Real-world experience for the outcomes and costs of treating hepatitis C patients: Results from the German Hepatitis C-Registry (DHC-R)

Outcomes und Kosten der Behandlung von Hepatitis-C-Patienten in der medizinischen Praxis: Ergebnisse aus dem Deutschen Hepatitis-C-Register (DHC-R)

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ABSTRACT

Background & Aims With long-term consequences like the development of liver cirrhosis and hepatocellular carcinoma, chronic hepatitis C virus (HCV) infection is associated with a significant health burden. Information on HCV treatment outcomes and costs in routine care is still rare, especially for subgroups. The aim of this study was to analyse the treatment outcomes and costs of subgroups in routine care and to compare them over time with previous analyses.

Methods Data were derived from a noninterventional study including a subset of 10298 patients receiving DAAs with genotypes 1 and 3. Sociodemographic, clinical parameters and costs were collected using a web-based data recording system. The total sample was subdivided according to treatment regimen, cirrhosis status as well as present HIV infection and opioid substitution treatment (OST).

Results 95 % of all patients achieved SVR. Currently used DAA showed higher SVR-rates and less adverse events (AE) compared to former treatments. Concerning subgroups, cirrhotic patients, HIV-coinfected patients and OST patients showed

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lower but still high SVR-rates. In comparison, cirrhotic had considerably longer treatment duration and more frequent (serious) AE. Overall, average treatment costs were € 48 470 and costs per SVR were € 51 129; for currently used DAAs costs amounted to € 30 330 and costs per SVR to € 31 692. After the end of treatment, physical health is similar to the general population in all patients except cirrhotic. Mental health remains far behind in all subgroups, even for currently used DAA.

Conclusions Over time, some relevant factors developed positively (SVR-rates, costs, treatment duration, adverse events, health-related quality of life (HRQoL)). Further research on HRQoL, especially on mental health, is necessary to evaluate the differences between subgroups and HRQoL over time and to identify influencing factors.

ZUSAMMENFASSUNG

Hintergrund und Ziele Die chronische Infektion mit dem Hepatitis-C-Virus (HCV) ist mit Langzeitfolgen wie der Entwicklung einer Leberzirrhose oder eines hepatozellulären Karzinoms assoziiert und stellt eine erhebliche Gesundheitsbelastung dar. Informationen über HCV-Behandlungsergebnisse und -kosten in der Praxis sind nach wie vor rar, insbesondere für Subgruppen. Ziel dieser Studie war es, die Behandlungsergebnisse und -kosten von Subgruppen in der Versorgung zu analysieren und sie mit früheren Analysen zu vergleichen.

Methoden Die Daten stammen aus einer nicht interventionellen Studie mit einer Untergruppe von 10 298 Patient*innen, die DAA erhalten und die Genotypen 1 und 3 aufweisen. Soziodemografische und klinische Parameter sowie Kosten wurden mithilfe eines webbasierten Datenerfassungssystems erhoben. Für die Analysen wurden verschiedene Subgruppen definiert: Die Gesamtstichprobe wurde nach Zirrhosestatus und nach vorhandener HIV-Infektion und Opioidsubstitutionsbehandlung (OST) unterteilt.

Ergebnisse 95 % aller Patienten erreichten eine SVR. Die derzeit verwendeten DAA wiesen im Vergleich zu früheren Behandlungen höhere SVR-Raten und weniger unerwünschte Ereignisse (AE) auf. Was die Untergruppen betrifft, so wiesen zirrhotische Patienten, HIV-Koinfizierte und OST-Patienten niedrigere, aber immer noch hohe SVR-Raten auf. Im Vergleich dazu hatten Zirrhotiker eine deutlich längere Behandlungsdauer und häufiger (schwere) Nebenwirkungen. Insgesamt beliefen sich die durchschnittlichen Behandlungskosten auf 48 470 € und die Kosten pro SVR auf 51 129 €; für die derzeit verwendeten DAAs beliefen sich die Kosten auf 30 330 € und die Kosten pro SVR auf 31 692 €. Nach Abschluss der Behandlung ist der körperliche Gesundheitszustand bei allen Patienten mit Ausnahme der Zirrhotiker mit dem der Allgemeinbevölkerung vergleichbar. Die psychische Gesundheit bleibt in allen Untergruppen weit zurück, selbst bei derzeit verwendeten DAA.

Schlussfolgerungen Im Laufe der Zeit entwickelten sich einige relevante Faktoren positiv (SVR-Raten, Kosten, Behandlungsdauer, unerwünschte Ereignisse, gesundheitsbezogene Lebensqualität [HRQoL]). Weitere Forschung zur HRQoL, insbesondere zur psychischen Gesundheit, ist erforderlich, um die Unterschiede zwischen den Subgruppen und die HRQoL im Zeitverlauf zu bewerten und Einflussfaktoren zu identifizieren.

Background and Aims

Hepatitis C is recognized as a disease of global importance since more than 170 million people worldwide are chronically infected with the hepatitis C virus (HCV) [1]. In Germany, survey data show an anti HCV-prevalence of 0.3 % in the general population [2]. However, considering a higher prevalence in risk-groups such as drug abuser, prison inmates, and HIV co-infected patients, recent studies estimate 275 000 chronically infected people [3].

Most HCV infections remain predominantly undiagnosed until severe, potentially lethal complications, like liver cirrhosis or hepatocellular carcinoma (HCC), occur in late and advanced stages of the disease, [4, 5]. Chronic HCV accounts for about a quarter of liver cirrhosis and HCC each [6] and, in addition, chronic hepatitis C is still one of the most common causes of liver transplantation [7]. Worldwide, 350 000 people die each year from these long-term consequences of HCV infection [1].

Eradication of the HCV virus is associated with a decreased risk of liver cirrhosis, HCC, liver-related mortality and all-cause mortality, as well as an increase in health-related quality of life (HRQoL) in infected patients. Therefore, achieving sustained virological response (SVR) is the main goal of antiviral treatment of HCV infection [8, 9, 10]. Compared to the first-generation DAAs, boceprevir and telaprevir, and to earlier treatment regimens, the introduction of the second-generation direct-acting antivirals (DAAs) has significantly improved antiviral therapy for HCV infection. SVR rates significantly increased in all genotypes and subgroups up to 99 % [11, 12]. Furthermore, second-generation DAAs have shorter treatment durations, favourable toxicity profiles and can also be used in patients who were not eligible for treatment in the past to age and other diseases besides HCV infection. Using these new regimens together with different nationwide screening strategies it will be feasible to achieve a nearly complete HCV eradication by the year 2030 [13, 14].

However, until now information on hepatitis C treatment outcomes and costs in routine care is rare, especially for subgroups. Therefore, the aim of this study was to analyze the outcomes and costs of treatment for HCV patients stratified by population and cirrhosis status in routine care and to compare them over time with previous analyses, using one of the largest databases worldwide generated by the German Hepatitis C-Registry (Deutsches Hepatitis C-Register; DHC-R) [15].

Methods

We analysed data acquired from the German Hepatitis C-Registry (Deutsches Hepatitis C-Register; DHC-R). With about 18 400 patients currently, the DHC-R is one of the largest registries for HCV worldwide. It is a prospective, multicenter, real-world registry study and collects data on treatment-naive (TN) and treatment-experienced (TE) HCV patients in clinics and medical practices throughout Germany. Patient enrolment started in 2014 and ended in March 2022.

The DHC-R is a project of the German Liver Foundation (Deutsche Leberstiftung), managed by the Leberstiftungs-GmbH Deutschland in cooperation with the Association of German Gastroenterologists in Private Practice (Berufsverband Niedergelassener Gastroenterologen Deutschlands e. V.; bng) with financial support from the German Center for Infection Research (DZIF) and the companies AbbVie Deutschland GmbH & Co. KG, Gilead Sciences GmbH, MSD Sharp & Dohme GmbH as well as Bristol-Myers Squibb GmbH & Co. KGaA and Janssen-Cilag GmbH (each until 2020-07-14) and Roche Pharma AG (until 2017-07-14). The registry was approved by the Ethical Committee of Ärztekammer Westfalen-Lippe (No.: 2014-395-f-S). Furthermore, the DHC-R was announced to the Federal Institute for Drugs and Medical Devices (BfArM: 2493) and the German Clinical Trials Registry (DRKS: DRKS00009717).

Patients had to provide written informed consent before being enrolled in the study. Inclusion criteria were chronic HCV infection with detectable HCV-RNA as well as an age of 18 years or older. Exclusion criteria were pregnancy, nursing women or women of childbearing age without reliable contraception, as well as contraindications for use of antiviral treatment. Treatment choice was at the discretion of the physician. To date, data from the DHC-R have been published in different publications, providing detailed information on epidemiological data, treatment practice, healthcare utilization and outcomes in different subgroups [16, 17, 18, 19, 20, 21].

Data were gathered using a web-based data recording system. The quality of the data was assessed by on-site monitoring and automated plausibility checks. Data collection included sociodemographic parameters, clinical parameters, healthcare utilization (e. g. pharmaceuticals) and treatment outcomes (SVR) for all patients. SVR was assessed 12 weeks after treatment (SVR12). Pharmaceutical costs for the German market are based on the German price database Lauer Taxe with status February 2020 [22]. Non-pharmaceutical costs, for instance laboratory tests, imaging techniques and hospitalization, were not considered in the analysis of costs, as they are relatively low for current therapies. The calculation of costs and costs per SVR for the defined subgroups (i. e., subdivided by cirrhosis status, present HIV infection and opioid substitution treatment) stratified by treatment regimen could not be calculated exactly, only approximately, since for some values only aggregated data were available.

For some patients, quality of life (HRQoL) was also assessed on a voluntary basis. HRQoL was determined using the German version and transformation of the Short-Form-36, version 2 (SF-36v2) [23]. Patients were asked to complete the questionnaires at four different times: (i) baseline, (ii) treatment week 12, (iii) end of treatment, and (iv) 24 weeks after treatment.

In the preliminary phase of the present analysis, all required relevant variables were defined in a statistical analysis plan. The analysis is based on data from a defined subset of HCV patients with genotype (GT) 1 and 3 who initiated and finished treatment between February 2014 and December 2019. Genotype 1 and 3 represent the majority of infected patients in Germany and account for more than 90 % of all infections. Data were analyzed as of January 1, 2020. For the analyses, different subgroups were defined:

1. The total sample was subdivided according to cirrhosis status:
   a) non-cirrhotic
   b) cirrhotic
2. The total sample was subdivided according to present HIV infection and opioid substitution treatment (OST):
   a) persons who are neither HCV/HIV co-infected nor in OST *(hereafter: non-HIV population)*
   b) HIV-infected and/or OST patients

In addition, the analyses were stratified according to the various treatment regimens. EBR/GZR, SOF/VEL, G/P and SOF/VEL/VOX are defined as currently used DAAs; all further treatments are referred to as previous treatments. In total, data from 10 298 patients provided by 281 outpatient practices and hospital-based outpatient clinics were analyzed. Statistical analyses were carried out using IBM SPSS Statistics 21 (IBM Corporation, Armonk, New York, USA). They are primarily descriptive to reflect the noninterventional nature of the study. Subgroup analyses were carried out using the t-test or the $\chi 2$-test depending on the type of variable. Differences were considered significant at a level of $p \leq 0.05$.

Furthermore, the results were compared with those of a previous study, which also included data from the DHC-R collected between February 2014 and February 2017 [12].

All methods were carried out in accordance with relevant guidelines and regulations.

Results

Patient characteristics

A total of 10 298 patients who met the inclusion criteria were included in the analyses. On average, the patients were 53 years old, 60 % of them male. The mean weight was 77 kg, the mean height 173 cm, and the mean BMI 25,9 kg/m2. Almost all patients were Caucasian. The most common routes of transmission were intravenous drug use (30 %) and blood or blood products (14 %), although for 41 % of patients the route of transmission was unknown. Transmission through intravenous drug use varied with respect to genotype (GT 1b: 11 %; GT 3: 53 %). At baseline, 87 % of patients had a viral load of 6 million IU/ml or less, 12 % had a viral load greater than 6 million IU/ml and 1 % did not have their viral load analyzed.

Information on liver cirrhosis was mostly based on imaging techniques and elastography due to the non-interventional nature of the study. More than three-quarters of all patients received a

▶ **Table 1** Patients characteristics at baseline.

Parameter	GT 1a n = 3598	GT 1b n = 4490	GT 1 unknown n = 297	GT 3 n = 1913	All patients n = 10 298
Age, years (n = 10 298)	50.7	56.4	54.7	46.4	52.5
Sex, female (n = 10 298)	30.9 %	51.9 %	48.8 %	28.0 %	40.0 %
Ethnicity (n = 10 298)					
▪ Caucasian	97.0 %	97.7 %	97.0 %	96.4 %	97.2 %
▪ African	1.2 %	0.5 %	1.0 %	0.4 %	0.7 %
▪ Asian	1.2 %	1.6 %	1.3 %	2.7 %	1.6 %
▪ Hispanic	0.7 %	0.2 %	0.7 %	0.3 %	0.4 %
▪ Other	0.0 %	0.0 %	0.0 %	0.1 %	0.0 %
Height, cm (n = 10 298)	174.7	169.9	171.7	174.3	172.5
Weight, kg (n = 10 292)	78.1	75.8	76.6	79.2	77.2
Body-Mass-Index, kg/m^2 (n = 10 292)	25.5	26.2	25.9	26.0	25.9
Duration of Infection, years (n = 6826)	17.8	21.9	21.0	15.9	19.2
Route of Transmission (n = 10 298)					
▪ Blood or Blood Products	9.3 %	20.8 %	18.5 %	5.3 %	13.8 %
▪ Drug Abuse	43.6 %	10.5 %	20.9 %	53.1 %	30.2 %
▪ Sexual Transmission	10.5 %	1.8 %	5.1 %	3.3 %	5.2 %
▪ Surgical or Medical Treatment	3.5 %	10.1 %	8.4 %	4.5 %	6.7 %
▪ Other	2.2 %	3.3 %	3.4 %	2.3 %	2.7 %
▪ Unknown	31.0 %	53.7 %	43.8 %	31.6 %	41.3 %
Treatment Status (n = 10 298)					
▪ naïve	58.9 %	58.8 %	45.1 %	74.8 %	61.4 %
▪ experienced	41.1 %	41.2 %	54.9 %	25.2 %	38.6 %
Liver Cirrhosis* (n = 10 298)	33.9 %	29.4 %	35.0 %	34.9 %	32.5 %
APRI-Score at Baseline (n = 9265)	1.0	1.1	1.3	1.3	1.1
APRI-Score at Baseline (n = 9265)					
▪ ≤ 0.5	1410	1630	94	537	3671
▪ > 0.5–1.5	1283	1608	106	747	3744
▪ > 1.5	537	790	57	466	1850
Baseline Viral Load IU/ml (n = 10 298)	4 380 255	2 811 421	3 955 026	3 120 391	3 450 838
Baseline Viral Load (n = 10 298)					
▪ ≤ 6 million IU/ml	83.7 %	89.4 %	86.2 %	85.3 %	86.6 %
▪ > 6 million IU/ml	15.1 %	8.9 %	13.1 %	14.1 %	12.2 %
▪ unknown	1.2 %	1.6 %	0.7 %	0.6 %	1.3 %
Child-Pugh Score (n = 3348)					
▪ Unknown	39.1 %	40.7 %	42.3 %	39.7 %	40.1 %
▪ A	53.5 %	52.5 %	47.1 %	52.8 %	52.7 %
▪ B	6.6 %	5.9 %	8.7 %	6.4 %	6.3 %
▪ C	0.9 %	0.9 %	1.9 %	1.0 %	1.0 %
Comorbiditiy (n = 10 298)					
▪ no	18.9 %	27.2 %	25.6 %	25.8 %	24.0 %
▪ yes	81.1 %	72.8 %	74.4 %	74.2 %	76.0 %

▶ **Table 1** (Continuation)

Parameter	GT 1a n = 3598	GT 1b n = 4490	GT 1 unknown n = 297	GT 3 n = 1913	All patients n = 10 298
Treatment regimen (n = 10 298)					
▪ SOF+RBV	0.4 %	0.4 %	1.3 %	14.5 %	3.1 %
▪ SOF+IFN+RBV	4.4 %	3.5 %	4.7 %	10.1 %	5.1 %
▪ SMV+IFN+RBV	0.0 %	0.1 %	0.0 %	0.1 %	0.0 %
▪ SOF+SMV	2.4 %	4.1 %	4.0 %	0.0 %	2.7 %
▪ SOF+SMV+RBV	0.4 %	0.6 %	1.0 %	0.0 %	0.4 %
▪ SOF+DCV	6.3 %	6.3 %	11.8 %	15.0 %	8.1 %
▪ SOF+DCV+RBV	0.5 %	0.6 %	1.7 %	6.3 %	1.7 %
▪ SOF/LDV	37.1 %	31.2 %	46.8 %	0.8 %	28.0 %
▪ SOF/LDV+RBV	8.3 %	6.2 %	10.1 %	5.2 %	6.8 %
▪ OBV/PTV/r+DSV	0.9 %	14.3 %	2.4 %	0.0 %	6.6 %
▪ OBV/PTV/r+DSV+RBV	8.5 %	4.5 %	3.0 %	0.0 %	5.0 %
▪ EBR/GZR	7.8 %	19.9 %	3.7 %	0.0 %	11.5 %
▪ SOF/VEL	3.8 %	1.2 %	1.3 %	12.3 %	4.2 %
▪ G/P	18.0 %	6.4 %	7.7 %	33.8 %	15.6 %
▪ SOF/VEL/VOX	1.3 %	0.8 %	0.3 %	1.9 %	1.2 %

* Based on all available data.

sonographic examination of the liver. In total, one-third of the patients demonstrated liver cirrhosis at baseline. Child-Pugh score information was available for 2007 of these patients. A total of 1764 had stage A cirrhosis (indicating compensated liver function), 211 had stage B cirrhosis (indicating moderate liver function) and 32 had stage C cirrhosis (indicating poor liver function). At baseline, the mean aspartate aminotransferase to platelet ratio index score was 1.1. For 40 % of the patients, the score was up to 0.5, for 40 %, it was between 0.5 and 1.5, and for 20 %, it was over 1.5.

Overall, 61 % of patients were treatment-naïve. The most frequent treatment regimen was SOF/LDV (28 %). Among GT 1a, GT 1b, and GT 1 patients, most received SOF/LDV (37 %, 31 %, and 47 %, respectively), and among GT 3 patients, most received G/P (34 %). Over three-quarters of the patients (76 %) had one or more comorbidities. The most common comorbidities were cardiovascular disease (27 %), psychiatric disorders (15 %), diabetes mellitus (9 %), and thyroid dysfunction (9 %). A history of drug abuse and alcohol abuse was observed for 2166 (21 %) and 552 (5 %) patients, respectively. Patient characteristics are summarized in ▶ **Table 1**.

Treatment response and duration

The overall SVR-rate was 95 % (n = 9761). Of the remaining patients, 189 (1.8 %) were lost to follow-up and 348 (2.4 %) achieved no SVR because of different reasons: 15 showed no response at the end of therapy (0.1 %), 244 developed a relapse at the end of therapy (2.4 %), 27 showed a reinfection (0.3 %), and 62 were still HCV RNA qualitative positive (0.6 %) at 12 weeks after the end of treatment.

The average length of treatment was 12 weeks (SD: 4.5 weeks) and varies between treatment regimen, cirrhosis-status and subpopulation. Cirrhotic patients show a longer treatment duration than non-cirrhotic patients (14.4 vs. 11.0, $p \leq 0.001$) and HIV-infected and/or OST patients show a shorter duration compared to non-HIV population (11.5 vs. 12.2, $p \leq 0.001$).

Considering the overall SVR rate of 95 %, depending on the treatment regimen, the SVR rates varied from 77 up to 97 %. Highest SVR rates were observed for SOF/LDV (96.9 %), SOF/VEL/VOX (96.7 %), G/P (96.4 %), EBR/GZR (96.1 %), and OBV/PTV/r+DSV (96.0 %). The SVR rate was 96 % in noncirrhotic patients and 93 % in cirrhotic patients ($p \leq 0.001$). In terms of subpopulations, the SVR rate among the HIV-infected and/or OST patients is 93 % while for the non-HIV population it is 95 % ($p \leq 0.001$). Further information on response rates and treatment duration is summarized in ▶ **Table 2**.

Safety summary and adverse events during treatment

Non-serious adverse events (AE) were observed in 50 % of the treated patients. The most common non-serious AEs were fatigue [2131 (20.7 %) patients], headache [1348 (13.4 %) patients], nausea [607 (5.9 %) patients], insomnia [508 (4.9 %) patients], pruritus [463 (4.5 %) patients], arthralgia [453 (4.4 %) patients], and abdominal complaints [433 (4.2 %) patients]. Serious AE were relatively few in our sample. Overall, 4.0 % of patients had at least one serious AE. The most frequent serious AE was malignant neo-

▶ **Table 2** Treatment outcomes by patient group.

Patient group	n	Treatment duration, weeks	Treatment outcome		
			SVR	No SVR*	Lost to follow-up, not tested, %
Treatment regimen**					
SOF+RBV	315	22.8	77.1 %	16.6 %	6.3 %
SOF+IFN+RBV	525	12.5	91.0 %	8.0 %	1.0 %
SOF+SMV	282	12.2	93.3 %	6.7 %	0.0 %
SOF+SMV+RBV	43	13.4	90.7 %	7.0 %	2.3 %
SOF+DCV	832	15.2	94.4 %	3.4 %	2.2 %
SOF+DCV+RBV	171	19.7	93.0 %	2.9 %	4.1 %
SOF/LDV	2888	11.1	96.9 %	1.7 %	1.4 %
SOF/LDV+RBV	705	14.9	93.6 %	4.7 %	1.7 %
OBV/PTV/r+DSV	679	11.6	96.0 %	2.7 %	1.3 %
OBV/PTV/r+DSV+RBV	515	12.4	94.0 %	2.7 %	3.3 %
EBR/GZR	1183	12.0	96.1 %	2.8 %	1.1 %
SOF/VEL	430	11.9	91.9 %	4.4 %	3.7 %
G/P	1605	8.4	96.4 %	1.7 %	1.9 %
SOF/VEL/VOX	120	11.9	96.7 %	2.5 %	0.8 %
Cirrhosis status					
Non-cirrhotic	6950	11.0	95.9 %	2.8 %	1.7 %
Cirrhotic	3348	14.4	92.5 %	2.3 %	2.2 %
Subpopulations					
Non-HIV population	8423	12.2	95.2 %	3.3 %	1.5 %
HIV infected and/or OST patients	1875	11.5	92.9 %	3.8 %	3.3 %
Overall	**10 298**	**12.1**	**94.8 %**	**3.4 %**	**1.8 %**

* Patients with nonresponse, reinfection, relapse or still qualitative positive patients (/> 25 IU/ml nnb).
** No data on SMV+IFN+RBV due to a small number of cases (n = 5).

plasm of the liver [34 (0.3 %) patients]. 1.0 % of the patients discontinued therapy because of AE. In terms of treatment regimen, the currently used DAAs showed fewer AE, serious AE, and treatment discontinuations due to non-serious AE/serious AE compared to previous treatments (see ▶ **Table 3**).

Differences of the incidence of non-serious and serious AE may be due to different patient characteristics, such as a different proportion of cirrhotic patients. ▶ **Table 3** summarizes the safety summary stratified by treatment regimens, cirrhosis status, and subpopulation. Serious AE and death were more frequent in cirrhotic compared to non-cirrhotic patients ($p \leq 0.001$) as well as in HIV-infected and/or OST patients compared to the non-HIV population ($p \leq 0.001$). Therapy discontinuation due to non-serious AE/serious AE differs regarding cirrhosis-status ($p \leq 0.001$), while there was no significant difference with respect to subpopulation ($p = 0.920$).

Pharmaceutical costs and costs per SVR

The average pharmaceutical costs amounted to € 48 470 for the entire observation period. Regarding treatment regimens, it is obvious that the costs of the currently used DAAs (EBR/GZR, SOF/VEL, G/P, SOF/VEL/VOX) differed significantly from those of the former treatment regimens; the average costs of the newer therapies were € 30 330, while that of the former therapies were € 57 171. In terms of cirrhosis status, costs for the currently used treatment of non-cirrhotic patients amounted to € 30 242 (former treatments: € 49 477) and that for cirrhotic patients amounted to € 30 597 (former treatments: € 70 727). The non-HIV population had overall costs of € 30 151 (former treatments: € 57 634) and HIV-infected and/or OST patients had overall costs of € 30 916 (former treatments: € 54 692).

The average costs per patient who achieved an SVR were calculated on the basis of SVR rates and cost estimates in different patient groups. The average costs per SVR with currently used DAAs

▶ **Table 3** Safety summary by patient group.

Patient group	n	Dosis reduction	AE	Serious AE	Death	Therapy discontinuation due to AE/SAE
Treatment regimen*						
SOF+RBV	315	23 (7.3 %)	220 (69.8 %)	19 (6.0 %)	1 (0.3 %)	5 (1.6 %)
SOF+IFN+RBV	525	56 (10.7 %)	396 (75.4 %)	18 (3.4 %)	0 (0.0 %)	14 (2.7 %)
SOF+SMV	282	1 (0.4 %)	182 (64.5 %)	36 (12.8 %)	3 (1.1 %)	2 (0.7 %)
SOF+SMV+RBV	43	2 (4.7 %)	33 (76.7 %)	6 (14.0 %)	0 (0.0 %)	3 (7.0 %)
SOF+DCV	832	1 (0.1 %)	478 (57.5 %)	35 (4.2 %)	3 (0.4 %)	6 (0.7 %)
SOF+DCV+RBV	171	10 (5.8 %)	141 (82.5 %)	25 (14.6 %)	5 (2.9 %)	9 (5.3 %)
SOF/LDV	2888	3 (0.1 %)	1379 (47.7 %)	109 (3.8 %)	15 (0.5 %)	11 (0.4 %)
SOF/LDV+RBV	705	74 (10.5 %)	508 (72.1 %)	51 (7.2 %)	5 (0.7 %)	21 (3.0 %)
OBV/PTV/r+DSV	679	1 (0.1 %)	345 (50.8 %)	20 (2.9 %)	4 (0.6 %)	4 (0.6 %)
OBV/PTV/r+DSV+RBV	515	53 (10.3 %)	351 (68.2 %)	23 (4.5 %)	1 (0.2 %)	20 (3.9 %)
EBR/GZR	1183	1 (0.1 %)	428 (36.2 %)	28 (2.4 %)	3 (0.3 %)	2 (0.2 %)
SOF/VEL	430	0 (0.0 %)	148 (34.4 %)	12 (2.8 %)	2 (0.5 %)	1 (0.2 %)
G/P	1605	2 (0.1 %)	446 (27.8 %)	25 (1.6 %)	3 (0.2 %)	2 (0.1 %)
SOF/VEL/VOX	120	0 (0.0 %)	55 (45.8 %)	7 (5.8 %)	1 (0.8 %)	0 (0.0 %)
Cirrhosis status						
Non-cirrhotic	6950	83 (1.2 %)	3096 (44.5 %)	171 (2.5 %)	17 (0.2 %)	36 (0.5 %)
Cirrhotic	3348	145 (4.3 %)	2019 (60.3 %)	244 (7.3 %)	29 (0.9 %)	65 (1.9 %)
Subpopulations						
non-HIV population	8423	191 (2.3 %)	4223 (50.1 %)	311 (3.7 %)	34 (0.4 %)	83 (1.0 %)
HIV infected and/or OST patients	1875	37 (2.0 %)	892 (47.6 %)	104 (5.5 %)	12 (0.6 %)	18 (1.0 %)
Overall	**10 298**	**228 (2.2 %)**	**5115 (49.7 %)**	**415 (4.0 %)**	**46 (0.4 %)**	**101 (1.0 %)**

* No data on SMV+IFN+RBV due to a small number of cases (n = 5).

were € 31 535 (former treatments: € 51 592) in non-cirrhotic and € 33 077 (former treatments: € 76 461) in cirrhotic. Average costs per SVR of € 31 672 (former treatments: € 60 540) and € 33 279 (former treatments: € 58 872) were calculated for the non-HIV population and HIV-infected and/or OST patients, respectively. Overall, the average costs per SVR of the treatments currently used was € 31 692, compared with € 60 626 for previous therapies. Treatment costs and costs per SVR estimates are presented in ▶ **Table 4**.

Health-related quality of life

Complete information on health-related quality of life (HRQoL) was not available for the total population as some patients did not complete the questionnaires or did not participate at all in three included measurement time points (baseline, end of treatment, 24 weeks post = treatment). For this reason, three different sub-samples were used to perform our analyses and to include all patients available:

1. HRQoL of infected patients (baseline analysis)
2. Development of HRQoL during treatment (complete data analysis)
3. Differences in HRQoL depending on SVR (post-treatment analysis)

At baseline, a total of 4472 out of 10 298 patients filled out the questionnaire regarding HRQoL. One result of the analysis was that HCV-infected patients had lower scores regarding all scores of the SF-36 subscales compared to the general population in Germany. The most significant differences were observed for role-emotional (–23), role-physical (–19), and social functioning (–16). With respect to the two summary scores of the SF-36, there was a large difference for the mental component summary score between HCV patients and the general population (40 vs. 51), while the physical component summary scores were almost similar (48 vs. 50). Considering the subgroups, it is obvious that there was a difference between cirrhotic and non-cirrhotic patients as well as between HIV-infected and/or OST patients and the non-HIV HCV-infected population. In terms of cirrhosis status,

▶ **Table 4** Pharmaceutical costs and costs per SVR estimates by patient group.

	n	Treatment costs, €	SVR	Costs per SVR, €
Treatment regimen*				
EBR/GZR	1183	26 000.19	96.1 %	27 055.35
SOF/VEL	430	29 740.21	91.9 %	32 361.49
G/P	1605	31 489.63	96.4 %	32 665.59
SOF/VEL/VOX	120	59 607.96	96.7 %	61 642.15
Overall: Currently used DAA	3338	30 329.60	95.7 %	31 692.37
Overall: Treatments no longer/barely used (as of 02/2022)	6960	57 170.60	94.3 %	60 626.30
Cirrhosis status				
Non-cirrhotic	6950	42 529.78	95.9 %	44 348.05
Currently used DAA	2510	30 241.55		31 534.47
Treatments no longer/barely used (as of 02/2022)	4440	49 476.50		51 591.76
Cirrhotic	3348	60 802.20	92.5 %	65 732.10
Currently used DAA	828	30 596.64		33 077.45
Treatments no longer/barely used (as of 02/2022)	2520	70 726.88		76 461.49
Subpopulations				
Non-HIV population	8423	49 281.47	95.2 %	51 766.25
Currently used DAA	2560	30 151.42		31 671.66
Treatments no longer/barely used (as of 02/2022)	5863	57 634.35		60 540.28
HIV infected and/or OST patients	1875	44 826.60	92.9 %	48 252.53
Currently used DAA	778	30 916.03		33 278.83
Treatments no longer/barely used (as of 02/2022)	1097	54 692.07		58 871.98
Overall	**10 298**	48 470.36	94.8 %	51 129.07

* Only currently used DAA regimens are considered individually.

a greater difference was observed on the physical component summary score (PCS: 44 vs. 49; MCS: 39 vs. 41), whereas in terms of subpopulations, a greater difference was seen on the mental component summary score (PCS: 48 vs. 47; MCS: 37 vs. 41). An unexpected result in this context is that the HIV-infected and/or OST patients showed a higher physical component summary score than the non-HIV HCV-infected population. SF-36 baseline results by subgroup are shown in ▶ **Table 5**.

To analyze the development of quality of life during antiviral treatment, three measurement points (baseline, end of treatment, and approximately 24 weeks post-treatment) were analyzed. Cases for which baseline data were available were included for this analysis. Data are not available for all of these cases at the other two measurement points:

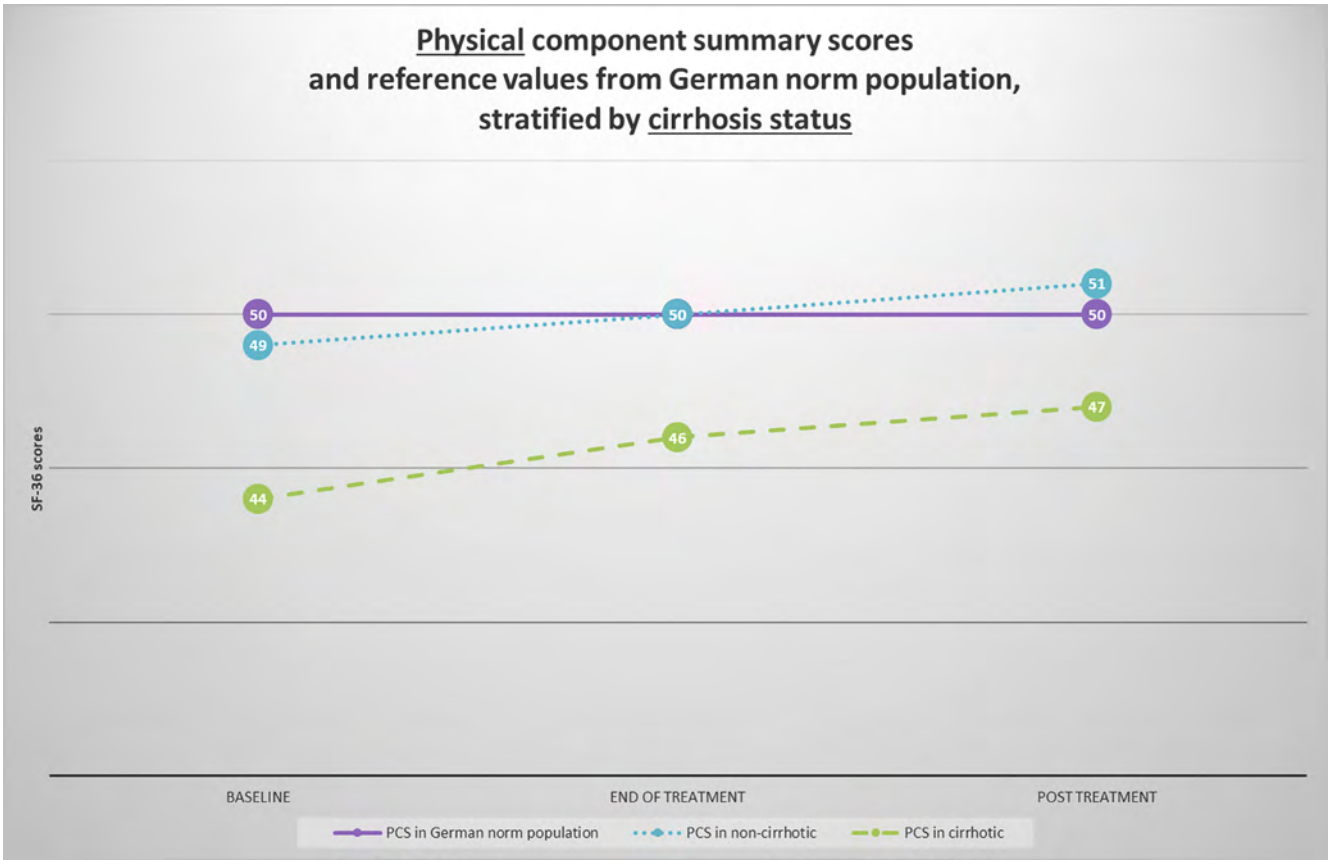
- Baseline (n = 4472)
- End of treatment (n = 2579)
- Post-treatment (n = 2135)

The present analysis showed an increase of the physical component summary score in all subgroups, whereas the increase was almost comparable between baseline and pos-t treatment: cirrhotic (+ 3), non-cirrhotic (+ 2), HIV-infected and/or OST patients (+ 3), non-HIV population (+ 3). The same applies to the mental component summary score, where the values also increased to a similar extent: cirrhotic (+ 4), non-cirrhotic (+ 5), HIV-infected and/or OST patients (+ 4), non-HIV population (+ 5). Development of quality of life in physical component summary score and mental component summary score is described in ▶ **Fig. 1** and ▶ **Fig. 3** for cirrhosis status and ▶ **Fig. 2** and ▶ **Fig. 4** for sub-populations.

To determine the impact of SVR on quality of life, post-treatment data were analyzed. In total, 2646 patients filled out the quality of life questionnaire post-treatment. A comparison of patients who achieved SVR and those who failed treatment demonstrates that achievement of SVR was associated with an increased HRQoL. All SF-36 subscales showed higher values. Differences in HRQoL were greatest in role-physical (10) and role-emotional (15). The physical component summary score and the mental component summary score varied by 2 and 4, respectively. Average scores for patients with and without SVR post-treatment are shown in ▶ **Table 6**. Furthermore, the influence of treatment regimens and subgroups on HRQoL after the end of treatment was analyzed. With regard to treatment regimens, it was found that the currently used DAAs and the former treatments showed, on average, the same physical and mental component summary

▶ **Table 5** SF-36 baseline results.

	CIRRHOSIS-STATUS						SUBPOPULATIONS						Total			German norm population		Diff
	Non-cirrhotic			Cirrhotic			Non-HIV population			HIV infected and/or OST patients								
SF-36 scales	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**Mean**	**SD**	
Physical functioning	3144	81	22.9	1328	70	26.2	3566	77	24.9	906	80	22.7	4472	78	24.5	86	22.3	8
Role-physical	3144	69	39.3	1328	53	42.5	3566	65	40.7	906	61	41.5	4472	64	40.9	83	32.6	19
Bodily pain	3144	76	26.9	1328	67	28.4	3566	74	28.0	906	73	26.4	4472	73	27.6	79	27.4	6
General health	3144	57	20.5	1328	49	20.4	3566	55	20.9	906	52	20.1	4472	55	20.7	68	20.3	13
Vitality	3144	49	21.0	1328	45	21.4	3566	49	21.5	906	44	19.4	4472	48	21.2	63	18.5	15
Social functioning	3144	74	25.2	1328	70	25.9	3566	74	25.4	906	69	25.4	4472	73	25.5	89	18.4	16
Role-emotional	3144	70	40.9	1328	60	44.0	3566	69	41.5	906	60	43.8	4472	67	42.1	90	26.3	23
Mental health	3144	63	19.6	1328	61	19.6	3566	64	19.7	906	58	18.7	4472	63	19.6	74	16.6	11
Sum scores:																		
Physical component summary score	3144	49	9.2	1328	44	10.0	3566	47	9.9	906	48	9.1	4472	48	9.7	50	10.3	2
Mental component summary score	3144	41	13.7	1328	39	13.9	3566	41	13.7	906	37	13.7	4472	40	13.8	51	8.2	11



▶ **Fig. 1** Physical component summary score over time and reference values from German norm population, stratified by cirrhosis status.

scores at the end of treatment (PCS: 49; MCS: 43). On the PCS, values were similar to those of the German norm population; individuals treated with G/P even had minimally higher values. In contrast, the values on the MCS were far below the average of the German norm population for both the previous and the currently used treatments. While higher values were recorded on PCS and MCS for non-cirrhotic compared to cirrhotic, the HIV- infected and/or OST patients showed minimally higher values on the PCS and considerably lower values on the MCS compared to the non-HIV population (see ▶ **Table 7**).

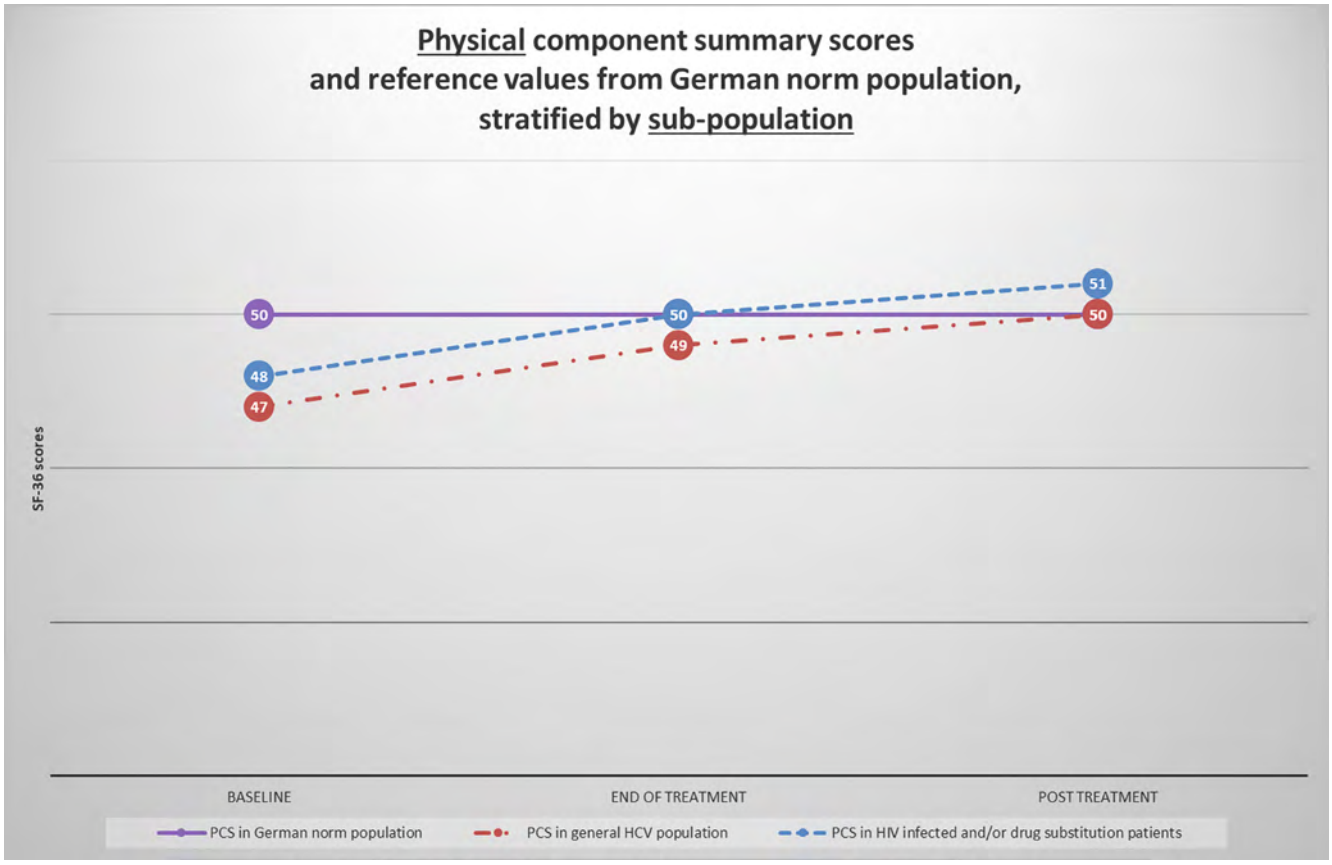
To analyze the transferability of HRQoL estimates, we compared patient characteristics (sex, age, cirrhosis-status) of patients with and without data on HRQoL. There was no significant difference regarding cirrhosis-status ($p = 0.142$), while age ($p < 0.001$) and sex ($p < 0.001$) differed significantly.

Discussion

Based on data from the German Hepatitis C-Registry, a large ongoing, non-interventional, multicenter, prospective, observational cohort study, the outcomes and costs of 10 298 chronically infected hepatitis C patients were analyzed. The focus was on identifying differences by population and cirrhosis status. Regarding subpopulation, 1875 were HIV-infected and/or OST patients (18 %), therefore the remaining 8423 formed the non-HIV and non-OST HCV-infected population of this study (82 %). In terms of cirrhosis status, 6950 of the 10 298 HCV-infected were non-cirrhotic (67 %) and 3348 were cirrhotic (33 %). We identified several differences but also similarities between the subgroups.

Treatment response and duration

Overall, we observed an SVR rate of 95 % in our study population. A previous analysis of the registry data (02/2014–02/2017) showed a rate of 94 % [12]. The SVR rate varies concerning treatment regimen, cirrhosis status (96 % in non-cirrhotic patients and 93 % in cirrhotic patients) and in terms of subpopulations (93 % in HIV-infected and/or OST patients and 95 % in the non-HIV population). This tendency is consistent with several other studies, which also show lower, but still high SVR-rates for cirrhotic patients, HIV-coinfected patients and OST patients treated with DAAs [24, 25, 26]. The average length of treatment was 12 weeks and is comparatively lower compared to 13 weeks in the prior analysis. Concerning subgroups, cirrhotic patients show a longer treatment duration than non-cirrhotic patients (14.4 vs. 11.0 weeks), which can be predominantly explained by medical necessity [27]. Furthermore, HIV-infected and/or OST patients show a shorter duration compared to non-HIV population (11.5 vs. 12.2 weeks), Higher treatment duration in the non-HIV population compared to HIV-infected and/or OST patients are explained by the different genotypes of the two subgroups and the resulting variation in treatment regimens, which are associated with different treatment durations [27, 28].



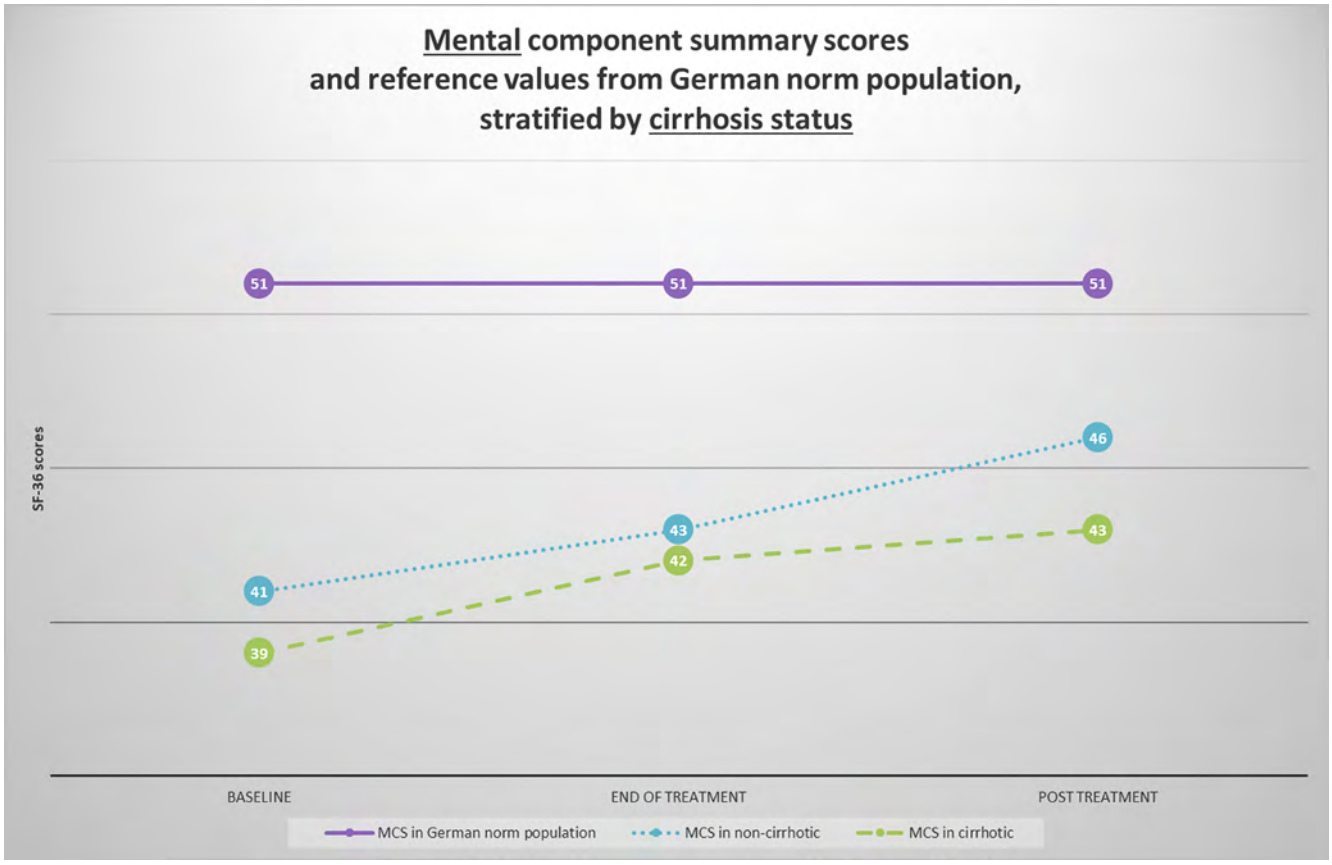
▶ **Fig. 2** Physical component summary score over time and reference values from German norm population, stratified by sub-population.

Safety summary and adverse events during treatment

Adverse events (AE) may occur during HCV treatment. While previous German real-world studies showed that 70–90 % of patients receiving interferon-containing regimens had at least one non-severe AE and 4–11 % had a severe AE during treatment [29, 30], recent studies in patients receiving predominantly interferon-free regimens show non-severe AE (58 %) and severe AE (3 %) less frequently, confirming better tolerability of interferon-free regimens [12]. In our sample, which received predominantly interferon-free regimens, non-severe AE occurred in half of the sample and severe AE in 4 %. Regarding subgroups, the incidence of non-severe and severe AE varies between the non-HIV population and the group of HIV-infected and/or OST patients, as well as between non-cirrhotic and cirrhotic patients.

Pharmaceutical costs and costs per SVR

The average pharmaceutical costs summed up to € 48 470, in a previous analysis (02/2014–02/2017) the costs amounted to € 67 131 [12]. The costs vary between cirrhosis-status (€ 42 530 for non-cirrhotic and € 60 802 for cirrhotic) and sub-populations (€ 49 282 for non-HIV- population and € 44 827 for HIV = infected and/or OST patients). With the introduction of DAAs in 2011, overall SVR-rates have increased continuously over time, while costs have also risen initially [29, 30]. Since our previous analysis (02/2014–02/2017), however, costs have now fallen due to a shorter treatment duration and lower pharmaceutical prices. This is also confirmed by the significantly lower costs per SVR (€ 69 840 vs. € 51 129) [31]. The price development becomes even more apparent if only the costs of the currently used treatment regimens (EBR/GZR, SOF/VEL, G/P, SOF/VEL/VOX) are considered. Overall, the costs for these DAAs are € 30 330 and the cost per SVR amounts to € 31 792. This trend applies to both non-cirrhotics and cirrhotics, as well as to the non-HIV population and HIV-infected and/or OST patients. Concerning subgroups, the average costs per SVR were € 44 348 (currently used DAAs: € 31 535; former treatments: € 51 592) in non-cirrhotic and € 65 732 (currently used DAAs: € 33 078; former treatments: € 76 462) in cirrhotic. Average costs per SVR of € 51 766 (currently used DAAs: € 31 672; former treatments: € 60 540) and € 48 253 (currently used DAAs: € 33 279; former treatments: € 58 872) were calculated for the non-HIV population and HIV-infected and/or OST patients, respectively. The higher pharmaceutical costs and costs per SVR in cirrhotic compared to non-cirrhotic can be primarily attributed to the longer treatment duration [25]. Higher costs in the non-HIV population compared to HIV-infected and/or OST patients are also due to the different genotypes and the associated different treatment regimens and treatment duration, as described above [27, 28]. However, for all subgroups, the costs per SVR are much lower in relation to the DAAs currently used compared to the previous treatments, ranging from € 31 535 to € 33 279.



▶ **Fig. 3** Mental component summary score over time and reference values from German norm population, stratified by cirrhosis status.

Health-related quality of life

Compared to the general population in Germany, all scores in SF-36 subscales showed lower values in HCV-patients. The same applies to an earlier analysis [12]. In terms of cirrhosis status, a greater difference is seen on the PCS (PCS: 44 vs. 49; MCS: 39 vs. 41), whereas in terms of subpopulations, a greater difference is seen on the MCS (PCS: 48 vs. 47; MCS: 37 vs. 41). The higher score of HIV-infected and/or OST patients compared to non-HIV population on the PCS could be due to the fact that this group is younger on average. A younger age is associated with a higher quality of life. Differences between cirrhotic and non-cirrhotic in HRQoL can be explained by the disease itself; liver cirrhosis is associated with a further decline in HRQoL as the stage progresses [32, 33].

Over time, the analysis shows an increase of the PCS and MCS in all subgroups. With the exception of cirrhotic, the PCS in all subgroups reaches at least the value of the general population after 24 weeks, while the MCS is not reached by any subgroup and remains far behind the general population. The low value on the MCS in our sample cannot be confirmed by the literature. Studies on HRQoL in HCV-infected people in other countries show much higher MCS at baseline and after treatment compared to our sample [34, 35].

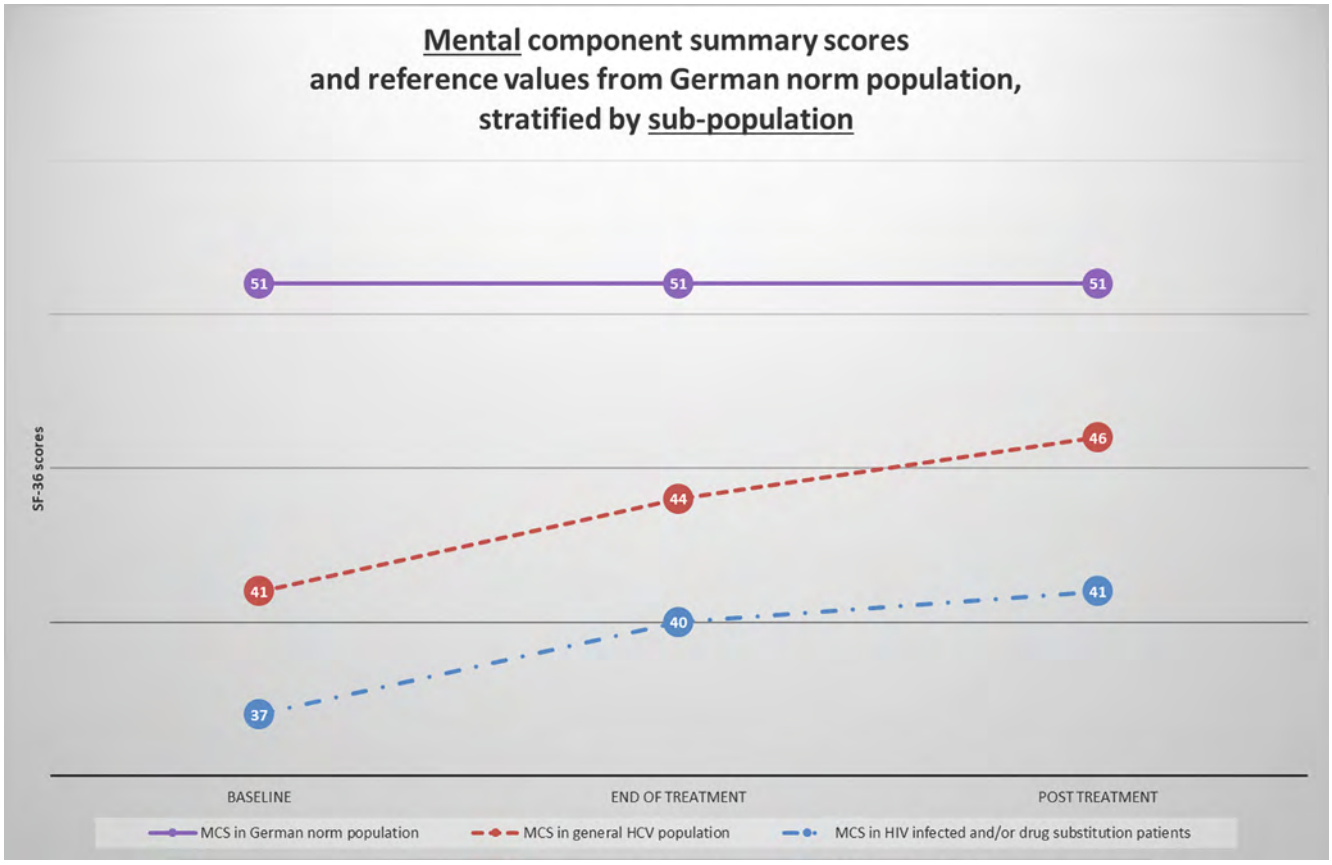
Limitations

The study has some known limitations associated with uncontrolled, observational, retrospective studies. Patients were recruited by the study sites based on their availability and willingness to participate, and thus were not randomly selected for participation, which could lead to response bias. However, due to the large patient sample, a potential bias can be considered low. Another limitation could be that not all data are available for all patients, as the documentation of all treatments and monitoring is at the discretion of the treating physicians. Moreover, the calculation of costs and costs per SVR for the subgroups stratified by treatment regimen could not be calculated exactly, but only approximately.

These limitations are in contrast to several strengths of our study, such as the large patient sample, detailed information on patient characteristics, a quality assurance system for data collection and, particularly, a large number of study centers throughout Germany that reflect routine care in daily practice.

Conclusions

Overall, some relevant factors developed positively in comparison to our previous analysis: SVR-rates slightly increased (2014–2017: 94 %; 2014–2019: 95 %), costs (2014–2017: € 67 131; 2014–2019: € 48 470) and treatment duration (2014–2017: 12.9 weeks; 2014–2019: 12.1 weeks) decreased, especially for currently used



▶ **Fig. 4** Mental component summary score over time and reference values from German norm population, stratified by sub-population.

▶ **Table 6** Post-treatment HRQoL – SVR vs. no SVR.

	No SVR			SVR			p-value	Total		
SF-36 scales	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**		**n**	**Mean**	**SD**
Physical functioning	73	75	25.4	2573	80	23.9	p = 0.079	2646	80	24.0
Role-physical	73	60	42.2	2573	70	38.6	p = 0.030	2646	70	38.8
Bodily pain	73	75	26.5	2573	78	26.5	p = 0.340	2646	78	26.5
General health	73	54	16.6	2573	62	19.3	p ≤ 0.001	2646	61	19.3
Vitality	73	48	19.6	2573	52	20.5	p = 0.100	2646	52	20.4
Social functioning	73	70	23.6	2573	77	23.9	p = 0.014	2646	77	24.0
Role-emotional	73	58	44.4	2573	73	39.8	p = 0.002	2646	72	40.0
Mental health	73	64	18.5	2573	67	18.5	p = 0.172	2646	67	18.5
Sum scores:										
Physical component summary score	73	47	9.5	2573	49	9.2	p = 0.067	2646	49	9.2
Mental component summary score	73	39	13.4	2573	43	13.0	p = 0.010	2646	43	13.0

▶ **Table 7** Post-treatment HRQoL sum scores by patient group.

Patient group	n	Physical component summary score		Diff. to German norm population (Mean 50; SD: 10.3)	Mental component summary score		Diff. to German norm population (Mean 51; SD: 8.2)
		Mean	SD		Mean	SD	
Treatment regimen*							
EBR/GZR	387	48	10.1	2	44	12.7	7
SOF/VEL	110	49	9.0	1	41	13.0	10
G/P	425	51	8.5	−1	43	12.1	8
SOF/VEL/VOX	44	49	9.7	1	44	13.2	7
Overall: Currently used DAA	966	49	9.2	1	43	12.5	8
Overall: Treatments no longer/barely used (as of 02/2022)	1613	49	9.0	1	43	13.1	8
Cirrhosis status							
Non-cirrhotic	1814	50	8.5	0	43	12.9	8
Cirrhotic	765	46	10.0	4	42	13.2	9
Subpopulations							
Non-HIV population	2039	49	9.4	1	44	12.8	7
HIV infected and/or OST patients	540	50	8.3	0	40	13.4	11
Overall	**2579**	**49**	**9.2**	**1**	**43**	**13.0**	**8**

* only currently used DAA regimens are considered individually).

DAAs, and non-severe adverse events occurred less often (2014–2017: 58 %; 2014–2019: 50 %) [12]. In addition, a positive effect of treatment with DAAs on HRQoL was confirmed, but a difference between the general population and HCV-infected still remains after 24 weeks in cirrhotic regarding the PCS and in all subgroups concerning the MCS. However, the strength varies depending on the subgroup and the several items of the SF-36. Further research on HRQoL of DAAs, especially on MCS, is necessary to evaluate the association between subgroups and HRQoL over time and to identify influencing factors.

With respect to the described differences between non-cirrhotic and cirrhotic as well as between non-HIV population and HIV-infected and/or OST patients, further studies are also needed to identify predictors that help to further explain this gap.

Contributors' Statment

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Conflict of Interest

The authors declare that they have no conflict of interest.

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