Late presentation of chronic hepatitis C patients in the era of direct-acting antivirals—Data from the German Hepatitis C-Registry

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1 | INTRODUCTION

Chronic liver disease due to hepatitis C virus (HCV) infection is a major public health burden with an estimated 71 million people worldwide suffering from replicative HCV infection.1 Even if diagnosed in an early stage of disease, missing linkage to care or reluctance to treat might defer treatment until progression to an advanced stage of liver disease. To reduce liver-related morbidity and mortality by 65% by 2030 as targeted by the World Health Organization (WHO) innovative prevention measures, a timely treatment uptake and identification and well-managed care of those with advanced liver disease will be needed.2 In this context, a consensus definition of late presentation for viral hepatitis defining it as significant fibrosis (≥F3; advanced liver disease) or late-stage liver disease (hepatic decompensation or hepatocellular...
carcinoma (HCC)) in chronic viral hepatitis had been established to improve patient care and disease management across Europe. Using a common definition will allow cross-country or regional comparisons and an investigation of temporal trends after targeted interventions. With direct-acting antivirals (DAAs), a highly effective and well-tolerated HCV treatment can be offered almost to every patient. Achieving sustained virological response (SVR) after end of treatment equals HCV cure in most cases and has a beneficial impact on disease progression and liver-related complications. To reduce the burden of chronic viral hepatitis, access to DAAs is unrestricted in Germany. Late presentation (LP) might be different for patients coinfected with HIV and HCV compared to those monoinfected with HCV, as HIV accelerates liver disease progression and different patient populations might be affected, concerning mode of transmission, risk behaviour and genotype (GT). We aimed to investigate the extent of LP since unrestricted access to DAA therapy in Germany for HCV monoinfected and HIV/HCV coinfected patients in the period 2014–2018.

2 | METHODS

2.1 | Study population

The German Hepatitis C-Registry (DHC-R) is a national multicentre real-world cohort currently including about 17,700 patients recruited by more than 250 centres. It is registered at the German Clinical Trials Register (ID DRKS00009717). The study protocol was approved by the Institutional Review Board (Ethics Committee of Aertztekammer Westfalen-Lippe) and conducted in accordance with the Declaration of Helsinki.

Treatment-naïve patients infected with HCV and aged ≥18 years, who have been screened and referred for treatment at one of the study-sites between 1 of February 2014 and 31 of December 2018 inclusive were included in our analysis. An informed consent form was mandatory for every patient to be registered. HCV monoinfected and HIV/HCV coinfected participants were analysed separately. In 2016, patients could be enrolled from August to December only, and therefore, data collected in 2016 was not included in our statistical analysis.

2.2 | Definition of liver disease

Advanced liver disease (ALD) was defined according to the consensus definitions of late presentation for care. Advanced liver disease was defined as chronic hepatitis C and no previous antiviral treatment in case of an aspartate-aminotransferase-to-platelet-ratio-index (APRI) score ≥1.5, a transient elastography (FibroScan, Echosens, Paris, France) ≥9.5 kPa or a METAVIR stage ≥F3 determined by liver biopsy. Liver cirrhosis was diagnosed using a cirrhosis sum score. The cirrhosis sum score is defined as either one biopsy confirming cirrhosis (METAVIR F4) or one of the following findings: sonographically confirmed cirrhosis, clinical confirmation (e.g., ascites, oesophageal varices or bleeding, jaundice), an APRI-score ≥2 or a FibroScan ≥12.5 kPa.

2.3 | Statistical analysis

Statistical analysis was performed by e.ufactum GmbH (Butzbach, Germany) based on a database extract as of 20 January 2019.

Summary statistics (mean, median, standard deviation, 25th percentile, 75th percentile, minimum, maximum, number of values) or frequencies and proportions were assessed dependent on the scale level of the data. Proportions of patients presenting with ALD by year were compared using chi-square tests, Mann–Whitney U test and Fisher’s exact test.

Differences were considered significant at $p \leq .05$. All analyses were calculated using SPSS Windows Release 22.0.0.2 (IBM®, USA).

3 | RESULTS

3.1 | Study cohort

Eight thousand three treatment naïve patients were referred for DAA treatment in the observational period. 28% (2197/8003) of these patients already suffered from ALD. 62% (4995/8003) were male and the average age was 49.8 ± 13.2 years. HIV coinfection was present in 6.9% (551/8003) of patients. Hepatitis B virus (HBV) coinfection status was documented in 4323 (54%) patients and HBV coinfection was present in 116/4323 (2.7%) of patients. The most frequent GT in the overall study population was GT 1 (68%; 5410/8003) followed by GT 3 (23%; 1846/8003), GT4 (5%; 367/8003) and GT2 (4%; 367/8003). 6872 (86%) patients provided information on alcohol consumption and 1264/6872 (18%) of patients reported alcohol consumption of any amount. Mean BMI at baseline was 25.7 ± 4.8 kg/m² ($n = 7463$). 85% (320/376) of HIV/HCV coinfected patients were virally suppressed (<40 cp/ml), and 448/551 (81%) were administered antiretroviral treatment (ART). A detailed description of baseline characteristics by liver disease and HIV/HCV coinfection status can be found in the supplemental digital content Tables S1–S7.

3.2 | Late presentation over time

LP for viral hepatitis was as high as 37% (439/1184) for treatment naive patients in 2014 and decreased significantly to 29% (873/3055; $p < .001$) and 26% (430/1655; $p < .001$) in 2015, 2017 and 2018, respectively (Figure 1). Lowest proportions of LP were observed in 2017 with no further decrease in 2018. In 2018, LP was significantly lower in patients being HIV/HCV coinfected compared to HCV monoinfected patients ($p = .047$).

4 | DISCUSSION

Overall, 28% (2197/8003) of patients presented with ALD, with the highest proportion (37%; 439/1184) in 2014. This finding is in line...
with results from Denmark and France and confirms our results from the GECCO cohort.4–6 Quite recently, reports from Spain for 2018 and 2019 demonstrated a stable prevalence of LP in the last years.7 Despite the broad availability of DAA treatment, the rate of patients already affected by ALD at time of treatment initiation remained at around 25%, with a significantly lower proportion only in HIV/HCV coinfected patients in 2018. We observed a significant decrease in the proportion of patients presenting late for viral hepatitis comparing 2014 to the following years 2015, 2017 and 2018. The largest drop was observed in the year from 2014 to 2015, which was likely due to the foreseeable approval of first-generation DAAs in 2012/2013 and an associated delay of treatment into the year 2014. Treatment uptake was about 3 times higher in 2015 compared to 2014 (1100 patients vs. 3055 patients), which reflects most likely the effect of the implementation of DAAs for HCV treatment and unrestricted access in Germany. But several reports observed that treatment uptake did not reduce the incidence of HCV infections in all high-risk groups.6,8 Conceivably, (re-) infections, specifically in HIV-MSM using PrEP might counterbalance the effect of treatment uptake, highlighting the need for intensified prevention measures and behavioural changes.9 Data from several European countries reporting LP in >25% of HCV infected patients despite unrestricted access to DAA treatment is alarming, particularly under consideration that the proportion of LP in low- and middle-income countries might be even higher. Moreover, a possibly more difficult access to HCV treatment and expert service appointments from 2020 onwards due to the corona virus pandemic worldwide might cause a further increase in LP in the next years. Clearly, much greater efforts need to be made in terms of screening and early referral for treatment to achieve the WHO 2030 elimination targets.

In our cohort, HIV/HCV coinfected patients presented less often with ALD in 2018 compared to those HCV monoinfected, highlighting the importance of a close linkage to care. The considerably high proportions of patients with ALD should bring the importance of a continued follow-up of these patients in expert centres into focus. In a retrospective analysis from Germany, de novo HCCs occurred in 3.1% of treated patients and all affected patients had underlying cirrhosis at treatment initiation or developed cirrhosis after treatment failure.10 Addressing the burden of severe liver disease is not only a matter of treatment and prevention but also an important task to prevent liver-related complications (decompensations, HCCs) effectively.

Our study has some limitations. As there was an enrolment pause between October 2015 and July 2016, we could not evaluate LP in 2016, which would have been quite interesting, as we observed an increase in the proportion of LP in 2016 in the GECCO cohort.6 Furthermore, about 10% of patients might have contributed to the GECCO cohort as well, as there has been an overlap in the founding years of the GECCO registry.

To conclude, 28% of treatment naïve patients with chronic HCV presented late for care in the years 2014–2018 in Germany. Although we observed a significant decrease of this proportion...
for HCV monoinfected and HIV/HCV coinfected patients, 27% of HCV monoinfected and 17% of HIV/HCV coinfected patients still presented with ALD in 2018 despite an increase in treatment uptake and unlimited access to DAAs. Our findings should contribute to improvement of diagnostic strategies and prevention measures to reduce the burden of LP and highlight the importance of a close long-term follow-up to prevent liver-related complications.

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CONFLICT OF INTEREST
Jenny Bischoff has nothing to disclose. Stefan Mauss reports personal fees (consulting or/and speaker fee) from AbbVie, Gilead, Janssen, MSD, MyrPharma, ViV. Thomas Lutz reports Grants/research support from AbbVie, Gilead Siences, GSK, MSD, Deutsche Leberstiftung e.V., Heidelberg Immunotherapeutik, DAGNÄ e.V. Christiane Cordes has nothing to disclose. Gerd Klausen has nothing to disclose. Stefan Scholten: Advisory Committees or Review Panels: Abbvie, BMS, Gilead, GSK, Janssen-Cilag, MSD, ViV Healthcare, TAD; Grants/Research Support: Abbvie, BMS, Gilead, Janssen-Cilag, MSD, ViV Healthcare, Hexal; Speaking and Teaching: Abbvie, BMS, Gilead, Janssen-Cilag, MSD, ViV Healthcare. Heribert Hillenbrand has nothing to disclose. Markus Cornberg reports personal fees (consulting or/and speaker fee) from Abbvie, Falk Foundation, Gilead, Janssen-Cilag, GSK, MSD, Spring Bank, SOBI, outside the submitted work. Axel Baumgarten has nothing to disclose. Jürgen K. Rockstroh: has received honoraria for consulting or speaking at educational events from Gilead, Janssen, Merck, ViV and Theratechnologies.

ETHICAL APPROVAL
The DHC-R is registered at the German Clinical Trials Register (ID DRKS00009717). The study protocol was approved by the Institutional Review Board (Ethics Committee of Aerztkammer Westfalen-Lippe).

DATA AVAILABILITY STATEMENT
The data supporting the findings of this study are available from the corresponding author JKR upon reasonable request.

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REFERENCES
1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45-S57.
2. Organization WH. Combating Hepatitis B and C to reach elimination by 2030. http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/. Accessed September 4, 2018.
3. Mauss S, Pol S, Buti M, et al. Late presentation of chronic viral hepatitis for medical care: a consensus definition. BMC Med. 2017;15(1):92.
4. Sanza A, Le Strat Y, Roudot-Thoraval F, et al. Severe liver disease related to chronic hepatitis C virus infection in treatment-naïve patients: epidemiological characteristics and associated factors at first expert centre visit, France, 2000 to 2007 and 2010 to 2014. Euro Surveill. 2017;22(30):30582.
5. Hansen JF, Hallager S, Ovrehus A, Weis N, Brehm Christensen P, Pedersen C. Late presentation for care among patients with chronic hepatitis C: prevalence and risk factors. Open Forum Infect Dis. 2018;5(1):ofx257.
6. Bischoff J, Boesecke C, Ingiliz P, et al. Has increased rollout of direct acting antiviral therapy decreased the burden of late presentation and advanced liver disease in patients starting hepatitis C virus therapy in Germany? J Clin Gastroenterol. 2020;54(2):192-199.
7. Buti M, Picchio CA, Lens S, et al. A retrospective registry review of chronic viral hepatitis patients and associated risk factors of late presentation to care in Spain, a country with unrestricted treatment access; Poster presented at the AASLD The Liver Meeting Digital Experience 2020.
8. Salazar-Vizcaya L, Wandeler G, Fehr J, et al. Impact of direct-acting antivirals on the burden of HCV infection among persons who inject drugs and men who have sex with men in the Swiss HIV cohort study. Open Forum Infect Dis. 2018;5(7):ofy154.
9. Jin F, Dore GJ, Matthews G, et al. Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(1):39-56. https://doi.org/10.1016/S2468-1253(20)30303-4
10. Finkelmeier F, Dultz G, Peiffer KH, et al. Risk of de novo hepatocellular carcinoma after HCV treatment with direct-acting antivirals. Liver Cancer. 2018;7(2):190-204.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

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