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doi:10.3748/wjg.15.996

World J Gastroenterol 2009 February 28; 15(8): 996-1003
World Journal of Gastroenterology ISSN 1007-9327
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BRIEF ARTICLES

Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis

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Received: October 19, 2008 Revised: February 1, 2009
Accepted: February 8, 2009
Published online: February 28, 2009

Abstract

AIM: To analyze the influence of human immunodeficiency virus (HIV) infection on the course of hepatitis C virus (HCV) infection.

METHODS: We performed a meta-analysis to quantify the effect of HIV co-infection on progressive liver disease in patients with HCV infection. Published studies in the English or Chinese-language medical literature involving cohorts of HIV-negative and -positive patients coinfected with HCV were obtained by searching the PUBMED, EMBASE and CBM. Data were extracted independently from relevant studies by 2 investigators and used in a fixed-effect meta analysis to determine the difference in the course of HCV infection in the 2 groups.

RESULTS: Twenty-nine trails involving 16750 patients were identified including the outcome of histological fibrosis or cirrhosis or de-compensated liver disease or hepatocellular carcinoma or death. These studies yielded a combined adjusted odds ratio (OR) of 3.40 [95% confidence interval (CI) = 2.45 and 4.73]. Of note, studies that examined histological fibrosis/cirrhosis, decompensated liver disease, hepatocellular carcinoma or death had a pooled OR of 1.47 (95% CI = 1.27 and 1.70), 5.45 (95% CI = 2.54 and 11.71), 0.76 (95% CI = 0.50 and 1.14), and 3.60 (95% CI = 3.12 and 4.15), respectively.

CONCLUSION: Without highly active antiretroviral therapies (HAART), HIV accelerates HCV disease progression, including death, histological fibrosis/cirrhosis and decompensated liver disease. However, the rate of hepatocellular carcinoma is similar in persons who had HCV infection and were positive for HIV or negative for HIV.

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Key words: Human immunodeficiency virus; Hepatitis C virus; Coinfection; Disease progression; Meta-analysis

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Deng LP, Gui XE, Zhang YX, Gao SC, Yang RR. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis. *World J Gastroenterol* 2009; 15(8): 996-1003 Available from: URL: http://www.wjgnet.com/1007-9327/15/996.asp DOI: http://dx.doi.org/10.3748/wjg.15.996

INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem, with an estimated global prevalence of 3% occurring in about 170 million infected persons worldwide. The natural history of HCV infection remains controversial because there is a considerable variability in the published estimates of the time span over which cirrhosis develops, as well as the proportion and characteristics of persons in whom it occurs. In common, the natural history of HCV infection remains including acute hepatitis, chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma, decompensated liver disease and death. Approximately 75%-85% of infected patients do not clear the virus for 6 mo, and chronic hepatitis develops. An estimated 5%-20% of HCV-infected patients have or will develop cirrhosis, and 1%-4% of them will annually develop hepatocellular carcinoma. The disease progress of HCV infection may be affected by many factors, including the age of infection, gender, ethnicity, duration of infection, alcohol consumption, mode of acquisition, and immunosuppression[1].

Coinfection with human immunodeficiency virus (HIV) and HCV, a major public health problem,

frequently shares the blood, sexual, and mother-to-child routes of transmission[2-4]. It is estimated that 4-5 million patients are coinfected with HIV and HCV in the world[5]. The prevalence of HIV-HCV coinfection is even up to 90% in persons injecting drugs[6].

Before an introduction of highly active antiretroviral therapies (HAART), the impact of HCV on the course of HIV infection is overshadowed by extrahepatic cause of death, related to immunodeficiency factors, namely opportunistic infection, lymphomas or wasting syndrome. The development of HAART results in a significant decrease in morbidity and mortality among HIV-infected patients. HCV is the leading non-AIDS cause of death in coinfected persons[7-9]. There is convincing evidence that coinfection with HIV worsens the prognosis of HCV-related liver disease. It was reported that persons coinfected with HIV and HCV would develop cirrhosis, and the incidence of end-stage liver disease is higher in HCV-infected individuals[10,11], especially in individuals with CD4 < 200 cells/μL and alcohol consumption[12]. Graham performed a meta-analysis of eight studies in 2001 to examine the risk of cirrhosis and ESLD in individuals coinfected with HIV and HCV and infected with only HCV, and found that the risk of progressing to cirrhosis and liver failure in individuals coinfected with HIV and HCV is two-fold and six-fold higher, respectively, than in those infected with only HCV[13]. However, this study did not compare the end-point event of death between the two groups. Since then, a large number of cohort studies showing the effect of HIV on liver disease progression have been published. Based on the above data, we conducted a meta-analysis of published studies to investigate the impact of HIV coinfection on the course of HCV, decompensated liver disease, cirrhosis, hepatocellular carcinoma and death.

The aim of this analysis was to summarize the main characteristics of the included studies in order to provide a point estimate of the effect of HIV-HCV coinfection on progressive liver disease compared with HCV infection, to examine the potential heterogeneity, and to identify the potential confounding variables in these studies.

MATERIALS AND METHODS

Literature search

Using variations on the terms of human immunodeficiency virus, AIDS, acquired immunodeficiency syndrome, hepatitis C, cohort study, death, end-stage liver disease, hepatocellular carcinoma, hepatic cirrhosis, and hepatic fibrosis, we conducted a search of the available studies published in English and Chinese from PUBMED, EMBASE and CBM from 1992 when HCV EIA became available to August 30, 2008 to show how concurrent HIV infection changes the course of hepatitis C infection. Combined key words were used to maximize the search results. The bibliographies of selected articles and reviews were also searched for pertinent studies.

Inclusion and exclusion criteria

All identified articles were screened, and we excluded articles that were determined to be irrelevant on the basis of a review of the title and/or abstract. Full texts of all remaining articles were retrieved and reviewed.

Only full-length and peer-reviewed original journal articles were included. Articles that did not provide the number of patients infected with HCV and HIV and clinical outcomes of liver disease were excluded. The remaining articles were independently examined in detail by at least 2 of the observers for the number of patients with HIV-HCV coinfection compared to those with only HCV infection. HCV infection was defined by a positive result of a second or third generation of HCV ELISA and confirmed by recombinant immunoblot assay or PCR. HIV infection was defined by a positive result of HIV ELISA and confirmed by Western blot assay. Patients selected for study did not exclude living patients to avoid bias against non-terminal severe liver disease. Outcomes included histopathological diagnosis of cirrhosis based on the criteria defined by Knodell *et al*[14] or clinically defined decompensated liver disease defined unambiguously as the presence of ⩾ 2 of the following conditions: bleeding esophageal varices, ascites, hepatic encephalopathy, or persistent conjugated hyperbilirubinemia not attributable to medications or hepatocellular carcinoma confirmed by ultrasonic or histopathological diagnosis, or mortality.

Data extraction

Quantitative data on the number of cohort subjects with HCV infection or HCV-HIV coinfection were extracted, and the number of patients in each infection group with the outcome of clinical decompensated liver disease or histological cirrhosis, hepatocellular carcinoma, and death was calculated. Contingency tables were created, and results were converted to odds ratio (OR). When risk estimates were presented, we used those adjusted for the greatest number of potential confounders.

Two independent reviewers abstracted each article separately. Where discrepancies arose, a third investigator arbitrated. When a report ⩾ 1 appeared to describe the same cohort of patients (which was established based on the cohort location and authors involved), we selected the most recent or the most complete study.

Statistical analysis

Analyses were conducted with Review manager (version 4.2, Cochrane Collaboration, Oxford, UK). We assessed the heterogeneity for each pooled estimate with Cochran's Q test. We used a fixed-effect model because of the anticipated variability among trails regarding the different outcomes. The overall mean difference was estimated. The significance was measured at $P < 0.05$. Significant heterogeneity was measured at $P < 0.10$. In the event of significant heterogeneity, results were further analyzed with respect to the outcomes of trails, such as histopathological diagnosis of cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death. Finally, we conducted sensitivity analyses

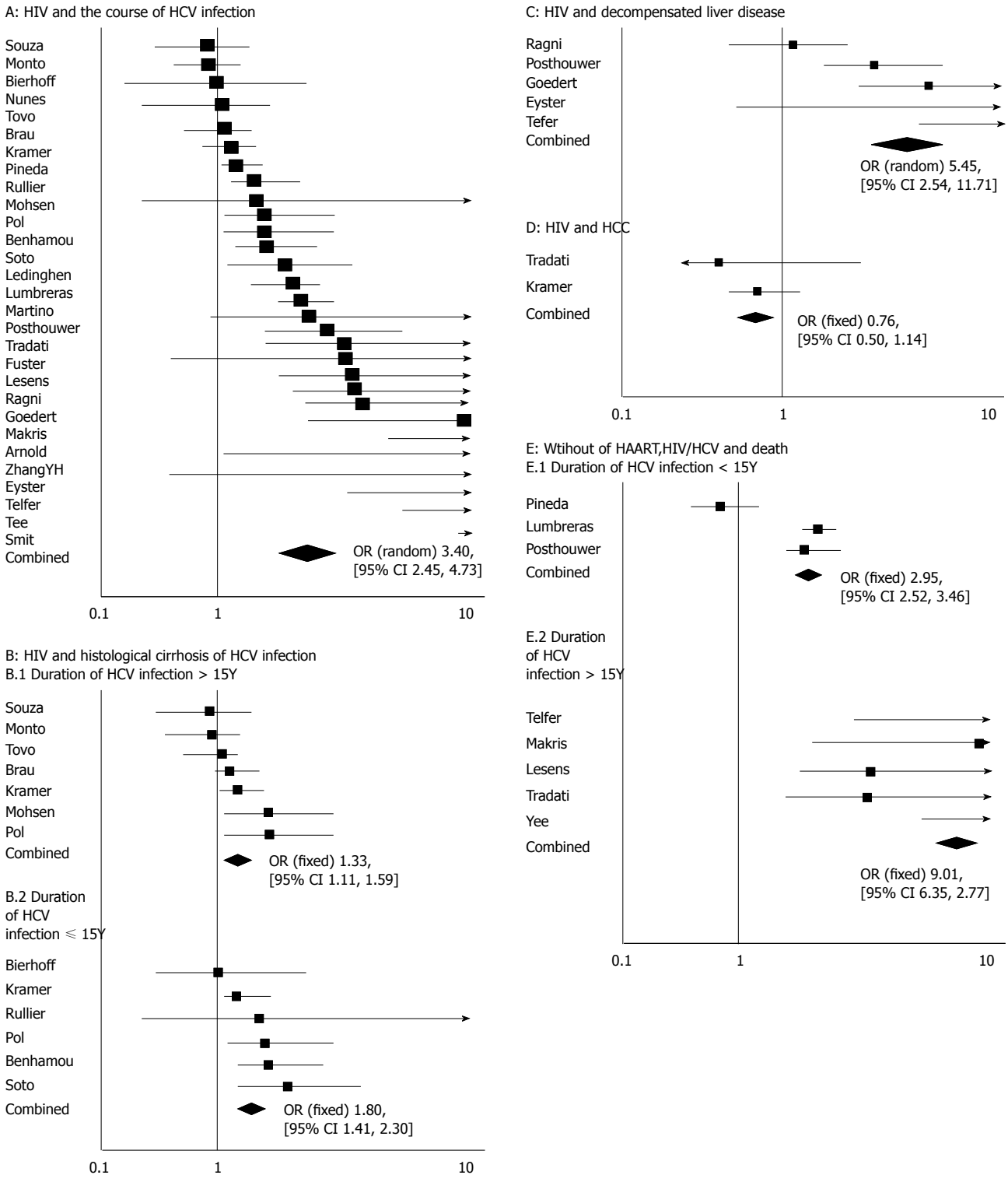

Figure 1 Impact of HIV infection on the course (A), cirrhosis (B), de-compensated liver disease (C), liver cancer (D), and death (E) in HCV-infected patients.

omitting each study in turn to determine whether the results were influenced excessively by a single study.

RESULTS

Included studies

After searching the PUBMED, EMBASE and CBM, a total of 422 studies were identified and screened for retrieval. Two hundred and ninety-seven case reports, case-control studies, or review articles were excluded. One hundred and twenty-five studies were collected for further review. Of these 125 studies, 96 were excluded due to lack of information on the progression of hepatitis C or lack of HCV infection control group. The remaining 29 studies[9,15-42] were included in the analysis (Figure 1A).

Study quality

The general characteristics of these studies and their

Table 1 Characteristics of these studies and their participating subjects

Reference country	Years (data collected)	Study design	Characteristics of patients	Total Patients infected with HIV-/HIV+	Duration of HCV infection HIV+/HIV- (yr)	Outcome	Covariates
USA[15]	1982-1991	Prospective cohort	Hemophilia; mean age 23 yr (2-69), 93% males, 97% whites	58/91	10-25	Liver failure	Liver function, CD4 count, excluding positive HBsAg
UK[16]	1979-1993	Retrospective cohort	Hemophilia, mean age 34 yr	109/74	15	Death, DLD	Age, type of hemophilia, CD4, 2%HBsAg+
UK[17]	1968-1995	Prospective cohort	Hemophilia, mean age 38.3 yr, 92% males, mean age of HCV infection 21 yr, follow-up time 28 yr	102/36	UK	Death	type of hemophilia, 2%HBsAg+, Pre-HAART
Italy[18]	1989-1994	Multicentre cohort	Voluntary liver biopsy patients; HIV-HCV coinfection, mean age 28 yr, 77% males, 97%IDU. HCV-infection: mean age 37 yr, 62% males, main routes of IDU and transfusion	431/116	11.3/7.6	Histological cirrhosis	Duration of HCV infection, HCV-VL, CD4, excluding alcohol, other hepatitis virus infection
Germany[19]	1989-1995	Retrospective	Voluntary liver biopsy patients; HIV-HCV coinfection, mean age 34 yr, 95% males. HCV-infection, : mean age 42 yr, 70% males	33/22	> 10	Histological fibrosis/ cirrhosis	Age, sex, CD4, 2 cases of HBsAg+
Italy[20]	1992-	Prospective Multicentre	Hemophilia, 98% males	243/141	> 20	HCC, cirrhosis, death	Age, type of hemophilia,
France[21]	UK	Retrospective	IDU, mean age 33 yr, 75% males, 35%Etoh	150/60	11.8/12.3	Histological cirrhosis	duration of HCV, 7.5%HBsAg+ EtOH
Canada[22]	1982-1998	Prospective, cohort	Hemolphilia, mean age 22.2/19.7 yr	53/81	17	Death	Type of hemophilia,
France[12]	1995-1998	Retrospective	Voluntary liver biopsy patients, 90%IDU, mean age 35.5 yr, 72% males	122/122	13	Histological fibrosis/ cirrhosis	pre-HAART era, 1 HBsAg+ Sex, Etoh, age of HCV infection, CD4, excluding HBsAg+
UK[23]	1985-1999	Prospective,	Hemophilia, mean age 17 yr	185/125	17	Death	HCV genotype, age of HCV infection, Etoh, 6 cases of HBsAg+
France[24]	1980-1995	Retrospective	IDU, mean age 31 yr, 73% males, HIV+ group: 62%IFN treatment. HIV- group: 77% IFN treatment	80/80	10.2/10.6	Cirrhosis, death	Alcohol, HCV genotype
USA[25]	1978-1999	Prospective	Hemaphilia, 96.2% whites	72/85	UK	DLD, death	HbsAg, alcohol
Greece[26]	1981-1987	Prospective	Hemophilia, 90% males, most whites, mean age of HIV+ 21 yr, mean age of HIV-18yr	624/1194	UK	DLD	Age, alcohol consume, CD4 count, duration of HCV infection, 7% HBsAg+
UK[27]	1994-2002	Retrospective	Voluntary liver biopsy patients, mean age 38.8 yr, 73% males, 77%IDU	153/55	23/21	Histological fibrosis/ cirrhosis	Sex, age of HCV infection, Etoh, HAART, excluding HBV
Spain[28]	1998-2001	Cross-section	Voluntary liver biopsy patients, mean age 40 yr, 75% males, genotype 1, IDU 88% of positive HIV, 88%HIV with ARV treatment	75/75	UK	Histological fibrosis/ cirrhosis	Sex, age of HCV infection, HAART, HCV-VL, excluding alcohol, HBsAg
France[29]	2000.4-2000.12	Prospective	Most of IDU, mean age 38 yr, most of genotype 3 or 4, 67% males, 11% with alcohol consume	33/33	15/14	Histological fibrosis/ cirrhosis	HCV genotype, HCV-VL, CD4, HIV-VL, excluding alcohol, HBsAg
China[30]	2001-2003	Retrospective	CHC of inpatients, all blood transfusion. HIV+ group, : mean age 38 yr, 50% males. HIV-group 39yr, 39% males, pre-HAART era	33/140	< 15	Clinical cirrhosis	CD4 count, excluding alcohol, HBsAg
USA[31]	1997-2004	UK	CHC, main genotype 1. IDU 76%. HIV+group: mean age 47 yr, 92% males, 15% alcohol consume. HIV-group: mean age 49 yr, 87% males, 31% alcohol consume	372/92	24/22	Histological fibrosis/ cirrhosis	HCV genotype, HCVVL, BMI, HIV-VL, CD4 count

USA[32]	UK	Prospective	Voluntary liver biopsy patients, main genotype 1, all IDU. HIV+ group: mean age 47 yr, 77% males. HIV-group: mean age 47 yr, 60% males, 83% with HAART	57/40	UK	Histological fibrosis/ cirrhosis	HCV-VL, HCV genotype, CD4, HIV-VL
USA[33]	1991-2000	Retrospective	CHC with inpatients, mean age 45 yr, 97% males, 58% without HAART	26641/4761	UK	HC, HCC	HAART
Canada[34]	1982-2003	Cohort	Hemophilia, 98% pre-HAART era	712/444	UK	Death	Type of hemophilia
Spain[35]	1997-2002	Multicentre Retrospective	Patients with decompensated HCV-related cirrhosis, HIV-infected: mean age 38 yr, 86% males, 86% IDU, HCV genotype1 63%, HbsAg 24%. HIV-uninfected:mean age 66 yr, 58% males, HCV genotype1, 83% other sources of HCV infection. 91% HIV-infected patients with HAART	1037/180	26/15	Death	Age, HCV genotype, HCV-VL, excluding HBsAg
Spain[36]	1990-2002	Prospective	IDU, 77% males, follow-up time 8.6 yr	1418/1465	9.6/13.5	Death	Age, sex, HAART, HAART, 4.6% HbsAg+
UK[37]	1961-2005	Multicentre	Hemophilia, mean age 43 yr, 94% males, HCV genotype1 53%	497/190	27	DLD	Age, alcohol consume, HCV genotype,HAART, 2.8%HBsAg+
Zambia[38]	2000-2004	Retrospective	HIV-infected: mean age 38 yr, 76% males, 50% IDU. HIV-unifected: mean age 48 yr, 51% males, 31% blood transfusion. 91% HIV patients with HAART, time of HAART 3.6 yr	247/162	19.8/15	Histological fibrosis/ cirrhosis	Age, sex, alcohol consume, HCV-VL, excluding HbsAg+
USA[39]	1999-2002	Retrospective	HIV+ :mean age 45 yr, 80% males, 72% IDU. HIV-: mean age 48 yr, 79% males, 58% IDU. 79% genotype 1. 95% HIV patients with HAART. time of HAART 3.6 yr	382/274	25/23	Histological fibrosis/ cirrhosis	Age, alcohol consume, HCV genotype, HCV-VL, CD4, HIV-VL, excluding HBsAg
Dutch[40]	1985-2006	Prospective	IDU, mean age 30 yr, 64% males, follow-up time 9 yr (5-14)	565/256	8/10	Death	HAART, CD4
Zambia[41]	2003-2004	Retrospective	HIV+: mean age 40 yr, 79% males, 79% IDU. HIV-: mean age 46 yr, 45% males, 25% IDU	65/53	18.7/20.6	Histological fibrosis/ cirrhosis	Liver function, HCV-VL, HCV genotype, CD4, excluding HbsAg, patients with DLD
France[42]	2004-2006	Retrospective	HIV+ mean age 43 yr, 67% males, 83% IDU HIV-: mean age 52 yr, 38% males, 45% blood transfusion; 88% HIV patients with HAART	656/287	23.5/22.1	Fibroscan of fibrosis/ cirrhosis	Age, sex, BMI, HCV-subtype, HCV-VL, HIV-VL, CD4 count excluding HbsAg+, alcohol

DLD: Decompensated liver disease; HCC: Hepatocellular carcinoma; IDU: Injection drug user; HAART: Highly active antiretroviral therapies; Etoh: Ethyl alcohol.

participating subjects are shown in Table 1. The number of patients participating in the studies ranged 55-2883. Their mean age was 21-50 years. Most patients were men. Of the 29 cohort studies, 13 were retrospective in design, 11 were prospective in design, and 1 was a cross-study in design, and 4 did not show the type of design. We evaluated data of 16750 HCV-positive patients. Of them, 6242 were positive for HIV and 10508 were negative for HIV. Fourteen studies assessed the histological cirrhosis[9,18,19,21,27-32,38,39,41,42], 7 studies assessed the death[17,22,23,34-36,40], 3 studies assessed the decompensated liver disease[15,26,37], 2 studies assessed the outcome of decompensated liver disease and death[16-25], 1 study assessed the outcome of histological cirrhosis, hepatocellular carcinoma and death[20], 1 study assessed the outcome of histological cirrhosis and death[24], and 1 study assessed the outcome of hepatocellular carcinoma and death[33], respectively. Most studies did not provide a racial distribution. There was a similar variability in HCV viral load.

Studies in immunocompetent persons showed that the progression of chronic HCV infection is affected by many external and host factors, including duration of HCV infection, alcohol consumption, coinfection with other hepatitis viruses, *etc*. Other studies assessed the duration of hepatitis C except for 6 studies[25,26,28,32-34]. In

these studies, HCV infection was typically assumed due to the exposure to clotting factor, blood transfusion, or initiation of injecting drugs. The mean duration of HCV infection ranged 10-28 years. In our analysis, 3 studies excluded patients who consumed alcohol excessively, 15 studies attempted to assess the significance of alcohol use by quantifying grams of alcohol consume per day, the other studies did not show alcohol consume of patients. Because of the various methods to describe alcohol consumption in these studies, this important factor could not be incorporated into further analyses. Twelve studies excluded patients with detectable hepatitis B surface antigen from their cohort, 4 studies did not describe the state of hepatitis B surface antigen in their cohort, the other 12 studies reported the number of patients with positive HBV surface antigen (Table 1).

Meta-analysis

Inclusion of all end points in studies: The combined unadjusted OR for the 29 studies was 3.40 (95% CI = 2.45 and 4.73) by the random effect model (Figure 1A and B). The test for heterogeneity was significant ($P < 0.001$). Since some factors led to the significant heterogeneity, including different outcomes of our analysis, duration of HCV infection, we also performed subgroup analyses determined a priori.

Analysis of the end points of histological cirrhosis and liver cancer: Seventeen studies assessed liver fibrosis or cirrhosis in patients with HIV-HCV coinfection and HCV infection. The outcome of cirrhosis in in studies was confirmed by histological diagnosis. All studies addressed the effect of duration of HCV infection on progression to severe liver disease. Since the test for heterogeneity had no statistical significance ($P = 0.15$), the fixed effect model was used for subsequent analyses. Thirteen studies examining the end point of histological cirrhosis had a pooled OR of 1.47 (95% CI = 1.27 and 1.70). Cirrhosis was stratified by duration of HCV infection in years. The combined OR for duration of HCV infection within 15 years was 1.80 (95% CI = 1.41 and 2.30) in 6 studies, whereas that for duration of HCV infection exceeding15 years was 1.33 (95% CI = 1.11 and 1.59) in 7 studies (Figure 1B). Five studies examined the end point of decompensated liver disease (DLD). The test for heterogeneity was significant ($P = 0.008$). The random effect model was used for subsequent analyses. The pooled OR for DLD was 5.45 (95% CI = 2.54 and 11.71, Figure 1C). Only 2 studies assessed the end point of hepatocellular carcinoma. The pooled OR for liver cancer was 0.76 (95% CI = 0.50 and 1.14, Figure 1D).

Analysis of end point of death: Eight studies assessed the end point of death in the two groups before HAART. The combined OR for the 8 studies was 3.60 (95% CI = 3.12 and 4.15) using the fixed effect model. Death was stratified by duration of HCV infection in years. The combined OR for duration of HCV infection within 15 years was 2.95 (95% CI = 2.52 and 3.46), whereas that for duration of HCV infection exceeding 15 years was 9.01(95% CI = 6.35 and12.77, Figure 1F).

DISCUSSION

Our meta-analysis quantitatively assessed the influence of HIV infection on the course of HCV infection. The overall OR for histological cirrhosis or decompensated liver disease or liver cancer or death was 3.40 (95% CI = 2.45 and 4.73) by the random effect model. However, these studies had a significant heterogeneity. Some factors could explain the heterogeneity, including different outcomes in these studies, methodological differences in study design, different number of patients in cohort, bias in selection of patients for biopsies, effect of duration of HCV infection on progression to severe liver disease, and publication bias.

We also performed subgroup analyses to determine the priority according to the different outcomes and duration of HCV infection. Striking differences were found in studies examining different end points of histological cirrhosis, decompensated liver disease, hepatocellular carcinoma or death. The combined adjusted OR for histological cirrhosis, decompensated liver disease, hepatocellular carcinoma and death was 1.47 (95% CI = 1.27 and 1.70), 5.45 (95% CI = 2.54 and 11.71), 0.76 (95% CI = 0.50 and 1.14), and 3.60 (95% CI = 3.12 and 4.15), respectively. There was a smaller difference between HIV-HCV coinfected and HCV-infected patients with regard to the development of cirrhosis or liver cancer, but there was a substantial increased risk of developing decompensated liver disease or death.

In the pre-HAART era, many patients coinfected with HIV and HCV died of opportunistic infection, lymphoma or wasting syndrome due to severe immunodeficiency, which is the main risk factor for death of HIV-HCV coinfection patients. The declined HIV-related mortality after widespread use of HAART parallels the emergence of HCV-related liver disease as an important cause of mortality in coinfected patients. Studies indicate that HAART has a protective effect on fibrosis progression in patients with HIV-HCV coinfection. On the other hand, HAART may enhance liver damage in some HIV-HCV coinfected individuals through drug-related hepatotoxicity. Only 6 studies[28,32,35,38,39,42] in our analysis introduced the state of HAART in patients with HIV-HCV co-infection. The proportion of patients who were receiving HAART in cohort ranged 83%-95%. However, we could not acquire the primary data comparing progression of HCV infection in pre-HAART and HAART era, and the other studies were performed before the widespread use of HAART. We, therefore, did not examine the impact of HAART on the progression of HCV infection. This is an important limitation in our study and its impact on the progression of HCV-induced liver disease needs to be explored.

Other factors may have influenced the level of liver damage in HIV-HCV coinfected patients. Important fields for further study include the effects of HAART on HCV-related liver disease progression, duration of

HCV infection, and alcohol consumption.

The results of our study suggest that HIV infection can significantly change the natural history of HCV infection, especially in the development of death or decompensated liver disease. Because most cohorts in our analysis were composed of patients with hemophilia or injection drugs, and most patients studied were males, caution should be taken in generalizing the results of this meta-analysis of women and racial or ethnic populations not represented in these studies. All these factors may potentially impact the natural history of HCV infection.

COMMENTS

Background

Hepatitis C virus (HCV) infection is a major public health problem. Coinfecion with human immunodeficiency virus (HIV) and HCV frequently shares blood, sexual, mother-to-child routes of transmission. It is estimated that 4-5 million patients were coinfected with HIV and HCV in the world. HCV is the leading non-AIDS cause of death. A large number of cohort studies have examined the different impacts of HIV on HCV infection in terms of clinically unambiguous end points of decompensated liver disease and biopsy-proven cirrhosis.

Research frontiers

Interaction of HIV and HCV is a hot spot. HIV infection can change the natural history of chronic hepatitis C with an unusually rapid progression to cirrhosis. HIV-related immunodeficiency may be a determinant factor for higher hepatitis C viremia levels and more severe liver damage.

Innovations and breakthroughs

This study analyzed the impact of human immunodeficiency virus infection on the course of HCV infection, and compared the clinically unambiguous end points of decompensated liver disease, cirrhosis, hepatocellular carcinoma and death.

Applications

Meta-analysis suggests that HIV accelerates HCV disease progression, death, histological fibrosis/ cirrhosis and decompensated liver disease. However, the rate of hepatocellular carcinoma is similar in patients infected with HCV who are positive or negative for HIV. This has important implications for the timely diagnosis and treatment of patients coinfected with HCV and HIV.

Peer review

This manuscript is reasonably well written and contains interesting information.

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