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ORIGINAL ARTICLE

Characteristics of patients with hepatitis B virus and hepatitis C virus dual infection in a Western European country: Comparison with monoinfected patients

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Summary The epidemiology of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections is continuously evolving. Updated data on dual HBV and HCV infection are still needed.
Aims: To assess the main characteristics of patients with HBV and HCV dual infection, to compare these with those of patients infected with either HBV or HCV and, among patients with dual infection, to assess fibrosis according to HCV replication.

Abbreviations: Ag, antigen; ALT, alanine aminotransferase; BASL, Belgian Association for the Study of the Liver; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; NA, not available; SDs, standard deviations.

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Methods: Data of 23 patients with dual infection were compared to data from 92 age and sex-matched HBV or HCV monoinfected patients.
Results: Patients with dual infection were more often immigrants from Africa or Asia than HCV or HBV patients (52% vs. 20% and 22%, respectively, $P = 0.01$). Intravenous drug use was the route of transmission in 22% of patients with dual infection, which was less frequent than in HCV patients (41%) but more frequent than in HBV patients (0%). Extensive fibrosis or cirrhosis was as frequent among dual-infected patients as among those with HCV or chronic hepatitis B infection (19% vs. 29% vs. 14%, respectively, $P = 0.4$), even when fibrosis stage was reported considering the duration of infection. In dual-infected patients, the prevalence of extensive fibrosis or cirrhosis was similar in patients with and without detectable HCV RNA (18% vs. 20%).
Conclusions: Patients with HBV and HCV dual infection were more often immigrants from Africa or Asia and had similar fibrosis stages than HCV or HBV monoinfected patients. In patients with dual infection, extensive fibrosis or cirrhosis was not associated with HCV replication.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common causes of liver disease worldwide, leading to chronic hepatitis, cirrhosis and hepatocellular carcinoma. HBV and HCV infect around 360 million and 160 million people, respectively worldwide [1,2]. Since both viruses share several modes of transmission, HBV and HCV dual infection is commonly found among people at high-risk of parenteral infections and in endemic areas. It is estimated that prevalence of dual infection is 2—10% among HCV antibody-positive patients and 3—20% among hepatitis B surface antigen (HBsAg) carriers [3—6]. However, epidemiological data on patients with dual infection are scarce in Europe, and no updated data have been reported during the last decade [6—8]. As the epidemics of HBV and HCV are continuously evolving due to the improvements in health care conditions, continuous expansion of intravenous drug use and immigration to Europe from endemic areas, updated data of patients with HBV and HCV dual infection are needed for defining accurate strategies for case identification [9].

The influence of HBV and HCV dual infection on the severity of liver disease is still debated. In some previous series, dual-infected patients were more likely to develop advanced liver disease compared to those infected with HBV or HCV alone [8,10,11], while other studies showed no difference in terms of liver damage [3,4,7,12]. Furthermore, it is usually admitted that the two viruses inhibit each other, suggesting direct or indirect interference [13,14]. In most cases, HCV is thought to be the main driver of liver damage, although this pattern of HCV dominance is not uniform [3,4,11]. HCV RNA is however not detectable in all dual-infected patients and a recent study failed to identify differences in fibrosis stages according to the presence or absence of detectable HCV RNA [15]. Hence, whether HCV replication aggravates fibrosis among patients with dual infection remains a subject of debate.

In this study, we aimed to assess the main characteristics of patients with HBV and HCV dual infection, and compare these to those of patients with HBV or HCV monoinfection. In patients with dual infection, we also aimed to assess fibrosis stage according to the presence of detectable HCV RNA.

Patients and methods

Study design, patients and data collection

Patients were identified using the HBsAg Carriers Registry. The HBsAg Carriers Registry is a prospective registry conducted by 27 academic and non-academic Belgian centers including HBsAg positive carriers seen at outpatient clinics from the 1st of March 2008 to February 28th 2009. In each center, all consecutive HBsAg positive patients observed during a 1-year period were prospectively enrolled, irrespective of the presence or absence of anti-HCV antibodies. Further details on the HBsAg Carriers Registry have already been published [5].

Among the 1456 HBsAg carriers identified in the HBsAg Carriers Registry, 29 patients had positive anti-HCV and no other viral infection, notably no Delta or HIV infection. Data on all these patients were retrospectively collected, including demographic data, liver biochemistry, viral markers and assessment of hepatic fibrosis stage. Diagnosis of HBV and HCV dual infection was based on the presence of positive serum HBsAg in combination with either positive serum anti-HCV or detectable serum HCV RNA [8,12,15]. Each patient was age and sex-matched to 2 HCV patients with detectable HCV RNA and to 2 HBV patients (1 HBs inactive carrier and 1 patient with chronic hepatitis B) [16]. The status of inactive carriers was defined according to criteria recommended in guidelines: HBsAg-positive and HBeAg-negative patients with HBV DNA levels < 2000 IU/ml and normal ALT values [17,18]. As the definition of dual infection is controversial, in a second step, we performed a subgroup analysis considering as dual-infected patients only those who were HBs Ag positive and who had detectable HCV RNA. The HBV registry was approved by a central ethical committee (UZ Antwerpen, local reference: B30020072691—7/39/212) and by the local ethical committee of each participating center. All patients identified from the HBV registry signed an informed consent.

Serological tests, virological methods

Testing for HBsAg and HCV antibodies was carried out using commercial enzyme immunoassays. In this study,

third-generation assays were used: Ortho HCV 3.0 ELISA, Architect AntiHCV test (Abbott), Elecsys® AntiHCV II (Roche), AxSYM HCV 3.0 (Abbott). These third-generation tests yield very few false-positive results in immunocompetent patients [19,20]. A confirmatory test was not systematically used when HCV RNA was undetectable. HBV DNA and HCV RNA were searched for using sensitive quantitative methods according to the specific habits of each center, including a signal amplification assay based on branched DNA technology and a real-time polymerase chain reaction. The following tests were used for HBV DNA and HCV RNA detection and quantification. Two standardized PCR tests were used for HCV RNA detection and quantification: either Abbott RealTime HCV with a detection and quantification limit of 12 IU/ml, or Roche AmpliPrep/COBAS® TaqMan® HCV with a detection and quantification limit of 15 IU/ml. The signal amplification assay based on branched DNA technology was Bayer Versant HCV RNA 3.0 bDNA with a lower limit of quantification 520 IU/ml. Two standardized tests were used for HBV DNA detection and quantification: either Abbott HBV real-time PCR with a detection and quantification limit of 15 IU/ml, or Roche AmpliPrep/COBAS® TaqMan® HBV with a detection and quantification limit of 20 IU/ml. In treated patients, HBV DNA and HCV RNA were assessed before the start of any antiviral treatment.

Histological examination and fibrosis assessment

When performed, percutaneous or transjugular liver biopsies were assessed by light microscopy. Specimens were graded according to METAVIR score [21] by local pathologists. A central review of liver biopsies was not performed.

In some cases, transient elastography (FibroScan; Echosens, Paris, France) was used to assess the degree of fibrosis. Transient elastography is a rapid, non-invasive and reproducible method for measuring liver stiffness considered as an index of the amount of fibrotic tissue [22]. Values higher than 9.6 kPa for HCV patients and higher than 8.1 kPa for HBV patients were considered as indicative of extensive fibrosis or cirrhosis [23,24].

Statistical analysis

Continuous data were expressed as medians and 95% confidence intervals (95% CI). Qualitative data were described by frequencies and percentages. Variance analysis, the Chi-square test, the two-sided Fisher's exact test, the Mann-Whitney test, the Wilcoxon test and the two-sample Student's t-test were used for qualitative and semi-quantitative comparisons as appropriate. All tests were two-tailed at a 0.05 level. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using NCSS 2007 software (NCSS, Kaysville, UT, USA).

Results

Study population

Among the 29 cases of dual HBV and HCV infection identified in the HBsAg Carriers Registry, detailed data were not available for 6 patients. Thus, a total of 23 patients with dual infection were enrolled in the study. Among them, 13 patients had detectable HCV RNA. The duration of infection was 21 years among patients in whom the date of contamination was known precisely. Sixty-seven patients (60% of the study population) underwent a liver biopsy. In more details, a liver biopsy was performed in 14 dual-infected patients (and in 10 dual-infected patients with detectable HCV RNA), 29 HCV patients, 3 inactive HBV carriers and 21 patients with chronic hepatitis B. In other patients, fibrosis was assessed only by transient elastography. Twelve patients received a treatment: 4 patients received interferon-based therapy for HCV infection and nucleoside/nucleotide analogs treatment for HBV infection, 5 patients received only interferon-based therapy for HCV infection and 3 received only nucleoside/nucleotide analogs treatment for HBV infection. No patient received interferon-based therapy for HBV infection. For comparison, 46 HCV patients and 46 HBV patients matched by age and sex were chosen randomly as controls.

Characteristics of patients with HBV and HCV dual infection compared to those of HBV or HCV patients

The main features of the three groups of patients are presented in Table 1. Patients with dual infection were more often immigrants from Africa or Asia than were monoinfected patients with HCV or HBV (52% vs. 20% vs. 22%, $P = 0.01$). Intravenous drug use was the route of transmission in 22% of patients with dual infection, which was less frequent than in HCV monoinfected patients (41%) but more frequent than in HBV monoinfected patients (0%). The duration of infection was similar in patients with dual infection and HCV patients, but shorter than in patients with chronic hepatitis B. Other demographic characteristics did not differ between the three groups of patients.

Biological, virological and histological data are reported in Table 2. Patients with HBV and HCV dual infection had nearly normal ALT levels, which was similar to HCV patients and lower than patients with chronic hepatitis B ($P < 0.001$). Bilirubin levels, albumin levels and INR were normal in all groups. In patients with dual infection, HCV RNA was detected less frequently and HCV RNA levels were lower than in HCV monoinfected patients, while median HBV DNA levels were similar to HBV inactive carriers and lower than in those with chronic hepatitis B. Assessment of fibrosis was available for 112 patients. In 3 HCV patients, liver fibrosis assessment was made after a previous antiviral treatment, which could have influenced fibrosis. In all other cases, fibrosis was assessed in naïve patients. The prevalence of extensive fibrosis or cirrhosis was similar in patients with dual infection, in patients with HCV infection and in patients with chronic hepatitis B (19% vs. 29% vs. 14%, respectively, $P = 0.4$). When reported considering the duration of infection, patients with dual infection did not have a more severe fibrosis score than HCV or HBV monoinfected patients.

Characteristics of patients with dual infection who had detectable HCV RNA compared to those of HBV or HCV patients

When dual-infected patients were defined as those who were HBs Ag positive and who had detectable HCV RNA, the

Table 1 Demographic characteristics of patients with HBV and HCV dual infection compared to those of HBV or HCV patients.

	Patients with HBV and HCV dual infection ($n=23$)	HCV patients ($n=46$)	HBV patients ($n=46$)		*P*-value
			Chronic inactive HBs carriers ($n=23$)	Patients with chronic HBV infection ($n=23$)	
Age (years)[a]	47 (39—54)	46 (42—51)	49 (39—56)	50 (39—55)	0.95
Gender (*n* of male, %)	16 (70%)	32 (70%)	16 (70%)	16 (70%)	1
Origin (*n*, %)[b]				0.01	0.01
Caucasian	11 (48%)	36 (80%)	15 (65%)	21 (91%)	
African	10 (43%)	8 (18%)	7 (30%)	0 (0%)	
Asia	2 (9%)	1 (2%)	1 (4%)	2 (9%)	
Risk factors for infection (*n*, %)					< 0.001
Intravenous drug use	5 (22%)	19 (41%)	0 (0%)	0 (0%)	
Transfusion	4 (17%)	14 (30%)	1 (4%)	2 (9%)	
Other type of transmission	1 (4%)	8 (17%)	2 (9%)	3 (13%)	
Peri-natal transmission	2 (9%)	0 (0%)	3 (13%)	8 (35%)	
Unknown (*n*, %)	11 (48%)	5 (11%)	17 (74%)	10 (43%)	
Alcohol consumption (*n*, %)[c]					0.06
No alcohol consumption	15 (71%)	27 (60%)	5 (42%)	1 (25%)	
Alcohol consumption < 30 g/day	0 (0%)	8 (18%)	5 (42%)	2 (50%)	
Alcohol consumption > 30 g/day	6 (29%)	10 (22%)	2 (17%)	1 (25%)	
History of diabetes (*n*, %)[d]	4 (19%)	2 (5%)	2 (9%)	1 (4%)	0.2
Smoking (*n*, %)[e]	6 (29%)	23 (53%)	6 (37%)	4 (53%)	0.07
Body mass index (kg/m^2)[a]	24.6 (23.4—27.7)	26.5 (24.5—28.1)	29.3 (26.4—37.4)	30.3 (16.8—54.7)	0.4
Duration of infection (years)[a]	21 (11—32)	25 (22—31)	NA	46 (24—52)	0.008

CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NA; not available; Ag: antigen; ALT: alanine aminotransferase;
CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NA: not available.
[a] Data expressed as median (95% CI).
[b] Data available for 114 patients.
[c] Data available for 82 patients.
[d] Data available for 108 patients.
[e] Data available for 87 patients.

comparison of the main features and of biological, virological and histological data between the 4 groups of patients provided similar results than when dual infection was defined with the presence of anti-HCV antibodies regardless of the presence of HCV RNA (Supplementary Tables 1 and 2). Of note, the prevalence of extensive fibrosis or cirrhosis was similar in dual infected patients, in HCV patients and in HBV patients with chronic hepatitis (18% vs. 29% vs. 14%, respectively, $P=0.4$). Fibrosis reported according to the duration of infection was also similar between groups.

Characteristics of patients with dual infection according to the presence of detectable HCV RNA

Their characteristics according to the presence of detectable HCV RNA are reported in Table 3. When compared to patients without detectable HCV RNA ($n=9$), those with detectable HCV RNA ($n=13$) were more frequently male (100% vs. 54%, $P=0.02$), had less frequently detectable HBV DNA although the difference was not significant (50% vs. 71%, $P=0.4$), and had similar presence of extensive fibrosis or cirrhosis (18% vs. 20%, $P=0.9$). The

Table 2 Biological, virological and histological data of patients with HBV and HCV dual infection compared to those of HBV or HCV patients.

	Patients with HBV and HCV dual infection ($n=23$)	HCV patients ($n=46$)	HBV patients ($n=46$)		*P*-value
			Chronic inactive HBs carriers ($n=23$)	Patients with chronic HBV infection ($n=23$)	
Virological data					
Detectable HBV DNA (n, %)[a]	11 (55%)	—	18 (78%)	23 (100%)	0.002
HBV DNA level (IU/ml)[g]	143 (0—31,000)	—	339 (43—857)	850,000 (177,000—24,716,980)	< 0.001
HBe Ag positive (n, %)	4 (17%)	—	0 (0%)	5 (22%)	0.07
Detectable HCV RNA (n, %)[b]	13 (59%)	46 (100%)	—	—	< 0.001
HCV RNA level (IU/ml)[g]	415,000 (0—1,210,000)	750,000 (374,126—1,450,693)	—	—	0.04
HCV genotype 1 (n, %)[c]	3 (25%)	29 (63%)	—	—	0.06
HCV genotype 2 (n, %)[c]	1 (8%)	3 (6%)	—	—	
HCV genotype 3 (n, %)[c]	4 (33%)	10 (22%)	—	—	
HCV genotype 4 (n, %)[c]	3 (25%)	4 (9%)	—	—	
HCV genotype 5 (n, %)[c]	1 (8%)	0 (0%)	—	—	
Biological data					
ALT (upper limit of normal)	1.25 (0.5—2)	1.4 (1.25—1.8)	0.75 (0.5—0.9)	2.1 (1.3—5.2)	< 0.001
Bilirubin (mg/dL)	0.4 (0.3—0.5)	0.6 (0.5—0.8)	0.6 (0.4—0.6)	0.6 (0.5—0.9)	0.04
Albumine (mg/dL)	4.2 (4.0—4.4)	4.5 (4.2—4.7)	4.6 (4.3—4.8)	4.5 (4.4—4.7)	0.005
INR	1.2 (1.0—1.18)	1 (1—1)	1 (1—1)	1 (1—1)	0.3
Assessment of liver damage[h]					
Liver biopsy performed (n, %)[d]	14 (64%)	29 (66%)	3 (13%)	21 (91%)	< 0.001
Activity score in patients who underwent a liver biopsy[g]	1.5 (0—2)	1 (1—2)	1 (0—1)	2 (1—3)	0.06
Fibrosis assessed by liver biopsy and/or by transient elastography[g]	2 (0—2)	2 (1—2)	1 (0—2)	2 (2—2)	0.2
Extensive fibrosis or cirrhosis (n, %)[e]	3 (19%)	13 (29%)	3 (16%)	3 (14%)	0.4
Fibrosis per year of infection[f, g]	0.07 (0.01—0.13)	0.08 (0.04—0.12)	NA	0.04 (0.02—0.008)	0.5

Ag: antigen; ALT: alanine aminotransferase; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NA: not available.
[a] Data available for 62 patients.
[b] Data available for 68 patients.
[c] Data available for 58 patients.
[d] Data available for 112 patients.
[e] Data available for 101 patients.
[f] Data available for 43 patients.
[g] Data expressed as median (95% CI).
[h] According to the METAVIR scoring system.

Table 3 Characteristics of patients with HBV and HCV dual infection according to the presence of detectable HCV RNA.

	Patients without detectable HCV RNA ($n = 9$)[a]	Patients with detectable HCV RNA ($n = 13$)[a]	*P*-value
Demographic data			
Age (years)[b]	41 (36–59)	51 (25–64)	0.3
Gender (*n* of male, %)	9 (100%)	7 (54%)	0.02
Duration of infection (years)[b]	21 (12–21)	32 (15–43)	0.14
Virological data			
HBe Ag positive (*n*, %)	2 (22%)	2 (15%)	0.7
Detectable HBV DNA (*n*, %)[d]	5 (71%)	6 (50%)	0.4
HBV DNA level (IU/ml)[b]	5493 (0–34,000,000)	84 (0–100,000,000)	0.3
Biological data			
ALT (upper limit of normal)	0.5 (0.5–4)	1.5 (0.5–3)	0.16
Bilirubin (mg/dL)	0.4 (0.3–1.6)	0.5 (0.1–3.2)	0.8
Albumine (mg/dL)	4.3 (2.7–4.5)	4.2 (3.4–4.6)	0.9
INR	1.1 (1.04–1.18)	1.0 (1–1)	0.14
Assessment of liver damage[c]			
Activity score in patients who underwent a liver biopsy	0.5 (0–1)	2 (0–2)	0.2
Fibrosis assessed by liver biopsy and/or by transient elastography	1 (0–3)	2 (0–4)	0.2
Extensive fibrosis or cirrhosis (*n*, %)[e]	1 (20%)	2 (18%)	0.9
Fibrosis per year of infection[b]	0.05 (0–0.09)	0.07 (0.06–0.13)	0.6

Ag: antigen; ALT: alanine aminotransferase; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus.
[a] HCV RNA was not determined in 1 dual-infected patient.
[b] Data expressed as median (range).
[c] According to the METAVIR scoring system.
[d] Data available for 20 patients.
[e] Data available for 16 patients.

median HBV DNA level was numerically lower in patients with detectable HCV RNA than in those without. Other characteristics were similar between the two groups of patients.

Discussion

No data have been reported on HBV and HCV dual infection in Europe during the last decade. As the epidemiology of HBV and HCV is continuously evolving, updated data are important for optimizing strategies for case identification which is essential in patient care. The present study took advantage of a large database of chronic HBsAg carriers that has been conducted in 27 centers in Belgium. As patients were enrolled consecutively over a one-year period, the current study offers a unique opportunity to reassess the epidemiology of HBV and HCV dual infection. Three main conclusions can be drawn.

Firstly, more than half of patients with dual infection were immigrants from Africa or Asia. Although immigration is currently considered the main source of new cases of HBV and HCV infection in Europe [25,26], this proportion was higher than in those with HBV or HCV monoinfection. Of note, this finding was not observed in the last European studies, which underlines the need for updated data focusing on the changes in epidemics of HBV and HCV infections [7,8,15]. During the past decade, immigration from areas of high prevalence for viral hepatitis to developed countries has greatly increased. For example, 231 million individuals migrated to another country in 2013 compared to 154 million individuals in 1990 worldwide [27]. In contrast, intravenous drug use was less frequently a route of transmission for infection in patients with dual infection than in those with HCV infection alone, even though the mode of transmission was not known in a significant proportion of patients. Hence, in addition to individuals at high risk for parenteral infections, strategies for identification of dual infected patients should focus on people coming from endemic areas [26].

Secondly, the severity of liver disease was not different in patients with HBV and HCV dual infection compared to those with chronic hepatitis B infection or HCV infection alone, even when fibrosis was reported considering the duration of infection, and even when we used the more restrictive definition of dual infection (presence of HBs Ag with detectable HCV RNA). We chose to compare dual-infected patients to well characterized controls. For HBV controls, patients were classified as inactive carriers or as patients with chronic hepatitis, as recommended [16]. Even if our results are driven by the choice of the group to which dual-infected patients were compared, the prevalence of extensive fibrosis or cirrhosis was not higher in dual-infected patients regardless the comparison group. Of note, in most of dual-infected patients in whom the route of contamination was known,

HBV and HCV infections were supposed to have occurred at the same time, which is not surprising when considering that HBV and HCV usually share similar routes of transmission. However, previous studies have indicated that, in rare cases, HCV infection may have occurred in patients already infected with HBV [28,29]. Whether HBV and HCV infection had occurred simultaneously or subsequently may be a confounding factor influencing fibrosis progression. Although the limited number of patients did not allow drawing definite conclusions and despite that some dual-infected patients had undetectable HCV RNA, this finding contrasts with the accepted concept that HBV and HCV dual infection leads to a more severe liver disease [8,10,11]. Several studies already failed to identify dual HBV and HCV infection as a risk factor for advanced fibrosis or cirrhosis compared to patients with HBV or HCV infection alone [3,7,12]. The largest European study to date observed a higher prevalence of cirrhosis in patients with dual infection compared to those with chronic HBV infection alone [7]. However, this association was lost after adjustment for age, indicating that age was the main determinant of the outcome. In our study, this confounding factor was avoided by including age and sex-matched controls.

Thirdly, patients with dual infection and detectable HCV RNA had a similar prevalence of extensive fibrosis or cirrhosis to those without detectable HCV RNA. In this study, a significant proportion of patients with dual HBV and HCV infection (41%) were HCV RNA undetectable, which is similar to what has been reported by others [7,12,15]. In the same line, our study did not demonstrate that the presence of detectable HBV DNA among dual-infected patients was associated with a higher incidence of extensive fibrosis or cirrhosis. These results contrast with those of a recent study in which dual-infected patients with detectable HBV DNA had a higher risk of cirrhosis than HCV patients [35]. We acknowledge that our study was not powered to assess the risk of cirrhosis among dual-infected patients according to viral replication. Nevertheless, the relevance of viral replicative status on clinical outcome of patients with dual infection is still unclear [7,30]. While experimental models indicated that HBV and HCV are able to replicate together in the same cell [14,31], clinical data suggest that the two viruses often alternate dominance [15], a situation that differs from the one of HBV and HDV dual infection in which HDV often acts as a dominant virus over HBV [32,33]. Regarding outcomes, whether replication of both viruses increases fibrosis progression is still debated. Previous studies that have assessed this issue failed to identify dual HBV and HCV replication as a factor associated with more frequent advanced liver fibrosis [15,34]. This is at least in part because concomitant replication of HBV and HCV is not commonly seen. Furthermore, the presence of HCV RNA in serum can vary over time. Thus, patients with HBV and HCV dual infection are a heterogeneous population showing a large spectrum of virological profiles with variable outcomes, which explains why HCV replication cannot be considered as the main driver of the severity of the liver disease in all patients.

This work has several limitations. The number of patients with dual infection was limited and some patients that were identified in the HBsAg Carriers Registry could not be studied. Due to the cross-sectional design of the study, data on long-term evolution were not available. As HBV and HCV replication can vary over time, evaluation of a single time point may not fully reflect the replication pattern of the two viruses [15,36]. Finally, tests used for assessing viral replication differed between centers both for HBV and HCV, and the lower limit of detection was not homogeneous. However, at the time the HBsAg Carriers Registry was conducted, Belgian centers already used sensitive tests for assessing HBV and HCV replication.

In conclusion, patients with dual HBV and HCV infection frequently originate from Africa or Asia. In this cross-sectional study, the fibrosis stage was similar among patients with dual infection and among patients with HBV or HCV monoinfection. Extensive fibrosis or cirrhosis was not associated with HCV replication among patients with dual infection.

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Authors' contributions

Astrid Marot: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Aïmen Belaid: acquisition of data; critical revision of the manuscript for important intellectual content.

Hans Orlent: acquisition of data; critical revision of the manuscript for important intellectual content.

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François D'Heygere: acquisition of data; critical revision of the manuscript for important intellectual content.

Christophe Moreno: acquisition of data; critical revision of the manuscript for important intellectual content.

Christopher Doerig: critical revision of the manuscript for important intellectual content.

Jean Henrion: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

Pierre Deltenre: study concept and design; acquisition of data; statistical analysis; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinre.2017.05.003.

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