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**UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE**
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# Trends in the burden of hospitalized patients with cirrhosis in Switzerland: a cross-sectional study of cirrhosis-related hospitalizations between 1998 and 2020

THESE

préparée sous la direction du Professeur Pedro Manuel Marques-Vidal
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(avec la collaboration du Professeur Darius Moradpour)

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DOCTEUR EN MEDECINE

par

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**Trends in the burden of hospitalized patients with cirrhosis in Switzerland: a cross-sectional study of cirrhosis-related hospitalizations between 1998 and 2020**

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## Résumé

**Introduction** : La cirrhose hépatique est une cause croissante de morbidité et de mortalité dans le monde, exerçant une lourde charge sur les systèmes de santé. De multiples données montrent un changement des étiologies de cirrhoses des hépatites virales aux étiologies alcooliques et métaboliques en Europe et aux Etats-Unis. Nous avons analysé les tendances des hospitalisations liées à la cirrhose en Suisse de 1998 à 2020.

**Méthode** : Utilisant une grande base de données hospitalière nationale, nous avons sélectionné les hospitalisations pour cirrhose chez les patients adultes de 1998 à 2020. Les hospitalisations avec un diagnostic principal de cirrhose ou un diagnostic principal lié à la cirrhose avec la présence obligatoire de la cirrhose en tant que diagnostic secondaire ont été considérées. Les caractéristiques démographiques et cliniques, la mortalité hospitalière et la durée de séjour ont été analysées. Les étiologies de cirrhose, les comorbidités et les coûts des hospitalisations étaient disponibles pour les années 2012 à 2020.

**Résultats** : Les hospitalisations liées à la cirrhose sont passées de 1'631 en 1998 à 4'052 en 2020. Parmi les patients, 68.7% étaient des hommes. L'alcool était la principale étiologie de cirrhose, passant de 44.1% (IC 95%, 42.4-45.9%) en 2012 à 47.9% (IC 95%, 46.4-49.5%) en 2020. Utilisant un diagnostic d'exclusion, la stéatose hépatique non alcoolique était la seconde étiologie de cirrhose avec 42.7% (IC 95%, 41.2-44.3%) des hospitalisations en 2020. Les cirrhoses liées à l'hépatite C ont diminué de 12.3% (IC 95%, 11.2-13.5%) en 2012 à 3.2% (IC 95%, 2.7-3.8%) en 2020. La durée médiane de séjour a diminué de 11 à 8 jours. Les hospitalisations avec un séjour en unité de soins intensifs ont augmenté de 9.8% (IC 95%, 8.4-11.4%) à 15.6% (IC 95%, 14.5-16.8%). La mortalité hospitalière a diminué de 12.1% (IC 95%, 10.5-13.8%) à 9.7% (IC 95%, 8.8-10.7%). Les coûts totaux sont passés de plus 49.9 millions CHF en 2012 à 85.0 millions CHF en 2020.

**Conclusion** : Les hospitalisations liées à la cirrhose et les coûts associés ont augmenté en Suisse de 1998 à 2020, mais la mortalité hospitalière a diminué. L'alcool et la stéatose hépatique non alcoolique étaient les étiologies les plus courantes et évitables des hospitalisations liées à la cirrhose.

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## ABSTRACT

**Objective** Liver cirrhosis is an increasing cause of morbidity and mortality worldwide with a heavy load on healthcare systems. We analysed the trends in hospitalisations for cirrhosis in Switzerland.

**Design** Cross-sectional study.

**Setting** Large nationwide inpatient database, years between 1998 and 2020.

**Participants** Hospitalisations for cirrhosis of adult patients were selected.

**Main outcomes and measures** Hospitalisations with either a primary diagnosis of cirrhosis or a cirrhosis-related primary diagnosis with a mandatory presence of cirrhosis as a secondary diagnosis were considered following the 10th revision of the International Statistical Classification of Diseases and Related Health Problems codes. Trends in demographic and clinical characteristics, in-hospital mortality and length of stay were analysed. Causes and costs of cirrhosis-related hospitalisations were available from 2012 onwards.

**Results** Cirrhosis-related hospitalisations increased from 1631 in 1998 to 4052 in 2020. Of the patients, 68.7% were men. Alcohol-related liver disease was the leading cause, increasing from 44.1% (95% CI, 42.4% to 45.9%) in 2012 to 47.9% (95% CI, 46.4% to 49.5%) in 2020. Assessed by exclusion of other coded causes, non-alcoholic fatty liver disease was the second cause at 42.7% (95% CI, 41.2% to 44.3%) in 2020. Hepatitis C virus-related cirrhosis decreased from 12.3% (95% CI, 11.2% to 13.5%) in 2012 to 3.2% (95% CI, 2.7% to 3.8%) in 2020. Median length of stay decreased from 11 to 8 days. Hospitalisations with an intensive care unit stay increased from 9.8% (95% CI, 8.4% to 11.4%) to 15.6% (95% CI, 14.5% to 16.8%). In-hospital mortality decreased from 12.1% (95% CI, 10.5% to 13.8%) to 9.7% (95% CI, 8.8% to 10.7%). Total costs increased from 54.4 million US$ (51.4 million €) in 2012 to 92.6 million US$ (87.5 million €) in 2020.

**Conclusions** Cirrhosis-related hospitalisations and related costs increased in Switzerland from 1998 to 2020 but in-hospital mortality decreased. Alcohol-related liver disease and non-alcoholic fatty liver disease were the most prevalent and preventable aetiologies of cirrhosis-related hospitalisations.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The national database used for this cross-sectional study contains a large sample of hospitalisations for cirrhosis on a prolonged period of >20 years.
⇒ We used reliable demographic data and 10th revision of the International Statistical Classification of Diseases and Related Health Problems codes for definition of cirrhosis which have been showed to be accurate.
⇒ Because of missing data and quality of documentation of diagnoses, we were only able to analyse aetiologies of cirrhosis, complications and comorbidities for the years 2012–2020.
⇒ Cirrhosis linked to non-alcoholic fatty liver disease had to be determined after exclusion of other coded aetiologies which could have caused overdiagnosis because of missing data.
⇒ Due to the anonymised database, rehospitalisation rate could not be ascertained, and total costs were only available for part of the hospitalisations from 2012 to 2020.

## BACKGROUND

Chronic liver disease (CLD), especially cirrhosis, is an increasing cause of morbidity and mortality, responsible for 2.4% of all deaths in 2017, compared with 1.9% in 1990.[1] The ageing of the population has an important effect, considering that age-standardised mortality decreased by 22% between 1980 and 2010,[2] but the increase in prevalence of obesity and diabetes additionally contributes to the growing burden of CLD.[3] Multiple data show a shift in the aetiologies of cirrhosis from viral hepatitis to alcohol-related liver disease (ARLD) and non-alcoholic fatty liver disease (NALFD), especially in Western Europe, the USA and Australia.[1 3–9] In 2010, ARLD was the major cause of cirrhosis-related mortality and disability adjusted life years (DALYs) globally.[10] CLD and cirrhosis are also major causes of hospital admission and

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of increase in healthcare costs.[11–14] Hirode *et al* reported that CLD was responsible of over 80 billion US$ in hospitalisation costs in the USA between 2012 and 2016.[15] During the same study period, there was an increase of over 20% in CLD-related hospitalisation and of 26% in inpatient hospitalisation costs. Another study also showed a growing economic burden of CLD between 1996 and 2016, namely due to inpatients costs.[16] Moreover, CLD patients have an increasing number of comorbidities adding to the complexity of their management.[9]

The HEPAHEALTH Project guided by the European Association for the Study of the Liver concluded that in Switzerland, the age-standardised prevalence of cirrhosis was over 600 per 100 000, with an age-standardised mortality for liver disease of approximately 10 per 100 000 in 2016.[17] However, the trends of hospitalisations for cirrhosis in Switzerland are not well known. Projections for Switzerland estimated that by 2030, the prevalence of NAFLD would increase to 24.3% of the population, with an expected increase in secondary cirrhosis and liver-related mortality.[18] These estimations are in line with those established for Australia and Canada,[19 20] and predict a major economic burden on the healthcare system.[21] Therefore, understanding the trends of hospitalisations for cirrhosis in Switzerland is important to determine the current load on the inpatient system and to anticipate further impacts on the health system.

This study aimed to (1) analyse the trends in hospitalisations for cirrhosis in Switzerland between 1998 and 2020 and (2) assess the evolution of comorbidities, in-hospital mortality, length of stay (LOS) and related costs.

## METHODS

### Data source

We conducted a cross-sectional study of all hospitalisations for cirrhosis in Switzerland between 1998 and 2020 using data from the Swiss Hospital Statistics of the Swiss Federal Office of Statistics (https://www.bfs.admin.ch) which covers 98% of public and private hospitals. The database contains deidentified information regarding hospitalisations with demographic characteristics, diagnosis and comorbidity codes following the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) definition, LOS, procedures, outcomes such as intensive care unit (ICU) stay and discharge status, as well as total costs.

### Inclusion and exclusion criteria

To identify cirrhosis-related hospitalisations, we selected individuals, aged ≥20 years, with either a primary diagnosis of cirrhosis or a cirrhosis-related primary diagnosis with a mandatory presence of cirrhosis as a secondary diagnosis (online supplemental etable 1). Hospitalisations for a non-cirrhosis-related condition with a secondary diagnosis of cirrhosis were excluded. Because only age groups of 5 years were available in the original database, patients aged 15–19 years were also excluded.

### Definition of cirrhosis and of its complications

The diagnoses following the ICD-10 codes are used in Switzerland to determine hospital costs for billing purpose since the year 2012 with the introduction of diagnosis-related groups (DRG). Therefore, we analysed aetiologies and complications of cirrhosis only for the period 2012–2020, as documentation of comorbidities was lacking in the database up to that year. Patients could have multiple diagnoses and aetiologies of cirrhosis during the same hospitalisation, as reported in Hirode *et al*.[15]

Aetiologies of cirrhosis were described as hepatitis B virus (HBV), hepatitis C virus (HCV), ARLD, NAFLD and non-alcoholic steatohepatitis (NASH) using ICD-10 codes (online supplemental etable 2). Defining the metabolic cause of cirrhosis was difficult because there is no specific ICD-10 code for NAFLD and one specific code for NASH. Therefore, we elected to separately analyse the NASH aetiology defined by a reliable ICD-10 code and the NAFLD aetiology for which we opted for an exclusion method. The method was as follows: (1) excluding all patients with HBV, HCV, ARLD and NASH; (2) excluding other aetiologies of cirrhosis or CLD (online supplemental etable 2).

Complications of cirrhosis were defined by ICD-10 codes for ascites, spontaneous bacterial peritonitis, oesophageal or gastric varices with or without bleeding, hepatic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma (HCC) and portal vein thrombosis (online supplemental etable 3).

### Other variables

Gender, age group and geographical location were extracted from the database. For geographical location, seven administrative regions (Lake Geneva, Mittelland, Northwest, Zurich, Eastern, Central, Ticino) were defined, and cirrhosis-related hospitalisations rate per 100 000 inhabitants of each region were computed using demographical data from the Swiss Federal Office of Statistics for the years 1999–2020 as available.

The following comorbidities were considered from 2012 to 2020: coronary artery disease, congestive heart failure, chronic kidney disease, diabetes and stroke (online supplemental etable 4).

LOS in days was obtained following the Swiss and the Organization for Economic Co-operation and Development (OECD) categorisation. LOS was defined from the day of admission until discharge and was only impacted by transfers between institutions but not by transfers between different departments inside the same hospital.

In-hospital costs were extracted from the database but only available from the year 2012 onwards. Total costs were expressed in Swiss francs (CHF), with 1 CHF=1.09 US$ = 1.03 € (as of 29 September 2023).

### Statistical analysis

Statistical analyses were performed using Stata V.16.0 for windows (Stata Corp, College Station, Texas, USA). Categorical variables were expressed as number (%) and continuous variables were expressed as average±SD



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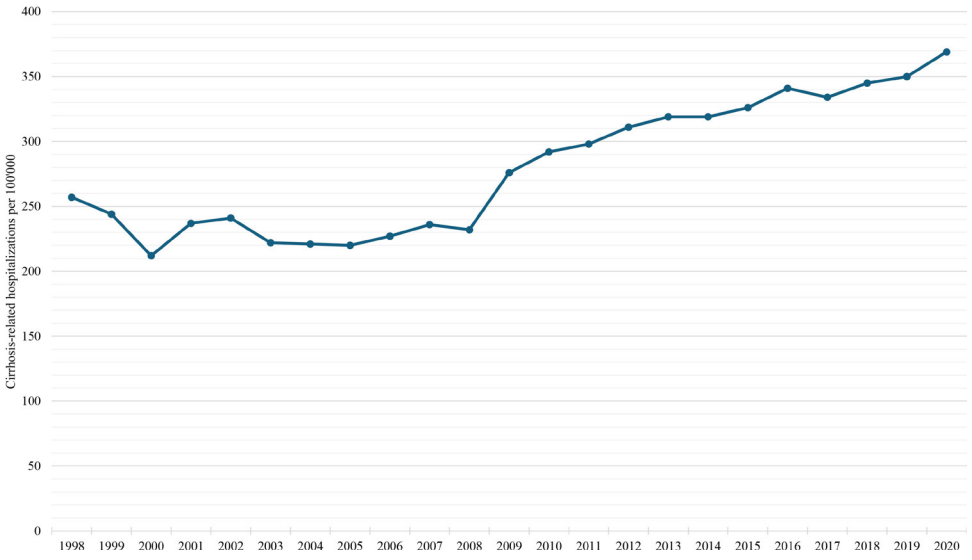


**Figure 1** Evolution of cirrhosis-related hospitalisations per 100 000 hospitalisations between 1998 and 2020.

or as median (IQR). Trends were assessed using Poisson regression for categorical variables and linear regression for continuous variables. Due to the skewed distribution of LOS, they were log-transformed prior to analysis. As a cross-sectional study describing real data without a prespecified key hypothesis, no correction for multiple testing was applied, and statistical significance was assessed for a two-sided test with p<0.05.

### Patient and public involvement

No patient involved.

## RESULTS

### Study population

Of the 24 780 982 hospitalisations occurring in Switzerland between 1998 and 2020, 69 487 (0.28%) were related to cirrhosis. Of those, 43 850 (63.1%) had a primary diagnosis of cirrhosis, and 25 637 (36.9%) had a cirrhosis-related diagnosis as primary diagnosis (online supplemental efigure 1). Among the cirrhosis-related hospitalisations, 68.7% were men, 77.1% were Swiss and the largest age groups were 45–64 years old. The median LOS was 10 (5–17) days as per the OECD categorisation; 13.9% of hospitalisations comprised an ICU stay, and in-hospital mortality was 11.4%.

### Trends of cirrhosis-related hospitalisations

The yearly number of cirrhosis-related hospitalisations more than doubled from 1631 in 1998 to 4052 in 2020; expressed as rate per 100 000 hospitalisations, the increase was smaller, from 257 to 369 per 100 000, a 44% increase (figure 1).

Table 1 (and online supplemental etable 5) shows the trends of cirrhosis-related hospitalisations from 1998 to 2020 according to age categories, sex, origin, LOS, ICU stay and in-hospital mortality. Age category 45–64 years was the most frequent but decreased from 57.1% in 1998 to 47.2% in 2020, while the proportion of age category 65–84 years increased from 28.3% to 43.9% in the same period (*P* for trend <0.001). Men represented 2 out of 3 hospitalisations, and Swiss nationals represented over 75% of hospitalisations. These proportions remained stable during the study period.

The Lake Geneva region had the highest proportion of cirrhosis-related hospitalisations, but it decreased from 38.9% in 1998 to 25.2% in 2020 (*P* for trend <0.001). The hospitalisation rate per 100 000 inhabitants increased in all regions except in Lake Geneva. Comparison of the hospitalisation rates by regions showed higher rates in the Italian (Ticino) and French (Lake Geneva)-speaking parts of Switzerland (figure 2 and online supplemental etable 6).

The median LOS decreased from 11 days in 1998 to 8 days in 2020, while the proportion of hospitalisations with an ICU stay increased from 9.8% to 15.6% (both *P* for trend <0.001).

Table 2 shows the trends in causes of cirrhosis between 2012 and 2020 (online supplemental efigure 2). ARLD was the leading and increasing cause of cirrhosis, from 44.1% in 2012 to 47.9% in 2020 (*P* for trend <0.001). NAFLD was the second cause of cirrhosis at 42.7% in 2020 without a significant trend from 2012 to 2020. HCV was the third cause of cirrhosis and decreased from 12.3% to 3.2% in 2020 (*P* for trend <0.001). NASH documentation increased from 1.2% in 2012 to 4.2% in 2020 (*P* for trend <0.001). HBV-related cirrhosis decreased from 3.4% to 2.2% in 2020 (*P* for trend 0.001). Other aetiologies of cirrhosis (online supplemental etable 2) accounted for a low proportion of hospitalisations, representing 3.5% at the end of our study period, and without any notable trend.

Cirrhosis-related complications were reported in 56.9% of cirrhosis-related hospitalisations in 2012 and increased to 61.4% in 2020 (*P* for trend 0.008). Cirrhosis-related hospitalisations with a diagnosis of HCC increased from 24.4% in 2012 to 27.9% in 2020 (*P* for trend<0.001). As



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**Table 1** Trends of cirrhosis-related hospitalisations between 1998 and 2020 (summary table)

| | Total | 1998 | 2000 | 2002 | 2004 | 2006 | 2008 |
|---|---|---|---|---|---|---|---|
| Sample size (hospitalisations), No | 24 780 982 | 634 606 | 925 310 | 1 062 452 | 1 112 012 | 1 194 584 | 1 270 763 |
| Cirrhosis-related hospitalisations per 100 000 (95% CI) | 280 (278 to 282) | 257 (245 to 270) | 212 (203 to 222) | 241 (232 to 250) | 221 (212 to 229) | 227 (218 to 235) | 232 (223 to 240) |
| Cirrhosis-related hospitalisations, No | 69 487 | 1631 | 1961 | 2560 | 2453 | 2708 | 2943 |
| Age in years, % (95% CI) | | | | | | | |
| <25 | 0.2 (0.1 to 0.2) | 0.4 (0.2 to 0.9) | 0.0 (0.0 to 0.2*) | 0.1 (0.0 to 0.3) | 0.0 (0.0 to 0.2) | 0.3 (0.1 to 0.6) | 0.1 (0.0 to 0.2) |
| 25–44 | 8.1 (7.9 to 8.3) | 12.4 (10.9 to 14.1) | 12.7 (11.3 to 14.3) | 12.3 (11.1 to 13.6) | 12.0 (10.8 to 13.4) | 9.3 (8.2 to 10.5) | 8.9 (7.9 to 10.0) |
| 45–64 | 51.1 (50.8 to 51.5) | 57.1 (54.7 to 59.6) | 53.9 (51.6 to 56.1) | 52.6 (50.7 to 54.6) | 53.0 (51.0 to 55.0) | 51.7 (49.8 to 53.6) | 51.5 (49.7 to 53.4) |
| 65–84 | 38.8 (38.4 to 39.1) | 28.3 (26.1 to 30.5) | 32.3 (30.2 to 34.4) | 33.4 (31.5 to 35.2) | 33.7 (31.8 to 35.6) | 36.7 (34.9 to 38.6) | 37.5 (35.7 to 39.3) |
| 85+ | 1.9 (1.8 to 2.0) | 1.7 (1.1 to 2.5) | 1.2 (0.7 to 1.8) | 1.6 (1.2 to 2.2) | 1.2 (0.8 to 1.7) | 2.0 (1.5 to 2.6) | 2.0 (1.5 to 2.5) |
| Sex, % (95% CI) | | | | | | | |
| Male | 68.7 (68.4 to 69.1) | 68.5 (66.2 to 70.7) | 67.2 (65.1 to 69.3) | 67.8 (66.0 to 69.6) | 66.2 (64.3 to 68.1) | 68.5 (66.7 to 70.2) | 67.9 (66.1 to 69.5) |
| Female | 31.3 (30.9 to 31.6) | 31.5 (29.3 to 33.8) | 32.8 (30.7 to 34.9) | 32.2 (30.4 to 34.0) | 33.8 (31.9 to 35.7) | 31.5 (29.8 to 33.3) | 32.1 (30.5 to 33.9) |
| Origin, % (95% CI) | | | | | | | |
| Swiss | 77.1 (76.7 to 77.4) | 78.6 (76.5 to 80.6) | 84.9 (83.2 to 86.4) | 79.2 (77.6 to 80.8) | 77.7 (76.0 to 79.3) | 78.1 (76.5 to 79.6) | 76.1 (74.5 to 77.6) |
| Other | 22.9 (22.6 to 23.3) | 21.4 (19.4 to 23.5) | 15.1 (13.6 to 16.8) | 20.8 (19.2 to 22.4) | 22.3 (20.7 to 24.0) | 21.9 (20.4 to 23.5) | 23.9 (22.4 to 25.5) |
| Hospital outcomes | | | | | | | |
| Length of stay (Swiss), days, median (IQR) | 9 (4–16) | 10 (4–17) | 10 (4–18) | 10 (4–18) | 9 (4–17) | 9 (4–15) | 9 (4–16) |
| Length of stay (OECD), days, median (IQR) | 10 (5–17) | 11 (5–18) | 11 (5–19) | 11 (5–19) | 10 (5–18) | 10 (5–16) | 10 (5–17) |
| Intensive care stay, % (95% CI) | 13.9 (13.6 to 14.1) | 9.8 (8.4 to 11.4) | 10.9 (9.5 to 12.4) | 9.9 (8.7 to 11.1) | 11.4 (10.2 to 12.7) | 9.7 (8.7 to 10.9) | 12.7 (11.5 to 14.0) |
| In-hospital mortality, % (95% CI) | 11.4 (11.2 to 11.7) | 12.1 (10.5 to 13.8) | 12.6 (11.2 to 14.1) | 13.0 (11.7 to 14.3) | 11.3 (10.0 to 12.6) | 12.4 (11.2 to 13.7) | 11.2 (10.1 to 12.4) |

| | 2010 | 2012 | 2014 | 2016 | 2018 | 2020 | P for trend |
|---|---|---|---|---|---|---|---|
| Sample size (hospitalisations), No | 1 065 703 | 1 051 780 | 1 091 112 | 1 147 011 | 1 151 135 | 1 099 393 | |
| Cirrhosis-related hospitalisations per 100 000 (95% CI) | 292 (281 to 302) | 311 (301 to 322) | 319 (308 to 330) | 341 (330 to 352) | 345 (335 to 356) | 369 (357 to 380) | |
| Cirrhosis-related hospitalisations, No | 3108 | 3273 | 3478 | 3910 | 3977 | 4052 | |
| Age in years, % (95% CI) | | | | | | | |

Continued



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**Table 1** Continued

| | 2010 | 2012 | 2014 | 2016 | 2018 | 2020 | P for trend |
|---|---|---|---|---|---|---|---|
| <25 | 0.2 (0.1 to 0.4) | 0.0 (0.0 to 0.1*) | 0.1 (0.0 to 0.3) | 0.2 (0.1 to 0.3) | 0.3 (0.1 to 0.5) | 0.3 (0.2 to 0.5) | 0.015 |
| 25–44 | 7.0 (6.1 to 7.9) | 6.7 (5.9 to 7.6) | 7.0 (6.2 to 7.9) | 5.4 (4.8 to 6.2) | 6.0 (5.3 to 6.8) | 5.5 (4.8 to 6.2) | 0.002 |
| 45–64 | 53.2 (51.4 to 54.9) | 50.4 (48.7 to 52.1) | 49.7 (48.0 to 51.3) | 49.1 (47.6 to 50.7) | 46.3 (44.7 to 47.8) | 47.2 (45.7 to 48.8) | <0.001 |
| 65–84 | 38.2 (36.5 to 40.0) | 41.0 (39.3 to 42.7) | 41.7 (40.1 to 43.4) | 43.2 (41.6 to 44.7) | 45.3 (43.8 to 46.9) | 43.9 (42.3 to 45.4) | <0.001 |
| 85+ | 1.5 (1.1 to 2.0) | 1.9 (1.4 to 2.4) | 1.4 (1.0 to 1.9) | 2.1 (1.7 to 2.6) | 2.1 (1.7 to 2.6) | 3.1 (2.6 to 3.7) | 0.004 |
| Sex, % (95% CI) | | | | | | | |
| Male | 69.3 (67.6 to 70.9) | 68.9 (67.3 to 70.5) | 70.7 (69.1 to 72.2) | 69.5 (68.0 to 70.9) | 69.8 (68.3 to 71.2) | 70.8 (69.4 to 72.2) | <0.001 |
| Female | 30.7 (29.1 to 32.4) | 31.1 (29.5 to 32.7) | 29.3 (27.8 to 30.9) | 30.5 (29.1 to 32.0) | 30.2 (28.8 to 31.7) | 29.2 (27.8 to 30.6) | 0.001 |
| Origin, % (95% CI) | | | | | | | |
| Swiss | 76.8 (75.3 to 78.3) | 74.8 (73.3 to 76.3) | 76.7 (75.2 to 78.1) | 75.6 (74.2 to 77.0) | 76.7 (75.3 to 78.0) | 74.7 (73.3 to 76.0) | <0.001 |
| Other | 23.2 (21.7 to 24.7) | 25.2 (23.7 to 26.7) | 23.3 (21.9 to 24.8) | 24.4 (23.0 to 25.8) | 23.3 (22.0 to 24.7) | 25.3 (24.0 to 26.7) | 0.001 |
| Hospital outcomes | | | | | | | |
| Length of stay (Swiss), days, median (IQR) | 9 (4–16) | 9 (4–15) | 9 (4–16) | 9 (4–16) | 8 (4–15) | 8 (3–14) | <0.001 |
| Length of stay (OECD), days, median (IQR) | 10 (5–17) | 10 (5–17) | 10 (5–17) | 9 (4–16) | 8 (4–15) | 8 (3–14) | <0.001 |
| Intensive care stay, % (95% CI) | 14.5 (13.2 to 15.8) | 14.1 (12.9 to 15.3) | 16.6 (15.3 to 17.8) | 15.8 (14.7 to 17.0) | 16.4 (15.3 to 17.6) | 15.6 (14.5 to 16.8) | 0.002 |
| In-hospital mortality, % (95% CI) | 12.0 (10.8 to 13.2) | 12.4 (11.3 to 13.6) | 11.0 (10.0 to 12.1) | 10.3 (9.4 to 11.3) | 10.1 (9.2 to 11.1) | 9.7 (8.8 to 10.7) | 0.002 |

*One-sided, 97.5% CI.



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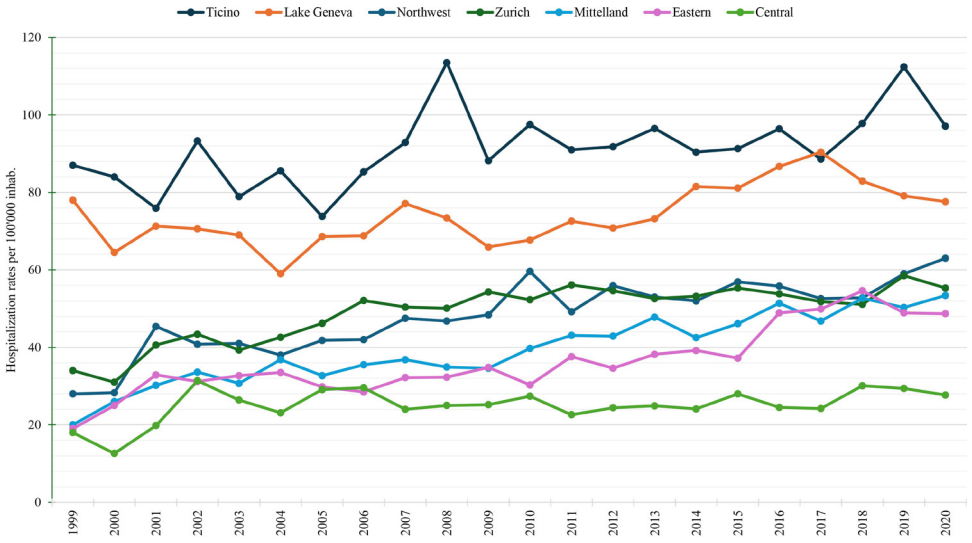


**Figure 2** Cirrhosis-related hospitalisations per 100 000 inhabitants according to hospital region.

shown in table 2, the percentage of hospitalisations with coronary artery disease, congestive heart failure, chronic kidney disease and diabetes as comorbidities increased. Chronic kidney disease and diabetes were the most frequent, reported in 29.1% and 27.4% of all cirrhosis-related hospitalisations in 2020, respectively.

### Trends of cirrhosis-related in-hospital mortality

In-hospital mortality among patients hospitalised for cirrhosis decreased from 12.1% in 1998 to 9.7% in 2020 (*P* for trend 0.002). Deceased patients were mostly men and of Swiss origin, like the study population but in the oldest age categories (online supplemental etable 7). Over 75% of deceased patients had at least one complication of cirrhosis. ARLD and NAFLD were the most common aetiologies of cirrhosis, and chronic kidney disease and diabetes were the most reported comorbidities among deceased patients, similar to the study population (online supplemental etable 8).

### Trends of cirrhosis-related hospitalisation costs

Total costs were only available for part of the hospitalisations since the year 2012, between 68% and 84% of hospitalisations depending on the years. Table 3 shows the trends in total costs stratified by age, sex, aetiology of cirrhosis, HCC and ICU stay. During the 2012–2020 period, total costs of cirrhosis-related hospitalisations amounted to over 610 million CHF. Annual costs increased from over 49 million CHF in 2012 to over 84 million CHF in 2020. ARLD-related cirrhosis had the biggest cost burden ranging from over 21 million CHF in 2012 to over 40 million in 2020. The cost burden related to HCV decreased from over 9.3 million CHF in 2013 to over 3.7 million CHF in 2020. Hospitalisations with ICU stay had a heavy impact on total costs as they accounted for over 300 million CHF out of the total 610 million CHF during that period.

## DISCUSSION

Our findings show that cirrhosis-related hospitalisations increased in absolute numbers and in proportion to the total hospitalisations from 1998 to 2020 in Switzerland. Patients hospitalised for cirrhosis had an increasing median age, more comorbidities, more cirrhosis-related complications and a rising proportion of HCC. However, the median LOS and the in-hospital mortality decreased during the same study period.

The increasing burden of hospitalisations for cirrhosis is in line with prior literature that showed similar trends of increasing age, comorbidities and complications of cirrhosis in the USA[15 22] and Australia.[9] Another cross-sectional study in Germany showed a significant increase in all hospital admissions of patients with cirrhosis between 2005 and 2018.[23]

There were significant geographical differences in hospitalisation rates between the seven administrative regions of Switzerland, with more cirrhosis-related hospitalisations in the Italian and French-speaking parts of Switzerland. Social differences could explain the geographical variance in hospitalisation rate, as supported by data from the Swiss Federal Office of Statistics that show differences in alcohol consumption with more daily intake of alcohol in the Italian and French-speaking regions compared with the German-speaking regions.[24] Similar geographical differences have been described in Germany.[23] Origin did not seem to affect the rate of cirrhosis-related hospitalisations, as the majority of patients were Swiss nationals, in a proportion similar to that found in the general population.[25]

ARLD was the leading and probably underestimated aetiology of cirrhosis, as alcohol overconsumption may not have always been documented. ARLD was an increasing cause of cirrhosis in Switzerland, a finding also reported in the USA,[22 26] and in Germany,[23] but not in Australia.[9] In another study in Portugal, ARLD did not increase but represented over 70% of cirrhosis-related hospitalisations

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Table 2 Trends of aetiologies of cirrhosis, hepatocellular carcinoma and comorbidities from 2012 to 2020

| | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|
| Cirrhosis-related hospitalisations, No | 3273 | 3420 | 3478 | 3646 | 3910 |
| Cirrhosis aetiology, % (95% CI) | | | | | |
| Alcohol (ARLD) | 44.1 (42.4 to 45.9) | 42.7 (41.0 to 44.3) | 45.2 (43.5 to 46.8) | 43.5 (41.9 to 45.1) | 44.1 (42.5 to 45.6) |
| Hepatitis B virus (HBV) | 3.4 (2.8 to 4.0) | 3.2 (2.6 to 3.8) | 2.8 (2.3 to 3.4) | 2.7 (2.2 to 3.3) | 3.2 (2.7 to 3.8) |
| Hepatitis C virus (HCV) | 12.3 (11.2 to 13.5) | 11.5 (10.5 to 12.6) | 9.9 (8.9 to 11.0) | 9.5 (8.6 to 10.5) | 7.9 (7.1 to 8.8) |
| NASH | 1.2 (0.8 to 1.6) | 1.2 (0.9 to 1.6) | 1.4 (1.1 to 1.9) | 1.7 (1.3 to 2.1) | 2.6 (2.1 to 3.1) |
| NAFLD | 41.3 (39.6 to 43.0) | 43.3 (41.6 to 45.0) | 41.9 (40.2 to 43.6) | 43.2 (41.6 to 44.8) | 43.4 (41.9 to 45.0) |
| Other | 2.9 (2.3 to 3.5) | 3.3 (2.7 to 3.9) | 3.1 (2.5 to 3.7) | 4 (3.4 to 4.7) | 3.3 (2.8 to 3.9) |
| Hepatocellular carcinoma, % (95% CI) | 24.4 (22.9 to 25.9) | 23.2 (21.8 to 24.6) | 22.7 (21.3 to 24.1) | 25.6 (24.2 to 27.1) | 26.6 (25.3 to 28.1) |
| Cirrhosis-related complications, No, % (95% CI) | | | | | |
| 0 | 43.1 (41.4 to 44.8) | 40.3 (38.6 to 41.9) | 40.5 (38.9 to 42.2) | 39.6 (38.0 to 41.2) | 39.2 (37.6 to 40.7) |
| ≥1 | 56.9 (55.2 to 58.6) | 59.7 (58.1 to 61.4) | 59.5 (57.8 to 61.1) | 60.4 (58.8 to 62.0) | 60.8 (59.3 to 62.4) |
| Comorbidities, % (95% CI) | | | | | |
| Coronary artery disease | 6.9 (6.1 to 7.8) | 7.0 (6.1 to 7.9) | 6.7 (5.9 to 7.6) | 7.7 (6.8 to 8.6) | 8.8 (8.0 to 9.8) |
| Congestive heart failure | 2.5 (2.0 to 3.1) | 3.3 (2.8 to 4.0) | 3.4 (2.8 to 4.0) | 3.7 (3.1 to 4.3) | 3.9 (3.4 to 4.6) |
| Chronic kidney disease | 24.6 (23.2 to 26.1) | 23.7 (22.3 to 25.2) | 26.0 (24.5 to 27.5) | 23.7 (22.3 to 25.1) | 25.7 (24.3 to 27.1) |
| Diabetes | 21.9 (20.5 to 23.3) | 21.8 (20.4 to 23.2) | 22.3 (21.0 to 23.8) | 24.0 (22.6 to 25.4) | 26.6 (25.2 to 28.0) |
| Stroke | 1.4 (1.0 to 1.8) | 0.8 (0.6 to 1.2) | 1.4 (1.1 to 1.9) | 1.2 (0.9 to 1.6) | 1.2 (0.9 to 1.6) |

| | 2017 | 2018 | 2019 | 2020 | P for trend |
|---|---|---|---|---|---|
| Cirrhosis-related hospitalisations, No | 3853 | 3977 | 4053 | 4052 | |
| Cirrhosis aetiology, % (95% CI) | | | | | |
| Alcohol (ARLD) | 46.2 (44.6 to 47.8) | 46.7 (45.1 to 48.2) | 47.7 (46.2 to 49.3) | 47.9 (46.4 to 49.5) | <0.001 |
| Hepatitis B virus (HBV) | 2.9 (2.4 to 3.5) | 2.9 (2.4 to 3.5) | 2.2 (1.8 to 2.7) | 2.2 (1.8 to 2.7) | 0.001 |
| Hepatitis C virus (HCV) | 7.3 (6.5 to 8.1) | 5.4 (4.7 to 6.1) | 4.2 (3.6 to 4.8) | 3.2 (2.7 to 3.8) | <0.001 |
| NASH | 2.9 (2.4 to 3.5) | 2.8 (2.3 to 3.4) | 4.4 (3.8 to 5.1) | 4.2 (3.6 to 4.9) | <0.001 |
| NAFLD | 41.8 (40.2 to 43.4) | 41.8 (40.3 to 43.4) | 42.2 (40.7 to 43.8) | 42.7 (41.2 to 44.3) | 0.888 |
| Other | 3.5 (2.9 to 4.1) | 4 (3.4 to 4.6) | 3.4 (2.9 to 4) | 3.5 (3.0 to 4.1) | 0.082 |
| Hepatocellular carcinoma, % (95% CI) | 26.1 (24.7 to 27.5) | 26.7 (25.4 to 28.1) | 28.4 (27.1 to 29.9) | 27.9 (26.5 to 29.3) | <0.001 |
| Cirrhosis-related complications, No, % (95% CI) | | | | | |
| 0 | 40.5 (38.9 to 42.1) | 39.0 (37.5 to 40.5) | 38.0 (36.5 to 39.5) | 38.6 (37.1 to 40.1) | 0.001 |
| ≥1 | 59.5 (57.9 to 61.1) | 61.0 (59.5 to 62.5) | 62.0 (60.5 to 63.5) | 61.4 (59.9 to 62.9) | 0.008 |
| Comorbidities, % (95% CI) | | | | | |
| Coronary artery disease | 8.4 (7.5 to 9.3) | 9.4 (8.5 to 10.4) | 10.1 (9.2 to 11.1) | 10.4 (9.5 to 11.4) | <0.001 |
| Congestive heart failure | 4.0 (3.4 to 4.7) | 4.4 (3.8 to 5.1) | 4.9 (4.3 to 5.6) | 5.1 (4.4 to 5.8) | <0.001 |
| Chronic kidney disease | 28.1 (26.7 to 29.6) | 28.0 (26.6 to 29.5) | 29.0 (27.6 to 30.4) | 29.1 (27.7 to 30.5) | <0.001 |
| Diabetes | 25.8 (24.4 to 27.2) | 25.9 (24.5 to 27.3) | 29.9 (28.5 to 31.3) | 27.4 (26.0 to 28.8) | <0.001 |
| Stroke | 1.8 (1.4 to 2.3) | 1.5 (1.2 to 1.9) | 1.8 (1.4 to 2.3) | 1.5 (1.1 to 1.9) | 0.007 |

between 2010 and 2017.[27] Alcohol consumption *per capita* is the highest in the European region but with notable differences between countries[3] and with a decreasing trend in Switzerland.[28] One likely explanation for the increasing ARLD-related cirrhosis is the increasing age of patients as supported by data showing that people over 65 in Switzerland had the heaviest proportion of daily drinking, without notable change from 1992 to 2017.[29]

The determination of the NAFLD aetiology by exclusion could have conducted to an overdiagnosis of NAFLD.



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Table 3 Trends of cirrhosis-related in-hospital costs between 2012 and 2020

| | Total | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|
| Cirrhosis-related hospitalisations, No | 33662 | 3273 | 3420 | 3478 | 3646 |
| Hospitalisations with known costs, No (%) | 25761 (76.5) | 2359 (72.1) | 2332 (68.2) | 2671 (76.8) | 2735 (75.0) |
| Cirrhosis-related hospitalisations costs, CHF | 610152311 | 49896864 | 54306349 | 64020179 | 65103522 |
| Age in years, CHF | | | | | |
| <25 | 1261276 | 14182 | 29976 | 346052 | 147440 |
| 25–45 | 31974242 | 2206545 | 3558052 | 2939755 | 2652137 |
| 45–64 | 291684368 | 24774862 | 28878129 | 33169136 | 30879398 |
| 65–84 | 264726800 | 21631913 | 20361284 | 25877177 | 29324404 |
| 85+ | 20505625 | 1269362 | 1478908 | 1688059 | 2100143 |
| Sex, CHF | | | | | |
| Male | 431439474 | 34527977 | 39758105 | 45897704 | 45975908 |
| Female | 178712837 | 15368887 | 14548244 | 18122475 | 19127614 |
| Cirrhosis aetiology, CHF | | | | | |
| Alcohol (ARLD) | 273852480 | 21285927 | 21257313 | 27387802 | 29283638 |
| Hepatitis B virus (HBV) | 26141384 | 2429630 | 2683778 | 2857437 | 2483470 |
| Hepatitis C virus (HCV) | 59955550 | 8805149 | 9336432 | 7917930 | 8222805 |
| NASH | 22218397 | 457530 | 1973426 | 1248320 | 1138103 |
| NAFLD | 233294381 | 18114198 | 20362712 | 24912112 | 24294538 |
| Hepatocellular carcinoma, CHF | 154284560 | 11382706 | 12603771 | 16373729 | 17946426 |
| Intensive care stay, CHF | 300309284 | 23650377 | 28101298 | 32525128 | 32462447 |

| | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|
| Cirrhosis-related hospitalisations, No | 3910 | 3853 | 3977 | 4053 | 4052 |
| Hospitalisations with known costs, No (%) | 2736 (70.0) | 3064 (79.5) | 3234 (81.3) | 3371 (83.2) | 3259 (80.4) |
| Cirrhosis-related hospitalisations costs, CHF | 66349751 | 69004824 | 74423357 | 82073306 | 84974159 |
| Age in years, CHF | | | | | |
| <25 | 113411 | 180986 | 307479 | 45567 | 76183 |
| 25–45 | 3734735 | 3152623 | 4364151 | 4704810 | 4661434 |
| 45–64 | 32600048 | 33449570 | 33923941 | 34953185 | 39056099 |
| 65–84 | 28122955 | 29302438 | 32926692 | 39187868 | 37992069 |
| 85+ | 1778602 | 2919207 | 2901094 | 3181876 | 3188374 |
| Sex, CHF | | | | | |
| Male | 48057284 | 48349453 | 51935620 | 57477669 | 59459754 |
| Female | 18292467 | 20655371 | 22487737 | 24595637 | 25514405 |
| Cirrhosis aetiology, CHF | | | | | |
| Alcohol (ARLD) | 25876459 | 33317114 | 33892524 | 40703134 | 40848569 |
| Hepatitis B virus (HBV) | 3194681 | 3268697 | 3317246 | 2808201 | 3098244 |
| Hepatitis C virus (HCV) | 6908038 | 5489925 | 4885031 | 4668409 | 3721831 |
| NASH | 2876366 | 2871657 | 2333849 | 3510404 | 5808742 |
| NAFLD | 28311587 | 25451390 | 28007575 | 32719353 | 31120916 |
| Hepatocellular carcinoma, CHF | 16731760 | 17174223 | 19281337 | 21682282 | 21108326 |
| Intensive care stay, CHF | 32198853 | 32691351 | 36503982 | 39058819 | 43117029 |

Multiple cross-sectional studies using similar databases had comparable difficulties to determine NAFLD because of the absence of specific ICD-10 codes.[9 23 27 30 31] However, based on the available data, we chose this approach to approximate the burden of NAFLD in cirrhosis-related hospitalisations, as previously performed.[15]



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As ARLD and NAFLD accounted for most cases of cirrhosis-related hospitalisations in our study, there is an urgent need for interventions at an individual and a population level to reduce the burden of cirrhosis in Switzerland. Interventions could be aimed at promoting healthy lifestyle, discouraging heavy alcohol intake, increasing price of alcohol and sugar-sweetened beverages, restricting alcohol and unhealthy food marketing, as well as improving screening and treatment of ARLD and NAFLD. A large and comprehensive review of preventive measures for the burden of liver disease has been published by Pimpin *et al*.[3]

HCV-related cases of cirrhosis demonstrated a steady decrease from 2012 to 2020 in Switzerland. The same trend has been described in Germany,[23] Portugal[27] and Spain,[32] and is most probably related to the efficacy of the new antiviral therapies. However, other countries could not show the same decrease in HCV-related cirrhosis,[9 15] most probably because affected patients do not benefit of universal access to treatment.

In-hospital mortality decreased in our study period, in line with the decrease from 11.6% in 2005 to 9.5% in 2018 reported in Germany.[23] Still, the evolution of cirrhosis-associated mortality was reported variably in the literature, with an increasing global mortality[1] but a decreasing age-adjusted mortality.[2] The decreasing in-hospital mortality in our study with an ageing and more comorbid population is encouraging and has also been described in Portugal.[27] One explanation could be linked to improved care pathways and more intensive inpatient care as suggested by the increase in costs. Multiple developments in the pharmacological and interventional treatment of complications of cirrhosis have been achieved and have been implemented in international guidelines for the management of cirrhosis.[33–35] Application of these guidelines as well as the increase in liver transplantation, which increased substantially during our study period,[36 37] could have contributed to the decreasing in-hospital mortality.

Analysis of the cirrhosis-related in-hospital costs displayed an increasing economic burden of cirrhosis between 2012 and 2020. Notably costs increased more than the number of admissions with a 70% increase in costs for only a 38% increase in hospitalisations with available information on healthcare expenditures. The proportion of costs related to hospitalisations with ICU stay in our study could suggest that increasing intensity of inpatient care may explain part of the rising costs. Furthermore, the increasing age, comorbidities and complications of cirrhosis during our study period could add to the rise in costs as reported by Hirode *et al*.[15] Additionally, our study only focused on cirrhosis-related hospitalisations and Gu *et al* emphasised the important role of cirrhosis as a comorbidity in their cross-sectional study where over 50% of admissions with cirrhosis between 2005 and 2018 were with cirrhosis as a comorbidity.[23] The increasing economic burden of cirrhosis has been described in the USA with a larger increase of in-hospital costs than in ambulatory care.[16] The heavy economic burden of cirrhosis documented in our study emphasises the importance of preventing hospitalisations in patients with cirrhosis and improving ambulatory care. Previous studies have proposed tools to improve screening, quality of care, management of cirrhosis and follow-up after discharge with some of them proving cost-effective.[14 38–41]

Our study has multiple strengths, including a large sample of hospitalisations for cirrhosis on a prolonged period of >20 years. The Swiss Hospital Statistics is a national database with reliable demographic data and use of ICD-10 codes for definition of cirrhosis has been shown to be accurate.[42 43] There are, however, limitations, also linked to the retrospective design of the study and the use of a hospital discharge database. Indeed, diagnoses depend on the quality of documentation by treating physicians and there can be some missing data or inaccuracy in documentation. Consequently, the quality of data available for the determination of aetiologies of cirrhosis, comorbidities and complications of cirrhosis was impacted by missing data or lack of precise documentation. Obesity for example was only scarcely reported which precluded use of the new metabolic dysfunction-associated steatotic liver disease (MASLD) definition in place of NAFLD. Despite consensus on the new MASLD definition,[44] we used the NAFLD definition because of the exclusion method adopted, corresponding to the nomenclature used at the time of the data collection. Also, use of DRG linked to ICD-10 codes for billing purpose since 2012 in Switzerland introduced economic incentives associated with documentation that can favour some diagnoses and underestimate others. Thus, the increase of NASH-related cirrhosis, cirrhosis-related complications and costs could also be linked to a learning effect of coding staff. Another limitation is related to the anonymised database which renders impossible to ascertain the rehospitalisation rate. Therefore, our study focused on hospitalisations for cirrhosis but not on cirrhotic patients because the number of hospitalisations for each single patient could not be assessed. As an exploratory cross-sectional study, no correction for multiple testing was performed. Still, had a Bonferroni correction been applied considering the 27 tests performed, the resulting threshold would be 0.002, which would not change most of our findings. Finally, costs were only available for part of the admissions, without details regarding distribution of the costs nor explanation of the cause for missing data. Therefore, the impact of the latter on the overall economic burden could not fully be ascertained.

In conclusion, cirrhosis-related hospitalisations and related costs increased in Switzerland from 1998 to 2020 but in-hospital mortality decreased despite patients getting older. ARLD and NAFLD were the two leading causes of cirrhosis and should prompt for interventions at an individual and population level to reduce the burden of cirrhosis on the healthcare system.



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**Contributors** JV conceived the study. TF-B analysed data and wrote most of the manuscript. PM-V collected and analysed data, performed the statistical analysis and wrote part of the manuscript. JV and DM revised the article for important intellectual content. PM-V had full access to the data and is the guarantor of the study.

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**Patient consent for publication** Not applicable.

**Ethics approval** This cross-sectional study used a national hospital database containing deidentified information and was therefore not subject to an ethical approval. Use of the data from the Swiss Hospital Statistics of the Swiss Federal Office of Statistics (https://www.bfs.admin.ch) is, however, subject to adoption of a code of ethics by the Swiss Public Statistics Charter which is in line with the European Statistics Code of Practice.

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**Data availability statement** Data are available upon reasonable request. The data that support the findings of this study are available from the Swiss Federal Office of Statistics (SFOS). Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://www.bfs.admin.ch with the permission of the SFOS.

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