ORIGINAL ARTICLE

Impact of common risk factors of fibrosis progression in chronic hepatitis C

S Rüeger,[1,2,3] P-Y Bochud,[4] J-F Dufour,[5] B Müllhaupt,[6] D Semela,[7] M H Heim,[8] D Moradpour,[9] A Cerny,[10] R Malinverni,[11] D R Booth,[12] V Suppiah,[12,13] J George,[13] L Argiro,[14] P Halfon,[15] M Bourlière,[16] A H Talal,[17] I M Jacobson,[17] E Patin,[18,19] B Nalpas,[19,20] T Poynard,[21] S Pol,[19,20] L Abel,[18,19,22] Z Kutalik,[2,3] F Negro[23,24]

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For numbered affiliations see end of article.

Correspondence to
Professor Francesco Negro, Divisions of Clinical Pathology and of Gastroenterology and Hepatology, Geneva University Hospital, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva 4, Switzerland;
Francesco.Negro@hcuge.ch

SR, P-YB, ZK and FN contributed equally.

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ABSTRACT

Objective The natural course of chronic hepatitis C varies widely. To improve the profiling of patients at risk of developing advanced liver disease, we assessed the relative contribution of factors for liver fibrosis progression in hepatitis C.

Design We analysed 1461 patients with chronic hepatitis C with an estimated date of infection and at least one liver biopsy. Risk factors for accelerated fibrosis progression rate (FPR), defined as ≥0.13 Metavir fibrosis units per year, were identified by logistic regression. Examined factors included age at infection, sex, route of infection, HCV genotype, body mass index (BMI), significant alcohol drinking (≥20 g/day for ≥5 years), HIV coinfection and diabetes. In a subgroup of 575 patients, we assessed the impact of single nucleotide polymorphisms previously associated with fibrosis progression in genome-wide association studies. Results were expressed as attributable fraction (AF) of risk for accelerated FPR.

Results Age at infection (AF 28.7%), sex (AF 8.2%), route of infection (AF 16.5%) and HCV genotype (AF 7.9%) contributed to accelerated FPR in the Swiss Hepatitis C Cohort Study, whereas significant alcohol drinking, anti-HIV, diabetes and BMI did not. In genotyped patients, variants at *rs9380516* (*TULP1*), *rs738409* (*PNPLA3*), *rs4374383* (*MERTK*) (AF 19.2%) and *rs910049* (major histocompatibility complex region) significantly added to the risk of accelerated FPR. Results were replicated in three additional independent cohorts, and a meta-analysis confirmed the role of age at infection, sex, route of infection, HCV genotype, *rs738409*, *rs4374383* and *rs910049* in accelerating FPR.

Conclusions Most factors accelerating liver fibrosis progression in chronic hepatitis C are unmodifiable.

Significance of this study

What is already known on this subject?

- Hepatitis C progression towards cirrhosis varies in each single patient, depending on the occurrence of several factors affecting liver fibrosis progression.
- Some factors influencing liver fibrosis progression are modifiable (alcohol drinking, obesity, diabetes, iron overload), whereas others are not (age at infection, sex, route of infection, HCV genotype and the host genetic background).
- Managing modifiable factors positively affects liver disease progression in hepatitis C, although it is unclear what the relative importance of modifiable versus unmodifiable factors is.

What are the new findings?

- The factors contributing to the highest extent to liver fibrosis progression in patients with hepatitis C cannot be modified: older age at infection, male sex, intravenous drug use (IVDU) as risk factor for HCV infection and HCV genotype 3 are the most important, together with genetic variants associated with *PNPLA3*, *MERTK* and the major histocompatibility complex region, with the potential exception of lifestyle associated with a past IVDU as risk factor for HCV acquisition.
- Significant alcohol consumption contributes to fibrosis progression, but only marginally, whereas anti-HIV, diabetes and body mass index do not.
- A significant proportion of the liver fibrosis progression in hepatitis C is explained by hitherto unidentified factors.

How might it impact on clinical practice in the foreseeable future?

- These results may help improving patients' profiling (including genetic testing) to prioritise currently expensive therapeutic interventions.

INTRODUCTION

The HCV is a major pathogen infecting 130–170 million individuals worldwide.[1] HCV causes persistent infection in ~75% of cases, mostly associated with chronic hepatitis and characterised by a relentless deposition of fibrotic tissue, culminating in the development of cirrhosis. The complications of cirrhosis are a major cause of mortality in hepatitis C and a leading indication for liver transplantation.[1]

Hepatitis C progression towards cirrhosis is variable, as it may be influenced by several factors, such as older age at infection, male sex, excessive alcohol drinking, obesity, insulin resistance, diabetes, HCV genotype 3, iron overload and immunosuppression.[2–4] Patients cumulating two or

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