Limited access to liver transplantation and TIPS despite high mortality, healthcare resource use and costs of cirrhosis in Germany

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Abstract

Background and Aims: Data on number of patients with cirrhosis in Germany are limited. We therefore aimed to estimate prevalence, comorbidities, mortality, utilization of healthcare resources and costs of patients with cirrhosis and incidence of decompen-sation of cirrhosis in Germany.

Methods: This longitudinal observational study was based on an anonymized representative claims database including 4.9 million persons insured by a statutory health insurance (SHI) between 2015–2020. Patients with decompensated and compensated cirrhosis were selected via diagnostic ICD codes and followed for 2 years.

Results: Prevalence of cirrhosis in 2015 was 250/100 000, resulting in 201 747 (95% CI: 197 540–206 040) patients extrapolated to the German population. Out of all patients with compensated cirrhosis in 2015 who did not deceased, 16.0% developed a decompensation within 3 years. Overall, 978 patients (Ø-age: 68 years; 60% male) were included in the decompensated, and 5135 patients (Ø-age: 66 years; 59% male) in the compensated cirrhosis cohort. Patients with decompensated cirrhosis had a...
higher burden of comorbidities (Charlson Comorbidity Index 7.3 vs. 4.4) and 3 times higher costs per quarter (7172 € vs. 2213 €) than patients with compensated cirrhosis. 1-year mortality after decompen- sation was 51% compared to 8% in compensated cirrhosis. Of note, only few patients with decompensated cirrhosis received a liver transplantation or transjugular intrahepatic portosystemic shunts (TIPS) (1% and 5%).

**Conclusion:** Patients with cirrhosis have a high healthcare burden in especially decompensated stage. Accordingly, 1-year mortality of decompensated cirrhosis in Germany is high. Despite high health resource utilization, only few patients have access to liver transplantation or TIPS.

**KEYWORDS**

cirrhosis, healthcare administrative claims, healthcare resource use, liver transplantation, mortality, TIPS

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1 | **INTRODUCTION**

Cirrhosis is the final stage of chronic liver diseases and contributes substantially to morbidity and mortality in worldwide populations. Patients with compensated cirrhosis are usually asymptomatic; thus, the disease is commonly discovered by coincidence, and the prevalence of compensated cirrhosis is often underestimated. Transition to a decompensated stage is defined by the first appearance of ascites, oesophageal variceal bleeding and hepatic encephalopathy. Mortality and morbidity increase tremendously after decomposition, but vary depending on the type and stage of decomposition.

Cirrhosis is one of the leading causes of death in Central Europe. There are limited current data on incidence and prevalence of cirrhosis in Germany. Those data have been derived in a medical-academic environment. Data from the Global Burden of Disease study, based on hospital and claims data, estimated a global prevalence of decompensated cirrhosis in 2017 of 132/100000; for Germany 198/100000. Global prevalence estimates for patients with compensated cirrhosis in 2017 are 1395/100000; and for Germany 1688/100000. In a cohort study in Germany between 1995 and 2004, Zipprich et al calculated a 4-fold higher 1-year mortality for decompensated cirrhosis compared to compensated cirrhosis (20.2% vs. 5.4%).

Of note, many studies on the epidemiology of cirrhosis have no longitudinal data on in- and outpatients. Furthermore, the epidemiology of cirrhosis has been changing in the last decades. Gu et al have demonstrated that there has been a change between 2005 and 2018 in aetiology, with increasing numbers of NASH-associated cirrhosis and declining proportion of HCV-related cirrhosis, and in complications (namely an increase of patients with ascites or infections and a decrease of patients with bleeding) of cirrhosis, which were relatively stable since 2015.

In the present study, we aimed to extend these data by estimating the number of patients with compensated and decompensated cirrhosis in a representative time period for the current situation in Germany directly before the Covid pandemic, from an anonymized German research database. This database comprises longitudinal data from over 4.9 million people, which allowed us to characterize age, gender, comorbidities, mortality, healthcare resource use, and costs in the outpatient situation and during hospitalization of cirrhosis.

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2 | **METHODS**

**2.1 Study design and data source**

This population-based observational cohort study was based on an anonymized German research database. This database comprises longitudinal data from over 4.9 million people insured in one of 70 statutory health insurances (SHI) contributing data to the database, covering about 6% of the German population. The dataset was adjusted by age and sex to match the demographic structure of the German population. Data from a 6-year time period (2015–2020) were available for analysis. Approximately 90% of the German population are enrolled in the SHI system and all sick funds offer comparable services and remuneration levels. Next to demographic data like age and gender, the database contains information on the outpatient and inpatient sector as well as information on drug prescriptions. Diagnoses in the inpatient and outpatient sector are coded according to the German Modification of the International Statistical Classification of Diseases, 10th Revision (ICD-10-GM). Outpatient drug treatments were identified through
relevant Anatomical Therapeutic Chemical Classification (ATC) codes and inpatient treatments through the German adaption of the International Classification of Procedures in Medicine (ICPM). Insured persons could be tracked in the database by an anonymized unique identification number that allowed longitudinal analyses as well as observations across different healthcare sectors. Opt-outs of patients were not possible, and dropouts were only possible because of a change of insurance fund or death. Included claims data were a sample of German insurance providers. Individuals who switched to insurance providers covered in the database or who switched out of insurance providers covered in the database may have experienced interruptions in their observation coverage. Therefore, the analysis included only individuals who maintained continuous insurance coverage from January 1, 2015, to December 31, 2020, within the dataset.

2.2 | Study population

In the first step, insured persons who had at least one outpatient or inpatient main or secondary claim (= coding) with a diagnosis of cirrhosis (ICD-10-GM K70.3, K74.6) in the year 2015 and who were continuously insured between January 1, 2015, and December 31, 2020, were selected. For diagnosis validation, patients who were selected because of a claim with an outpatient or secondary inpatient diagnosis needed to have a second claim in at least another quarter in 2015 with a diagnosis of cirrhosis to be eligible for the prevalent cirrhosis population. Defining prevalent patients via the coding of an outpatient and/or secondary inpatient diagnosis in at least two quarters is a common method used when working with German health claims data (M2Q-criteria) to avoid overestimation of patient numbers because of potential miscodings. In the third step, the prevalent cirrhosis patients in 2015 were separated into patients with (i.e., having at least one claim with at least one of the defined diagnoses listed below) or without decompensation.

Decompensation was defined by the ICD-10-GM codes for ascites (R18), hepatic encephalopathy (K72.7, -71, -72, -73, -74, -79), variceal haemorrhage (I98.3), and hepatorenal syndrome (HRS) (K76.7). Compensated cirrhosis patients who (i) developed a decompensation within the years 2016–2018 were stratified into the group ‘decompensated cirrhosis patients’ or (ii) did not develop a decompensation within the years 2016–2018 were stratified into the group ‘compensated cirrhosis patients’ (see Figure 1). Decompensated cirrhosis patients were followed up for 2 years from their individual index quarter (quarter of the first onset of a decompensation diagnosis within 2016–18); compensated cirrhosis patients were followed up for 2 years from the first quarter in 2016.

2.3 | Subgroups

For subgroup analyses, patients with compensated and decompensated cirrhosis with (a) alcoholic cirrhosis or alcohol abuse in 2015, (b) a transjugular intrahepatic portosystemic shunt (TIPS), (c) who developed liver cancer, or (d) who received a liver transplantation within the follow-up were observed in detail. Patients with compensated or decompensated cirrhosis could be included in more than one subgroup, if they meet more than one of the above-listed criteria. The codes for the selection of the subgroups are given in the Table S1.

![FIGURE 1 Patient flow of patients with compensated and decompensated cirrhosis.](image-url)
2.4 | Analysis

Since the database used is representative of the German population prevalence and incidence, estimates could be extrapolated to the German population in 2015 using Wilson confidence intervals (CIs). We used the Charlson Comorbidity Index (CCI), which is a weighted index to predict risk of death within 1 year for patients with 19 specific comorbidities. Each condition is assigned to a weight from 1 to 6, based on the estimated 1-year mortality.8

Overall mortality was assessed as the number of patients who died measured from the onset of the first diagnosis of decompensation or, in the case of the compensated cirrhosis patients from the first quarter in 2016. Mortality from patients with cirrhosis is presented as absolute and relative frequencies. Deceased patients are clearly identifiable in the database by the reason of leaving the SHI ‘death’, but without information available about the cause of death.

In the analysis of healthcare resource use, we analysed the number of hospitalizations and physician visits, which are shown as average values. Costs were adjusted by the time patients were observable in the follow-up period to avoid bias because of different observation lengths in patients who died or were alive. Per-patient costs were calculated per insurance day and expressed as costs per quarter in Euros from the perspective of the statutory health insurance funds. Categorical variables were compared using either Chi-square test or Fisher’s exact test (when at least one expected value in a cell was <5).

As the number of deceased patients within the decompensated and compensated cirrhosis patients highly differ, only patients who are still alive ‘(at risk)’ at the end of the 2 years of follow-up period and thus, observable for 2 years, were considered in the analysis of healthcare resource use (but not of costs).

2.5 | Ethics statement

Since the work is based on anonymized secondary data, there was no consultation with an ethics committee. This is in accordance with the recommendations of the Guideline of Good Practice of Secondary Data Analysis.9

3 | RESULTS

3.1 | Study population

The database comprised 4827449 insured persons, of whom 3680973 were continuously observable between 01.01.2015 and 31.12.2020. Of those, 10771 had at least one claim with a secured outpatient or inpatient main or secondary diagnosis of cirrhosis in 2015. After diagnosis validation (MQ-criteria), 2146 patients who did not meet the criterion of a second claim were excluded. The prevalent cirrhosis cohort in 2015 thus included 8625 patients (see Figure 2). Of these, 2213 patients had a decompensation diagnosis in 2015 and 6412 did not (= patients with compensation). 16.0% (n = 978) of the patients with compensated cirrhosis in 2015 who did not deceased in 2015 (n = 6113) developed a decompensation within the next 3 years (2016–18), 84.0% (n = 5135) did not. The analysis of healthcare resource use (but not of costs, see methods) refers to patients who were alive ‘(at risk)’ throughout the entire observation period (n = 385 decompensated cirrhosis patients and n = 4431 compensated cirrhosis patients).

The number of patients in the subgroups is shown in Figure 3. 56% of patients with decompensation and 42% without had a diagnosis of alcoholic cirrhosis in 2015. Every fifth patient with decompensation received compensation for liver cancer, in contrary to 4% with compensation during the follow-up period. 5% and 1% of patients with compensation received TIPS or liver transplantation in the follow-up period respectively. As a result of the small number of patients (<5), subgroups 3 and 4 of patients with compensated cirrhosis receiving a TIPS (subgroup 3), these patients are not included in analysis of healthcare resource use and costs.

3.2 | Prevalence and incidence of decompensation

Out of 3513141 patients in 2015, we identified 8625 patients with cirrhosis. The 12-month prevalence of cirrhosis in the database in 2015 was 0.25% (250/100000). The extrapolation to the German population resulted in 201747 (95% CI: 197540–206040) prevalent patients with cirrhosis. We identified 2213 patients (25.7%) with decompensation in 2015, which, extrapolated to the German population, results in a prevalent number of 17645 (95% CI: 17130–18159) patients with decompensated cirrhosis. We identified 6412 patients (74.3%) with compensated cirrhosis in 2015, which, extrapolated to the German population, results in a prevalence of 149983 (95% CI: 146360–153700) patients with compensated cirrhosis.

We identified 978 patients who developed a decompensation in 2016–2018, which, extrapolated to the German population, results to a 3-year incidence of 22876 (95% CI: 21490–24360) cases of decompensation.

3.3 | Patient characteristics and mortality

With an average age of 68 years (SD: 11 years), patients with decompensated cirrhosis were 2 years older than patients with compensated cirrhosis (66 years; SD: 12 years). 66% of decompensated cirrhosis patients were 65 years or older compared to 57% of compensated cirrhosis patients. The proportion of male patients is higher than that of female patients in both the decompensated (59.9%) and compensated cirrhosis groups (58.6%).

In subgroups analysis, patients with liver transplantations were the youngest (average age of 47 years (SD: 18) in decompensated and of 54 years (SD: 21) in compensated cirrhosis patients), while patients with liver cancer had the highest average age (with decompensation: 70 years (SD: 10) with compensation: 69 years (SD: 9) compared to the other subgroups.
The CCI after 2 years was 2.9 points higher in patients with decompensated cirrhosis (7.3 vs. 4.4) than in patients with compensated cirrhosis. Patients with liver cancer had the highest CCI compared to the other subgroups (decompensated: 9.2; compensated 7.5).

Within 1 year, 51% of decompensated and 8% of compensated cirrhosis patients died, within 2 years 61% and 14% respectively. The highest mortality rate after 1 year had patients with liver cancer in both groups (decompensated: 67.7%; compensated 23.7%), the same...
as within 2 years (76% vs. 38%). Patients with liver cancer die on average 1 month earlier than patients in the main group (mean decompensated: 6 vs. 7 months; mean compensated: 12 vs. 13 months).

The characteristics of patients with compensated and decompensated cirrhosis are shown in Table 1.

3.4 | Healthcare resource use

92% of patients with decompensated cirrhosis and 49% of patients with compensated cirrhosis had at least 1 hospitalization within 2 years and an average of 5 (decompensated) and 2 (compensated) hospital stays. Patients with decompensated cirrhosis were hospitalized on average 2 days longer than patients with compensated cirrhosis (11.2 vs. 9.7 days). We found that 11.3% of patients in the compensated group received aldosterone antagonists, 7.7% received furosemide, and 35.7% received beta blockers.

Patients with decompensated cirrhosis receiving TIPS or liver transplantation are on average almost twice as often hospitalized than patients in the main group (mean TIPS: 8.1 hospital stays; liver transplantation: 8.4 hospital stays vs. 4.6 hospital stays in the main group). Patients with decompensated cirrhosis receiving liver transplantation were hospitalized within 2 years with an average length of stay of 19 days (SD: 29) per hospitalization. Thereof, 25% of hospitalizations were directly related to the transplant procedure itself. These transplant-related hospitalizations had an average length of stay of 47 days. In contrast, the remaining 75% of hospitalizations, not directly attributed to the transplant procedure, had an average length of stay of 9 days. Patients with decompensated alcoholic cirrhosis had an average length of stay of 11 days (SD: 13) per hospitalization. Patients with decompensated cirrhosis had an average of 11 more physician visits within a year than patients with compensated cirrhosis (46 times (SD: 36) vs. 35 times (SD: 31)), with the general practitioner and internist being the most frequently visited specialists (see Figure 4). Patients with decompensated cirrhosis with liver transplantation had the highest number of physician visits within 1 year (59 times (SD: 29)).

3.5 | Costs

A patient with decompensated cirrhosis causes on average three times higher costs per quarter than a patient with compensated cirrhosis (7172 € vs. 2213 €; see Figure 5A). 73% of total costs of patients with decompensated cirrhosis occur for inpatient treatment, 8% in the outpatient sector, and 13% for medication. Costs of patients with compensated cirrhosis were less in the inpatient sector (46% vs. 73%), but more in the outpatient sector (15% vs. 8%), as well as more for medication (29% vs. 13%) and remedies and aids (9% vs. 5%; see Figure 5B).

Patients with decompensated cirrhosis who required liver transplantation had the highest costs per quarter (22797 €), followed by patients who required TIPS (9958 €) and patients who suffered from liver cancer (8393 €).

4 | DISCUSSION

In the present analysis of 4.9 million SHI-insured patients, we calculated a prevalence of cirrhosis in 2015 of 0.25% (250/100 000), resulting in 201 747 (95% CI: 197 540–206 040) patients extrapolated to the German population. 16.0% of patients with compensated cirrhosis developed a decompensation within 3 years. With an average age of 68 years, patients with decompensated cirrhosis were 2 years older than patients with compensated cirrhosis (66 years). Within 1 year, 51% and 8% of patients with decompensated and compensated cirrhosis died respectively. The highest 1-year mortality rates were observed in patients with liver cancer

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with compensated cirrhosis</td>
<td>Patients with decompensated cirrhosis</td>
</tr>
<tr>
<td>Number of patients</td>
<td>5135</td>
</tr>
<tr>
<td>Mean age in years at diagnosis (standard deviation)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59%</td>
</tr>
<tr>
<td>Female</td>
<td>41%</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (CCI) within 1 year (SD)</td>
<td>4.4 (3)</td>
</tr>
<tr>
<td>Mortality within 12/24 months (after decompensation)</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>8%</td>
</tr>
<tr>
<td>24 months</td>
<td>14%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unpaired t test.
<sup>b</sup>Chi-square test.
**FIGURE 4** Mean doctor visits per specialist within 1 year.

**FIGURE 5** (A) Total costs per patient and quarter (B) stratified by cost sector.
Patients with decompensated cirrhosis showed a higher resource use and costs compared to patients with compensated cirrhosis (at least 1 hospitalization within 2 years: 92% vs. 49%; hospital stays: 5 vs. 2; costs per quarter: 7172 € vs. 2213 €). Of note, very few patients with decompensated cirrhosis received a liver transplantation or TIPS.

Our estimated 1-year prevalence of cirrhosis of 0.25% is lower compared to estimates published so far. Gu et al.\(^2\) analysed data from the German Federal Statistical Office on all hospital admissions in Germany between 2005 and 2018 and reported a prevalence of cirrhosis (ICD-10 codes K74 or K70.3) of 0.94% in 2018, occurred in most cases as a comorbidity and not the primary disease. Differences in prevalence are also apparent in international comparisons. A cohort study from Cammarota et al.\(^10\) from 2016 with health insurance claims data of insured patients in Italy reported a prevalence of cirrhosis of 0.45%. The recent worldwide Global Burden of Diseases, Injuries, and Risk Factors Study has estimated prevalent 10.6 million cases of compensated cirrhosis and 112 million prevalent cases of compensated cirrhosis worldwide, which cause 2.4% of total deaths in 2017. In this study, a number of 244,706 prevalent cases of decompensated cirrhosis was estimated for Germany in 2017.\(^2\) Differences can be mainly explained by the different methodology of the studies, as we used strict inclusion criteria to not overestimate the number of cirrhosis patients (e.g., exclusion of patients with liver fibrosis/sclerosis). Furthermore, we identified 56% of patients with decompensation and 42% without a diagnosis of alcoholic cirrhosis in 2015. This is in line with previous analyses: Gu et al. reported that 52% of admissions between 2005 and 2018 were because of alcohol-related cirrhosis, and the number of admissions with alcohol-related cirrhosis represented the vast majority of causes of cirrhosis among all hospitalizations.

The observed risk of decompensation of 15.3% within 3 years in patients with compensated cirrhosis in our study fits relatively well with previously published data.\(^4,5,12\) We found that 11.3% of patients in the compensated group received aldosterone antagonists, 7.7% received furosemide, and 35.7% received beta blockers. These findings might suggest that a subset of patients in the compensated group might have had ascites previously and experienced a positive response to therapy and ongoing management of their condition. However, if the initial indication for giving aldosterone was because of decompensation, that is clinically detectable ascites, is not clear and can only be speculated.

Yet, we have observed high 1-year mortality of 51% and 8% in patients with decompensated and compensated cirrhosis, which is higher compared to several other studies. For example, Zipprich et al.\(^13\) calculated in their cohort study in Germany between 1995–2004 a 1-year mortality of 20.2% for decompensated and 5.4% for compensated cirrhosis patients. Differences in Zipprich et al. include the younger study population as well as study methodology, as clinical studies and RCTs have stricter inclusion criteria and, for example, exclude patients with certain comorbidities.\(^14\) In addition, our study is more actual. Gu et al. demonstrated a change in the demography and standard of care between 2005 and 2018, which were more stable beginning in 2015. Therefore, the data presented in the present study add necessary insight for the current situation on individual patients’ basis and in a longitudinal manner. Cammarota et al.\(^10\) reported a 1-year mortality of cirrhosis patients with hepatic encephalopathy of 40.0% and higher mortality rates in decompensated patients with cirrhosis and ascites (45.7%), which indicates that the presence and type of complications are predictors of 1-year mortality. More in general, decompensated cirrhosis comprises a broad spectrum of clinical states (such as bleeding complications alone, non-bleeding complications, multiple decompensation events, organ failures)\(^14\) or syndromes (acute decompensation, acute-on-chronic liver failure),\(^15,16\) which differ significantly with respect to short- and intermediate-term mortality rates.

It is important to consider the possibility that patients diagnosed with decompensation before 2015 experienced improvements in ascites symptoms during the study period, potentially leading to a lower percentage of decompensated cases in our dataset. This treatment effect should be taken into account when interpreting our findings and assessing the impact on mortality in the decompensated group.

Importantly, very few patients with decompensated cirrhosis in our cohort received a TIPS or liver transplantation. Although we can only speculate about the underlying reasons, this finding is concerning since both TIPS and liver transplantation are measures which can substantially improve survival in appropriately selected patients and are recommended in our national and international guidelines.\(^17–20\) Although the high average age and comorbidity burden suggest that numerous patients with cirrhosis have contraindications to TIPS and liver transplantation, it appears plausible that the access/referral of patients to referral centres with expertise in TIPS and liver transplantation might be suboptimal. In our study, we observed that decompensated cirrhotic patients who required liver transplantation and TIPS were hospitalized almost twice as often as patients in the main group. Although healthcare resource usage of patients with liver transplantation and TIPS was higher because of the severity of disease and procedure, it should be considered, that these patients also have a higher chance of survival because of the therapy.\(^21\) Ballester et al.\(^22\) did a retrospective chart review including records of 104 patients with TIPS. They found less emergency department visits and hospitalizations after TIPS. Therefore, it can be assumed that TIPS, but also liver transplantation, could lead to a reduction of costs in the future and even enable some patients to return to a working life.

Approximate 3/4 of the costs in decompensated patients occur in the inpatient sector (73%), followed by costs for medication (13%). A similar distribution of costs was found in the study by Cammarota et al.\(^10\) in which the inpatient sector also accounted for most costs in patients with decompensated cirrhosis (85%), as well as 13% for costs for medication. These findings are important, since for example recent results of a randomized controlled trial showed that the use of long-term human albumin reduced mortality in outpatients with ascites,\(^23\) a treatment which is considered...
as rather expensive. Yet, our results suggest that outpatient treatment modalities, which may reduce hospitalization frequencies, could help reducing costs of care in cirrhosis patients. Cost-effective management could also include using albumin infusion in patients with large-volume paracentesis, spontaneous bacterial peritonitis and for patients with hepatorenal syndrome as previous studies suggest.  

Patients had around one visit to gastroenterologists in our study. In the German healthcare setting, it is common for many gastroenterologists to have a specialization in internal medicine along with additional training and specialization in gastroenterology. However, in the database we used for our study, the designation of physicians is based solely on their specialist training without specific information about their additional specializations or subspecialty training. As a result, gastroenterologists who have dual specialization in internal medicine and gastroenterology might be categorized solely under ‘internal medicine’ or general practitioners in the database, leading to a potential underrepresentation of the number of visits specifically to gastroenterologists. Also, patients living in rural areas were included in the analysis, which might not have access to gastroenterologists and were treated by general practitioners.

Our study has several strengths and limitations. Based on a population-representative database, we were able to estimate incidence and prevalence of compensated and decompensated cirrhosis for Germany. Since the database consists of data from patients with statutory health insurance, patients of private health insurance companies (around 10% of the German population) were not included in the present study. Also, individuals without continuous enrollment into the insurances covered in the database had to be excluded. This may introduce some degree of selection bias and affect the generalizability of the findings to the entire population of cirrhosis patients in Germany. Another limitation is that some of the descriptive analyses in the subgroups were based on very small numbers of patients (e.g., patients with liver transplantation). Decompensated cirrhosis patients were followed-up for 2 years from the onset of their first decompensation diagnosis between 2016 and 2018. The outcomes in the second follow-up year of patients with first decompensation in the second half of 2018 could be potentially affected by COVID. However, as only 108 of 978 decompensated cirrhosis patients had their first decompensation diagnosis in the second half of 2018, we estimate the effect to be low. Our analysis for resource use (but not of costs) is based on patients who are still alive at the end of the 2-year follow-up period. The costs and healthcare resource use of deceased patients were not considered, although we assume that these patients incurred high costs before their death.

5 | CONCLUSION

In summary, this study demonstrates high mortality of patients with cirrhosis in Germany, particularly in patients with decompensation. Despite high health resource utilization, only few patients had access to liver transplantation or TIPS. In the future, the development of new treatment approaches and better implementation of existing treatment modalities that prevent decompensation or reduce mortality are required.

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

Christian M. Lange has received advisory and speaker’s honoraria from AbbVie, AstraZeneca, Boston Scientific, CSL Behring, Eisai, Falk, Gilead, MSD, Norgine, Novartis, Roche, Shionogi, and Sobhi. Jonel Trebicka has received speaking and/or consulting fees from Versantis, Gore, Boehringer-Ingelheim, Falk, Grifols, Genfit and CSL Behring. Alexander Gerbes did advisory activities and received honoraria for presentations from CSL Behring, Falk Foundation, Gore and Grifols. Ali Canbay received advisory and speaker honoraria from AbbVie, CSL Behring, Eisai, Falk, Gilead, Shionogi, Sobhi, Merz, Sanofi, and Takeda. Andreas Geier has received advisory and speaker honoraria from AbbVie, Alexion, AstraZeneca, Bayer, BMS, Burgerstein, CSL Behring, Eisai, Falk, Gilead, Heel, Intercept, Ipsen, Merck, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, and Sequana; he also obtained research support from Intercept, Falk (both NAFLD CSG), Novartis. Uta Merle has received advisory and speaker honoraria (paid to either her or her institution) from CSL Behring, Falk Foundation, Gilead, Microbiota, MSD and Takeda. Markus Peck-Radosavljevic received honoraria as speaker or advisor from AbbVie, AstraZeneca, Bayer Healthcare, Bristol-Myers Squibb, CSL Behring, Eisai, Eli Lilly, Gilead, Intercept, Ipsen, Merck-Sharpe-Dohme, Roche, Sanofi-Aventis, Shionogi and Sobhi. Frank Tacke’s lab has received research funding at Charité – Universitätsmedizin Berlin from Allergan, Bristol Myers Squibb, Gilead and Inventiva. He acted as a consultant for AstraZeneca, Allergan, Bayer, Boehringer Ingelheim, CSL Behring, Galapagos, Gilead, Intercept, Inventiva, Madrigal, Novartis, Novo Nordisk and Pfizer. Tobias Vogelmann is owner and employee, and Sina Theis is an employee of LinkCare GmbH; which received consulting honoraria from CSL Behring, Alynlam, Accuray, Therakos, Terumo and Sirtex. Hartmut Heinze is employee of CSL Behring. Alexander Zipprich has received advisory board and speaker honoraria from CSL Behring, Falk, Gore, and Grifols.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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