and DENV-3 seem to have more prominent liver tropism [52]. Painful hepatomegaly is seen in up to 30% of patients. However, an increase in serum transaminase levels can be found in up to 90% of patients infected with DENV. The elevation of transaminases is usually less than fivefold greater than upper limit of normal, but elevations greater than ten times the upper limit of normal were seen in 11.1% and 7.4% of cases, respectively [53]. Unlike conventional viral hepatitis, in DENV infection, the level of aspartate aminotransferase is usually higher than that of alanine aminotransferase [54]. Hepatomegaly is present in both DF and DHF/DSS, but more common in DHF [4] and DSS [55]. Although the majority of patients present with mild to moderate liver dysfunction, severe acute hepatitis may also occur [6, 7] even leading to a need for liver transplantation [28]. The age of the patients who develop fulminant hepatitis is variable, but it tends to occur in children younger than 15 years of age [29]. A retrospective study from Thailand reported up to 50% mortality rate in the pediatric population with DENV-associated acute liver failure [30]. DENV-induced hepatitis with chronic calcific changes is also reported in rare cases [31]. Liver dysfunction seen in DENV infections could be a result of direct viral effect on hepatocytes or a result of a dysregulated host immune response against the virus [5]. Since liver injury due to DENV is not uncommon, in endemic or epidemic areas, dengue should be included in the differential diagnosis of acute hepatitis.

Table 1 Major neglected and emerging viruses and their liver-related morbidity

Virus	Population group	Clinical presentation	Outcome	References
Hepatitis E	Immunocompetent adults	Acute self-limiting hepatitis	Favorable	[18–27]
	Children	Acute hepatitis	Unfavorable	
	Preexisting liver disease	Acute on chronic liver failure	Unfavorable	
	Pregnant women	Fulminant hepatitis	Mortality rate 25%	
	Immunocompromised, SOT recipients, HIV-positive, hematologic malignancies	Chronic hepatitis, cirrhosis	Progressive deterioration	
Dengue	Adults	Mild to severe acute hepatitis	Favorable	[6, 7, 28–31]
	Children (< 15 years)	Fulminant hepatitis	50% mortality rate	
Chikungunya	Adults	Mild to severe acute hepatitis	Favorable	[32–36]
West Nile	Children, adults	Mild to severe hepatitis		[8, 9, 37]
Zika	Adults	Mild hepatitis	Favorable	[12, 13]
Tick-borne encephalitis	Adults	Mild hepatitis	Favorable	[10, 11]
Adenoviruses	Children, immunocompromised	Severe hepatitis	Unfavorable	[16, 38–40]
Parvovirus B19	Children	Acute hepatitis	Favorable	[17, 41]
		Fulminant liver failure	Unfavorable	
	Adults	Acute hepatitis	Favorable	
		Chronic hepatitis (rare)	Unfavorable	
Lassa virus	Adults	Severe hepatitis (~ 25% infected persons)	Unfavorable	[42–44]

SOT solid organ transplant

Chikungunya Virus

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus. Three main genotypes of CHIKV (West African, East/Central/South African, and Asian) have been defined [56]. CHIKV originated in Africa and has since spread causing large outbreaks in Asia, Pacific Islands, the Indian subcontinent, Europe, and the Americas [57]. High fever, headache, myalgia, arthralgia, and rash are the typical clinical signs of CHIKV fever. Although numerous cell types, including hepatocytes, are susceptible to CHIKV, clinically manifest liver damage is rarely reported during CHIKV infection. However, a mild to moderate increase in liver function tests is commonly detected [32]. Cases of severe acute hepatitis were observed during the CHIKV outbreak on Reunion Island

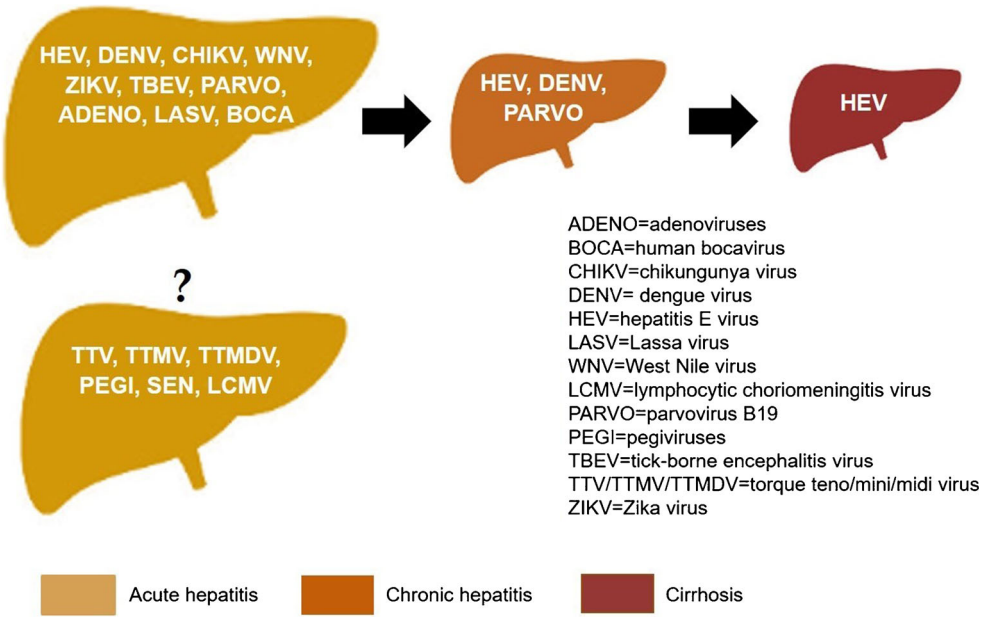

Fig. 1 Emerging and neglected hepatotropic viruses. Stages of liver disease

in 2006 [33]. Although information on liver enzymes was only available for 64% of the cases, the majority of patients had a greater than threefold increase of the liver enzymes [34]. A fatal case of CHIKV infection with liver involvement was reported in 2010 in a previously healthy man without comorbidities in Malaysia [35]. Additionally, three cases of chikungunya-associated acute hepatitis were detected during the 2014–2015 outbreak in the French Guiana [36]. Although rare, clinicians should be aware of CHIKV-associated hepatitis, especially in endemic areas.

West Nile Virus

West Nile virus (WNV) is a mosquito-borne flavivirus. There are at least eight genetic lineages of which WNV lineages 1 and 2 are associated with human diseases [58]. WNV is one of the most widely distributed arboviruses. The majority of WNV infections are asymptomatic; severe disease occurs mainly in elderly and immunocompromised patients and typically manifests as meningitis, encephalitis, or acute flaccid paralysis [59]. Reports on WNV-associated hepatitis are scarce. Hepatic involvement in WNV infection was first described in the Central African Republic. From 1980 to 1984, four patients with hepatitis aged from 13 to 35 years were documented with virus isolation from liver biopsies. In all but one case, clinical course was severe and associated with profound jaundice. Two patients died, while two others recovered [8]. In addition, in 2003, WNV antigen was detected in the liver (Kupffer cells) of a fatal case of hemorrhagic fever with multiorgan failure [9]. Abnormal liver function tests were documented in some reports on WNV infection [37]. Similarly, mild elevation of liver transaminases was documented in 23.7% of Croatian patients with WNV infection (data of the project CRONEUROABO) [60].

Zika Virus

Zika virus (ZIKV) is a mosquito-borne flavivirus. Phylogenetic analyses have identified two major lineages: Asian and African [61]. ZIKV is widely distributed in tropical and subtropical areas of Asia, Africa, and the Americas. Symptoms associated with ZIKV are generally mild, and majority of the infected patients do not develop any symptoms or the disease presents as febrile rash and conjunctivitis. Most reports showed no liver abnormalities during ZIKV infection [12]. In 2017, a case of ZIKV infection associated with severe liver injury and coagulation disorders was reported in a previously healthy Asian man returning from Cambodia [13]. Experimental studies showed that hepatocyte-derived cell lines are permissive for ZIKV replication and an overt cytopathic effect is produced, consistent with the development of an acute viral hepatitis [62]. Also, pathogenicity studies demonstrated the presence of ZIKV RNA in the liver of infected mice [63]. However, further studies are needed to evaluate the replication and specific mechanisms of hepatocyte injury due to ZIKV infection in humans.

Tick-Borne Encephalitis Virus

Tick-borne encephalitis virus (TBEV) is a tick-borne flavivirus. There are three TBEV subtypes: European, Far East, and Siberian which circulate in wide areas from Europe to Far East. The clinical spectrum of the disease ranges from mild meningitis to severe meningoencephalitis with or without paralysis. The disease caused by the European subtype has milder course and better outcome compared to Siberian and Far Eastern subtypes [64]. Abnormal liver function tests are relatively rare in TBEV infection. A Slovenian study found abnormal liver function tests in 22.2% of patients with TBE during the initial phase of disease [10]. Similarly, a Croatian study conducted in an endemic region for TBEV showed elevated liver enzymes in 22% of patients with TBE. Elevated AST and ALT levels were detected during the first and second phases of the disease in 64% and 36% of patients with TBEV, respectively. The most frequently observed AST/ALT elevated activity was twofold or threefold the usual normal values, and it normalized in 3 weeks to 4 weeks [11].

Adenoviruses

Adenoviruses are common viral respiratory pathogens in childhood; however, in the immunocompromised host, they can cause severe infections involving multiple organs including the liver [38]. In this population, adenovirus hepatitis is a rapidly progressive and highly lethal infection. In two case series, 64% and 66% of patients with adenovirus hepatitis were pediatric [16, 39]. In an Israeli study, younger children were more likely to show elevated enzyme levels [40]. In the majority of reports, serum AST levels consistently significantly exceeded serum ALT levels [16], but some reports have shown an inverse ratio with higher ALT levels [15, 65]. Necrosis seems to be one of the most consistent histologic findings in adenovirus hepatitis which can vary from focal and spotty to massive necrosis [16]. The overall mortality rate is about 62% in the pediatric population and 85% in adults [14, 16]. Adenoviruses are a rare cause of hepatitis in immunocompetent patients as well [66] and have been known to cause fulminant hepatic failure [38].

Parvovirus B19

Infections caused by parvovirus B19 are globally prevalent, with the seroprevalence rate of more than 76% in some countries [67]. Parvovirus B19 is an etiologic agent of erythema infectiosum ("fifth disease"), fever/rash illness of childhood, whereas in adults, the most common manifestation is arthropathy [68]. Liver diseases caused by parvovirus B19 infection are rare and may range from elevation of transaminases to acute hepatitis, fulminant liver failure, and even chronic hepatitis. A broad spectrum of liver disease has been reported in all age groups from neonates to the elderly [41]. Presentation as acute hepatitis or fulminant liver failure has been mostly reported in the pediatric age groups [17]. In adults, hepatitis course is found to be less severe than in children. Cases of chronic hepatitis caused by parvovirus B19 have also been reported. Additionally, the association of parvovirus B19 with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) has been described. A study conducted in Germany showed persistence of parvovirus B19 DNA in patients with chronic HBV and HCV infection, but the virus does not appear to cause any significant worsening of liver functions [69]. Due to infrequent testing and lack of awareness of parvovirus B19–associated hepatitis, these cases may be underreported.

Lymphocytic Choriomeningitis Virus and Lassa Virus

Lymphocytic choriomeningitis virus (LCMV) and Lassa virus (LASV) are zoonotic rodent-borne Old-World arenaviruses. LCMV is distributed worldwide, while LASV is confined to West Africa. Imported LASV infections outside Africa are rare. In New World primates (marmosets, tamarinds), LCMV can cause callitrichid hepatitis with elevated liver enzymes, jaundice, and sometimes hemorrhage. The WE strain of LCMV (LCMV-WE) is known for its hepatotropism and virulence in guinea pigs and primate models [42]. There is no evidence of LCMV-induced hepatitis in humans; however, liver involvement was described in some patients with solid organ transplant–associated LCM presenting with multiorgan failure [70, 71]. In contrast, it is well known that the major and most common lesions of Lassa fever in humans occur in the liver with variable levels of hepatocellular necrosis [42–44]. In addition, postmortem histological studies of patients with Lassa fever and monkeys infected with LASV or LCMV-WE showed that the most important pathological changes are hepatic [42, 44].

Bocavirus

Human bocavirus (HBoV) is a recently described (2005) human pathogen that has been associated with respiratory tract infections [72]. Three additional subtypes were subsequently identified in stool samples, named HBoV2, HBoV3, and HBoV4 [73, 74]. The reported prevalence of HBoV in children with acute respiratory infections has ranged from 2 to 19% [75]. The clinical features of HBoV infection have not yet been fully elucidated. Association of HBoV with hepatitis has been shown in few studies. Hepatitis was documented in two reports in both immunocompromised and immunocompetent children [76, 77]. One report described hereditably immunodeficient child with disseminated HBoV infection with clinical hepatitis without respiratory symptoms. Although no liver biopsy was done, virology results strongly suggested that HBoV was the causative agent [77]. In the other reports, HBoV was detected in an immunocompetent child with clinical hepatitis and respiratory symptoms. The sole detected pathogen was the HBoV, both in the nasopharyngeal aspirate and blood of the infected patient [76]. Moreover, in a Chinese study, HBoV DNA was detected by nested PCR in 2.1% of patients with liver disease [78]. Due to a small number of cases, tropism of HBoV to the hepatic tissue should be studied further.

Pegiviruses

Human pegivirus (HPgV; formerly referred to as GB virus C/GBV-C or hepatitis G virus) was discovered in 1995 [79]. HPgV is a lymphotropic virus, and its virulence determinants, organ tropism, and mechanisms of disease induction are unclear. The prevalence of HPgV viremia in healthy blood donors in developed countries is 1–5%, while up to 20% of blood donors in developing countries have active infection [80, 81]. HPgV is more prevalent in persons with bloodborne or sexually transmitted infections compared to the general population. Additionally, HPgV viremia is reported in up to 40% of HIV-infected individuals [82, 83]. Human pegivirus type 2 (HPgV-2) is a novel pegivirus identified in 2015 [84]. The pathogenicity of HPgV-2 in humans is still unknown. In general, pegiviruses may lack pathogenicity [80]; however, a new pegivirus, Theiler disease-associated virus, was found to have caused an acute hepatitis outbreak in horses [85]. Although several early studies found HPgV RNA in liver biopsies, attempts to find evidence of HPgV replication in the liver were either negative or inconclusive [81]. Some studies have shown that HPgV-2 mainly infects hepatitis C virus–infected subjects but appears not to worsen HCV-related liver damage [86, 87]. HPgV-2 can establish chronic and persistent infection, but the prevalence of chronic HPgV-2 infection is much lower (30–40%) than for HCV (55–85%) [84, 88].

Torque Teno Virus/Torque Teno Mini Virus/Torque Teno Midi Virus

Torque teno virus (TTV) was isolated from a patient with transfusion-transmitted hepatitis in 1997 [89]. Torque teno mini virus (TTMV) and torque teno midi virus (TTMDV), thus named because of their smaller genomes, are variants discovered in 2000 and 2007, respectively [90]. TTV has a high genetic variability, with five main genetic groups (1–5) and at least 39 genotypes identified so far [91–93]. Throughout the literature, TTV has been associated with various liver diseases, acute (cryptogenic) hepatitis, transfusion-associated hepatitis, and chronic hepatitis B and C. However, the data indicate that TTV is common and highly prevalent in the general population worldwide [92, 94, 95]. In a Pakistani study, 89.7%, 90.0%, and 92.5% of HBV patients, HCV patients, and healthy controls, respectively, were positive for TTV infection [92]. In a Chinese study, the TTV prevalence rates were 95%, 98%, and 97.5–100% in healthy infants, healthy adults, and patients with viral hepatitis (HBV/HCV), respectively [94]. High prevalence rates were also detected in a Brazilian study that identified TTV as the independent factor associated with the occurrence of HCC in chronic hepatitis C patients [96]. Studies have shown that the infection rates in infants are comparable to those in adults [94, 97]. However, an age-dependent increase of TTV infection has been noticed; e.g., infants before 1 month of age are negative for TTV DNA, suggesting a very efficient route of transmission in early infancy [94, 97]. TTMV is also distributed across the world among healthy populations. Although TTMDV was found in 40% of patients with chronic hepatitis in Korea, the role of this virus in clinical diseases is still unclear [98]. The high prevalence of TTV infection in the general population and also in patients with viral hepatitis strongly suggests that TTV has a little potential for causing hepatitis. Furthermore, a Canadian study substantiated these data in a transplant population, showing that high TTV viremia in children after liver transplantation (LT) is not associated with hepatitis after LT [99]. However, a recent study showed that plasma TTV DNA levels are associated with immune-related events after liver transplant and that TTV DNA may represent a potential biomarker of the state of immunosuppression during the first months after transplant [100]. Whether TTV co-infection with other hepatic viruses may increase the severity of liver damage is not clear and remains to be determined.

SEN Virus

SEN virus (SENV) was initially isolated from a blood of a HIV-positive person who had developed post-transfusion hepatitis of unknown etiology [101, 102]. It is a non-enveloped, single-stranded circular DNA virus which belongs to the family *Anelloviridae*, along with TTV, TTMV, and TTMDV. SENV is endemic throughout the world with the DNA prevalence rates in healthy persons that range from 1.8 to 22% [103]. SENV transmission occurs through parenteral and non-parenteral routes [104]. There are 9 SENV genotypes (A–I). Genotypes D and H were associated with transfusion-associated non-A-E hepatitis in one study; however, this association did not establish causality and the vast majority of SENV-infected patients did not develop hepatitis at the time of transfusion [105]. Subsequently, SENV was studied in different population groups worldwide. SENV infection is common among patients on hemodialysis, with no evidence that would suggest liver pathogenicity of the virus [106]. Moreover, no evidence was found that SENV caused hepatitis or worsened the course of hepatitis C [107]. SENV infection was frequently found in patients with chronic hepatitis C and had no influence on the severity of HCV-related liver disease or the HCV response to therapy [108]. In addition, SENV does not appear to be related to hepatocellular carcinoma [109]. Other studies showed that SENV is detected at almost the same frequency in patients with and without liver disease and it also does not seem to contribute to the pathogenesis of liver disease [110, 111]. Therefore, given the high prevalence of SENV in healthy persons and the abovementioned findings in patients with liver diseases, it seems that SENV, similar to TTV, has little potential for causing liver damage.

Future Perspectives: Zoonotic Hepatitis Viruses in the "One Health" Concept

During the last decade, highly diverse viruses related to human hepatitis viruses were found in animals other than primates [112]. Zoonotic potential of HEV is well documented in domestic pigs and wild boar as main reservoirs [113]. In addition, the recent identification and characterization of animal strains of HEV from rabbits and camels raise potential public health concerns for zoonotic transmission [114, 115]. Recently, several studies detected homologs of hepatitis C, described as non-primate hepaciviruses (HPHV) in domestic dogs and horses [116–118]. Soon afterwards, highly diverse HCV-related viruses were detected in rodents, bats, and cattle [119–121]. Similarly, several new pegiviruses have been described in horses (equine pegivirus; EPgV) [122]. In addition, in 2016, a so far unknown porcine pegivirus (PPgV) was described and persistent infection in the host, similar to human pegivirus, was reported. PPgV was detected in the liver, suggesting hepatotropism [123]. The presence of hepacivirus and pegivirus species in these animal species light on the possible evolutionary history of HCV and HPgV, in which potential cross-species transmission and zoonotic origins become more plausible [124]. The

discovery of new hepatitis-related animal viruses highlights the possible zoonotic transmission in the context of One Health. However, apart from certain HEV strains, zoonotic potential and hepatotropism of animal hepatitis viruses remain to be determined.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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