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Long-Term Effects of Direct-Acting Antivirals on Hepatitis C: Trends in Liver Disease–Related Hospitalisations in Italy

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ABSTRACT

This study aimed to evaluate the effectiveness of direct-acting antivirals (DAAs) on hepatitis C virus (HCV) hospitalisation trends in Italy, the country with not only the highest burden of HCV-related disease but also the highest number of patients treated for chronic HCV infection in Europe. Incident hospital discharge records in Italy from 2012 to 2019 that included a liver cirrhosis diagnosis without mention of alcohol, hepatocellular carcinoma (HCC), HCV and liver cirrhosis without mention of alcohol and/or HCC, cirrhosis with mention of alcohol, as defined by the International Classification of Diseases (ICD-9-CM) were reviewed. An interrupted time series analysis compared the incidence of cirrhosis and HCC before and after the introduction of DAAs (Year 2015). Overall, non-alcoholic cirrhosis significantly decreased after the introduction of DAAs ($\beta_3 = 0.03$) and for those 40–59 years of age ($\beta_3 = 0.025$). HCV with cirrhosis and/or HCC significantly reduced overall for those aged 40–59 and older than 60 ($\beta_3 = 0.002$). HCC-related hospitalisation rates significantly decreased in patients younger than 60 ($\beta_3 = 0.03$). Cirrhosis-related hospitalisations with mention of alcohol did not differ during the study period before and after the year 2015 ($\beta_3 = 0.4$). There was a significant reduction in HCV-related hospitalisations throughout Italy after introducing DAAs.

1 | Introduction

Since its discovery in 1989, the hepatitis C virus (HCV) has been recognised as a significant cause of chronic liver disease worldwide [1]. Chronic HCV infection causes substantial morbidity and mortality, with complications including cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and death [2]. The availability of direct-acting antiviral (DAA) treatment in the last decade has made HCV elimination a reality, thus potentially eliminating it as a global public health threat. According to studies conducted from 1995 to 2000, Italy has the highest HCV prevalence rate in Europe and, thus, the highest HCV-related mortality rate of any European Union (EU) country [3–5]. In 2016, the HCV-related mortality rate was 38 deaths per million people versus an average of 13 deaths per million people in other EU countries [5]. With HCV related cirrhosis hospitalizations accounting for more than 70% of overall cirrhosis and HCC, the burden of HCV related hospitalizations in Italy was also substantial [6, 7].

DAAs have proven effective in eradicating HCV and significantly improving liver function in patients with mild to moderate liver fibrosis [8, 9]. Additionally, patients with cirrhosis who eradicated HCV virus with DAAs have exhibited lower rates of

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HCC and other liver complications; however, an absolute risk of HCC remained persistent [10]. Though evidence highlights the efficacy of DAAs in reducing disease burden in patients with severe liver disease, few have qualitatively measured trends in HCV-related hospitalisations as an indicator of overall DAA effectiveness [11–13]. Thus, this study aimed to evaluate the effectiveness of DAAs on HCV hospitalisation trends in Italy, the European country with the highest HCV-related disease burden and number of DAA-treated patients.

2 | Methods

2.1 | Study Design and Study Population

The analysis was based on hospital-discharge records (HDRs) in Italy from 2012 to 2019. HDRs collect data on all inpatient and day admission hospital discharges in private or public hospitals at the national level. The discharge records include the patient's demographic and clinical information, diagnoses, and procedures, which are classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The analysis included records available in HDRs, referring to the primary or secondary diagnosis of liver cirrhosis without mention of alcohol (ICD9CM 571.5), cirrhosis with mention of alcohol (ICD9CM 571.2) and HCC (ICD9CM 155.0) from 1 January 2012 to 31 December 2019. Hospitalisations with a primary or secondary diagnosis of HCV among patients with a diagnosis of liver cirrhosis without mention of alcohol and/or HCC were also evaluated. HCV hospitalisation discharge records were those with diagnoses of hepatitis C carrier (ICD9CM V02.62), chronic hepatitis C with hepatic coma (ICD9CM 070.44), chronic hepatitis C without mention of hepatic coma (ICD9CM 070.54), unspecified viral hepatitis C without hepatic coma (ICD9CM 070.70) or unspecified viral hepatitis C with hepatic coma (ICD9CM 070.71).

Incident hospitalisations were evaluated and identified using the ICD-9-CM mentioned above codes and were included if there was no HDR for the same primary diagnosis in the 4 years before 2012. Only the first hospital discharge was considered an index admission; other hospital discharges within 4 years from the index admission were excluded to avoid the inclusion of multiple admissions of the same patient.

2.2 | Statistical Analysis

The annual hospitalisation rates for HCC, liver cirrhosis and HCV with and without mention of alcohol, were estimated as the number of individuals admitted for the first time to the hospital divided by the resident population at the beginning of each year as reported by ISTAT (the Italian National Institute of Statistics).

An interrupted time series analysis was conducted to compare the incidence of cirrhosis and HCC over the study period, before and after the introduction of the DAA treatments (March 2015). A 6-month latency window was utilised to assess the effect of treatment on HCV-related diseases. Specifically, the period from March to October 2015 was not considered because the impact of DAAs could be visible only after viral eradication, which required a median time of 6 months to be achieved.

A piecewise regression analysis was performed using an interrupted time series of the monthly hospitalisation rate, calculated as the percentage of incident hospitalisations divided by the resident population. The trend in the hospitalisation rates before and after the intervention were evaluated using the following model:

$$Y_t = \beta_0 + \beta_1 \cdot \text{time} + \beta_2 \cdot \text{intervention}_t + \beta_3 \cdot \text{time after intervention}_t + e_t$$

where Y_t represents the hospitalisation rate at time t; time is a continuous variable that represents the time in months from the beginning of the study period; intervention is a binary variable representing the period before (0) or after (1) the intervention; and time after intervention is a continuous variable representing the number of months after the intervention.

In the model, the parameters: β_0 estimates the hospitalisation rate at the beginning of the period of observation (baseline level); β_1 estimates the slope of the regression segment pre-intervention (baseline trend) and represents the variation of the outcome during the pre-intervention period; β_2 estimates the variation of the hospitalisation rate post-intervention or the difference between the initial rate of the post-intervention regression segment and the final rate of the pre-intervention period; β_3 estimates the variation of the slope of the post-intervention regression segment versus the slope of the pre-intervention regression segment, and represents the difference between pre-intervention and post-intervention slopes of the hospitalisation rate; e_t is the error term at time t, which represents the variability not explained by the model, expressed as a random variable with normal distribution.

Significant p values for coefficient β_2 indicate an immediate effect of the intervention, while significant values for β_3 indicate an effect over time [14].

The analysis was conducted separately for each of the following conditions of interest: incident cases with HCV diagnosis, cirrhosis without mention of alcohol, cirrhosis with mention of alcohol, and HCC cases. A linear regression model was used to predict hospitalisation rates and associated 95% confidence intervals through 2040. Statistically significant differences in age means among different groups were assessed using the absolute standardised difference (ASD). The difference was considered significant when the ASD exceeded 0.1.

3 | Results

The number of hospitalisations with incident HCV diagnosis, cirrhosis with and without mention of alcohol, and HCC by median age from 2012 to 2019 are shown in Table 1.

There were 157,081 cases of liver cirrhosis without mention of alcohol and 81,430 cases of cirrhosis with mention of alcohol during the observation period. The mean age was significantly lower (ASD = 0.462) for patients with a diagnosis of cirrhosis with mention of alcohol versus without (62.8 years vs. 68.9 years

TABLE 1 | Study population by incident diagnosis and age.

Incident diagnosis	Number of patients	Q1 (age in years)	Median (age in years)	Q3 (age in years)	Mean (age in years)	% Under 40
HCV + non-alcoholic cirrhosis and/or HCC	20,199	58	71	79	68.4	1.2
Non-alcoholic cirrhosis	157,081	60	71	79	68.9	2.3
Alcoholic cirrhosis	81,430	53	63	72	62.8	2.8
Hepatocellular carcinoma	81,328	62	72	79	69.9	1.2

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Q1, Quartile 1; Q3, Quartile 3.

of age, respectively). The interrupted time series of hospitalisations due to cirrhosis and HCC with and without mention of alcohol by age groups are shown in Figures 1–3.

Since 2012, annual hospitalisation rates for the diagnoses of interest have all declined (Table 2).

Specifically, non-alcoholic cirrhosis hospitalisations declined 38.5%, from 39.7 per 100,000 in 2012 to 24.4 in 2019; HCV and cirrhosis and/or HCC declined 36.8% from 5.7 to 2.1 per 100,000; cirrhosis with mention of alcohol declined 20%, from 18.8 to 15.1 per 100,000; and HCC fell 22.4%, from 18.9 to 14.6 per 100,000.

3.1 | Cirrhosis Without Mention of Alcohol

On average, 32.7 per 100,000 people were hospitalised for cirrhosis without mention of alcohol from 2012 to 2019. Hospitalisation trends for non-alcoholic liver cirrhosis, considering the two periods of pre and post-intervention, are shown in Figure 1A. As is shown in Table S1, by the estimation of the β_3 parameter, cirrhosis without mention of alcohol significantly decreased after the introduction of DAAs. No significant decrease is shown at the start of DAA use (in the first 6-month period), as expressed by the β_2 parameter ($p = 0.69$).

Figure 1B,C shows the pre- and post-intervention trends in cirrhosis without mention of alcohol by age group. As shown in Figure 1B, there was a significant reduction in hospital admissions for those 40–59 years of age ($p < 0.025$). The decrease observed for patients of age ≥ 60 over 60 was not significantly different from that observed during the pre-intervention period ($p = 0.29$), as is shown in Figure 1C.

3.2 | Incident HCV Diagnosis With a Primary or Secondary Diagnosis of Cirrhosis and/or HCC

From 2012 to 2019, the average rate of hospitalisations for the diagnosis of HCV and a primary or secondary diagnosis of cirrhosis and/or HCC was 4.2 per 100,000 residents. Figure 2A summarises the overall trend in hospitalisations before and after the introduction of DAAs.

While no significant decrease is seen at the start of the intervention (β_2 parameter, $p = 0.252$, Table S1), a significant decrease in the post-intervention period (2015–2019) was found (β_3 parameter, $p < 0.05$, Table S1). Figure 2B,C shows the trend of hospitalisations for the diagnoses of HCV chronic infection with a primary or secondary diagnosis of cirrhosis and/or HCC by age group. Hospitalisations significantly reduced for both age groups of those aged 40–59 years ($p < 0.0001$) and of those aged ≥ 60 years ($p < 0.002$).

3.3 | Diagnosis of Cirrhosis With Mention of Alcohol

The average rate of hospitalisations for cirrhosis with mention of alcohol was 17.0 per 100,000 residents. Figure 3A summarises the trend in hospitalisations for liver cirrhosis with mention of alcohol before and after the introduction of DAAs. Though monthly hospitalisations declined pre- and post-intervention, as observed in Table 2, there is no significant decrease in the hospitalisation rate before the year 2015 (pre-intervention) (β_2, p value 0.08, Table S1), nor in the hospitalisation rate from October 2015 (β_3, p value 0.442, Table S1).

Cirrhosis with mention of alcohol hospitalisations by age group is shown in Figure 3B,C. No significant decreasing trend ($p = 0.3$ and $p = 0.5$) was observed after 2015 for any age group analysed (40–59 vs. those of age ≥ 60, respectively).

3.4 | Diagnosis of HCC

The average hospitalisation rate for the primary diagnosis of HCC was 16.9 per 100,000 residents. Figure 4A summarises the trend in hospitalisations for HCC before and after the introduction of DAAs. Though monthly hospitalisations declined, there were no significant differences in the short-term (β_2, p value 0.8), nor in the monthly hospitalisation rate post-intervention (starting from October 2015, β_3, p value 0.066, Table S1). A significant decreasing trend was observed in those aged 40–59 years ($p < 0.035$, Figure 4B), while the decreasing trend noted in those of age ≥ 60 years was not statistically significant (Figure 4C, $p > 0.4$).

3.5 | Projection of Hospitalisations and Mortality for Cirrhosis Without Mention of Alcohol and HCC by 2030

Based on the observed trend of overall hospitalisation rates for liver complications with aetiologies not mentioning alcohol

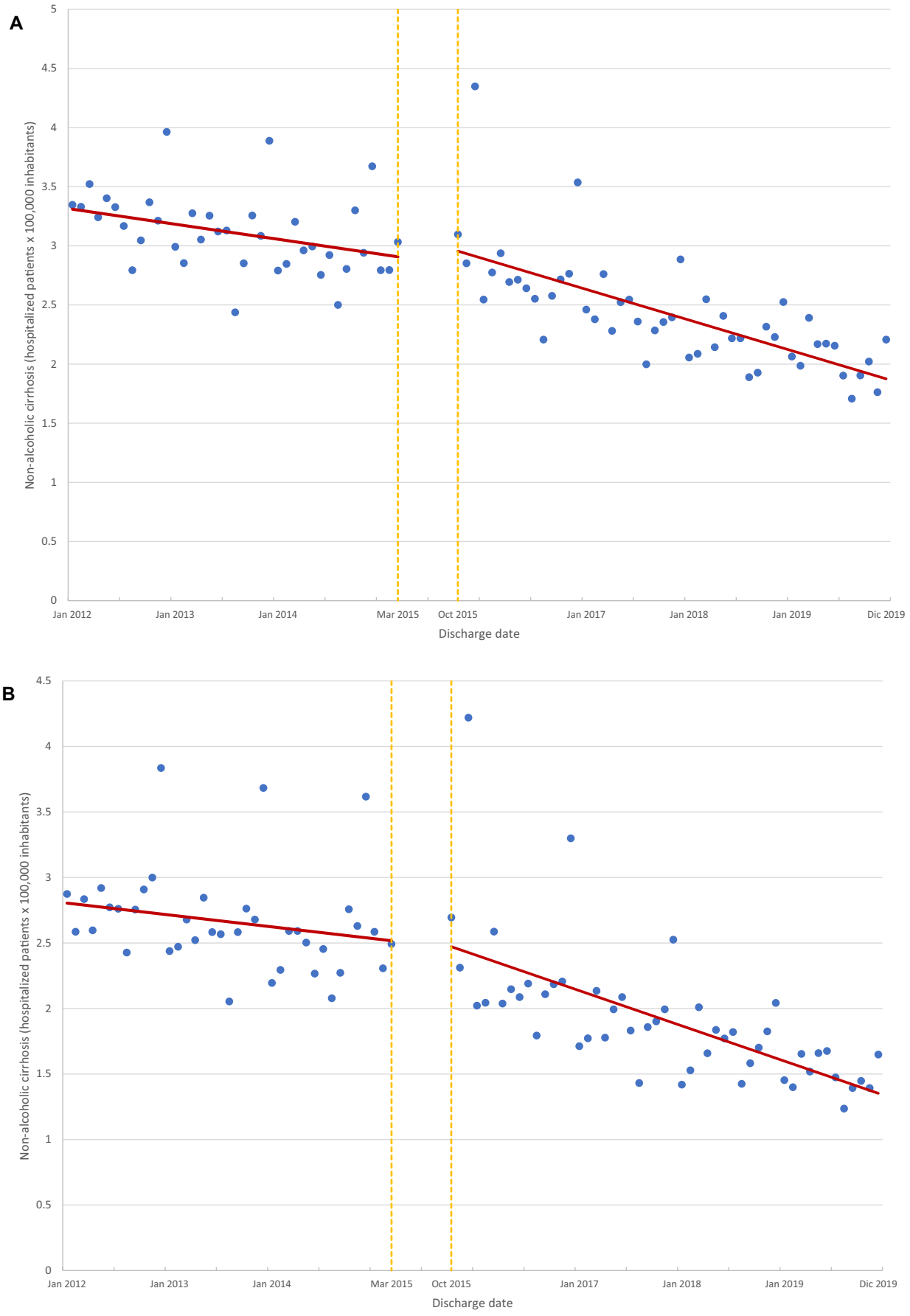


FIGURE 1 | Interrupted time series of hospitalisation for cirrhosis without mention of alcohol. (A) Overall; (B) age 40–59 years, (C) age ≥ 60 years.

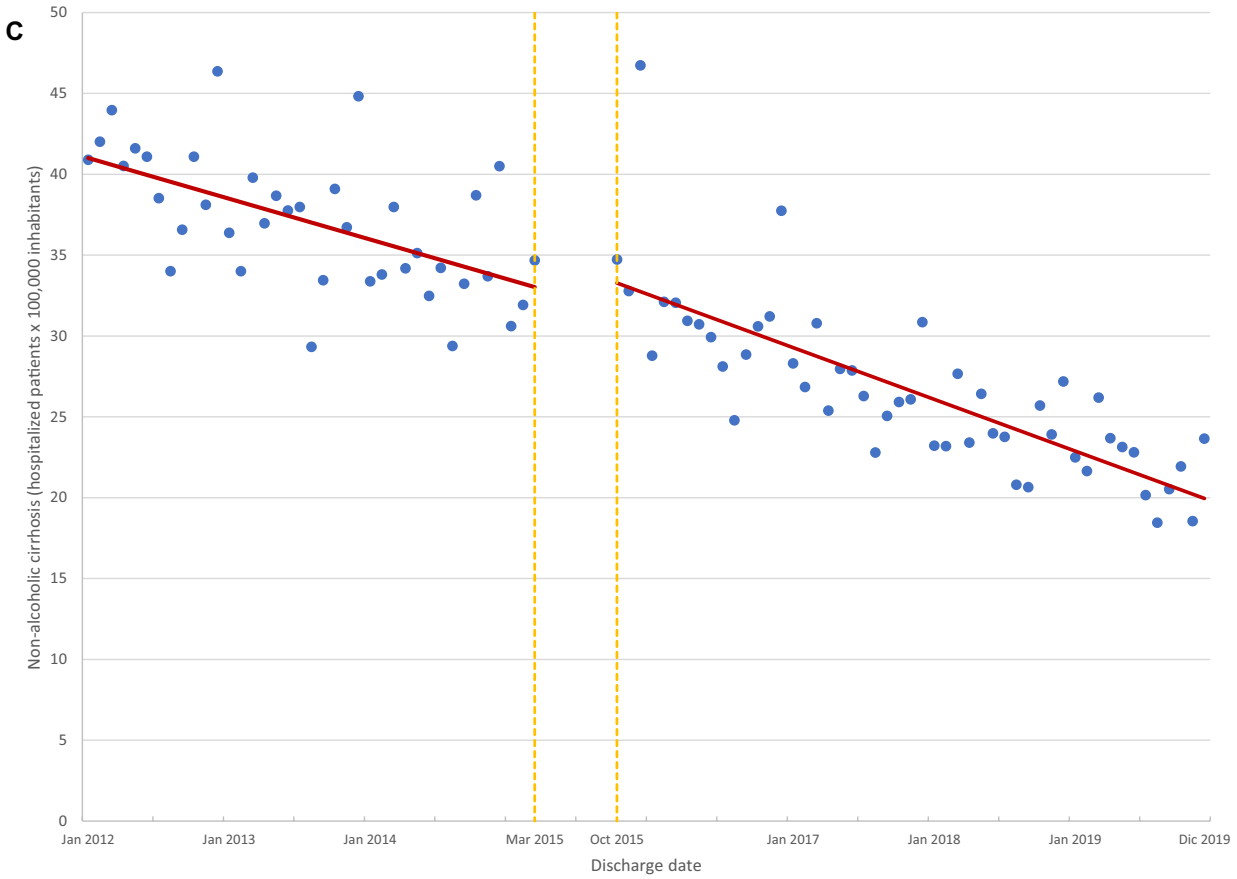


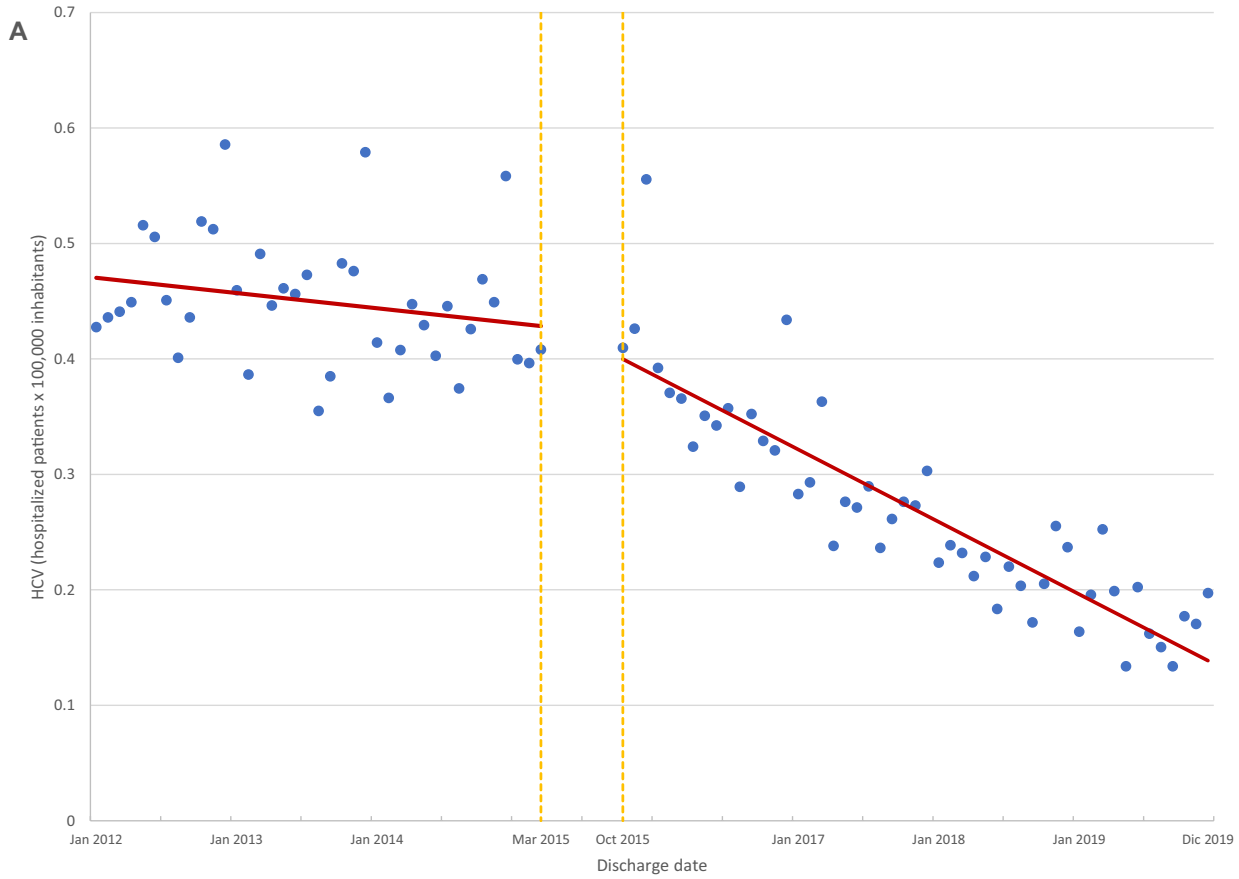
FIGURE 1 | (Continued)

(non-alcoholic cirrhosis and HCC) and assuming the same decreasing trend over the year 2030, the hospitalisation rate is estimated to be 15.0 per 100,000 by the year 2026, with a confidence interval ranging from 2024 to 2030. Consequently, a 65% reduction in hospitalisations for cirrhosis or HCC without mention of alcohol, compared to the rates observed in 2015, is expected by 2030, the year the World Health Organization aims to achieve the elimination of HCV (Figure S1).

4 | Discussion

This study aimed to estimate the burden of HCV-related hospitalisations in Italy from 2012 to 2019 using HDRs. While this study evaluated hospitalisation trends during the pre-coronavirus-19 (COVID-19) pandemic, a drastic reduction in hospitalisations for liver complications during COVID-19 was observed across all hospitals in Italy [15, 16]. The findings of this study, which showed a significant decrease in both diagnoses of cirrhosis without mention of alcohol and of HCV-related cirrhosis from 2015 to 2019, are not echoed by the COVID-19 reduction in hospitalisations for other causes.

The mean age of hospitalised patients with a diagnosis of cirrhosis without mention of alcohol and of cirrhosis specifically registered using an HCV codification was similar (mean age 68.4 (IQR 58–79) years of age versus 68.9 (IQR 60–79) years of age). In Italy, studies conducted from 1990 to 2000 showed the prevalence of HCV increasing steadily with age, with those > 50 accounting for most of the infections during that time [3, 17]. Because chronic liver disease may develop many years after infection, the past incidence of HCV is a significant determinant of the future burden of HCV-associated complications [18, 19]. Considering the past incidence of HCV infection, which started in Italy in the 1950s through nosocomial infection, HCV-related complications were estimated to peak in 2008, meaning the decreasing trend, observed in this study since 2012, could have been present before the introduction of DAAs [20]. Admission for liver cirrhosis complications without mention of alcohol could also be related to hepatitis B (HBV) and Delta (HDV). However, given the extent of HBV vaccination in Italy, the Italian native population younger than 45 years of age is immune to hepatitis B [21]. Additionally, liver cirrhosis due to HBV in Italian patients is well controlled by the use of antiviral drugs, which have been available since before the study period [22]. Given these considerations, the burden of liver cirrhosis complications due to HBV and/or HDV over the study period is potentially lower than complications due to HCV. In addition. these infections could affect only the hospitalisation rates of older patients admitted to the hospital with diagnosis of liver cirrhosis without mention of alcohol. On the contrary, in this analysis, the significant decrease in hospitalisations after 2015 was observed only for the cohort younger than 60 years of. More common comorbidities in older patients, as is reported in the PITER cohort, as well as comorbidities related to Metabolic Dysfunction-Associated Liver Disease (reported as cirrhosis without mention of alcohol in the ICD-9-CM), could have contributed to the lack of decreasing hospitalisation trends for liver cirrhosis in patients over 60 years of age [22–25]. However,



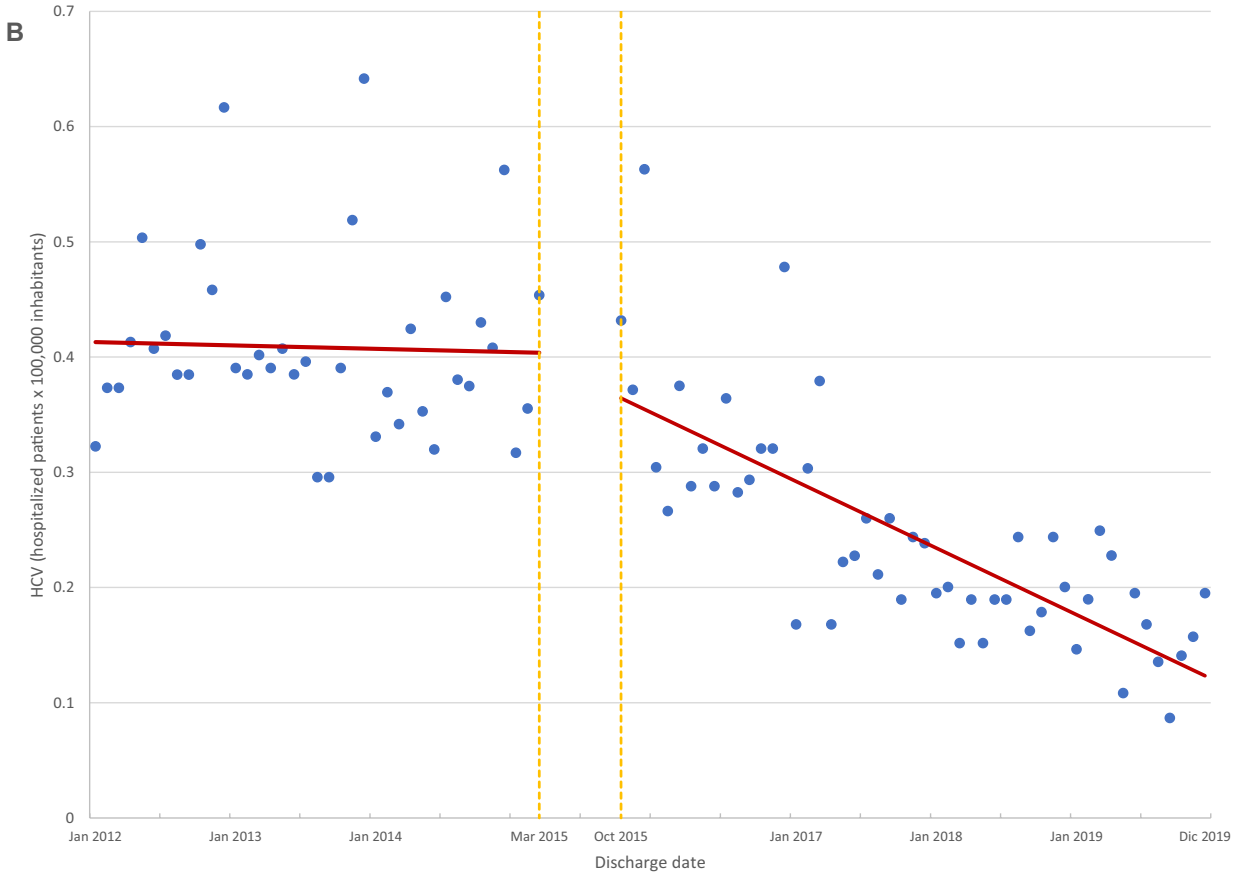


FIGURE 2 | Interrupted time series of hospitalisation for cirrhosis and/or HCC due to HCV. (A) Overall; (B) age 40–59 years, (C) age ≥ 60 years.

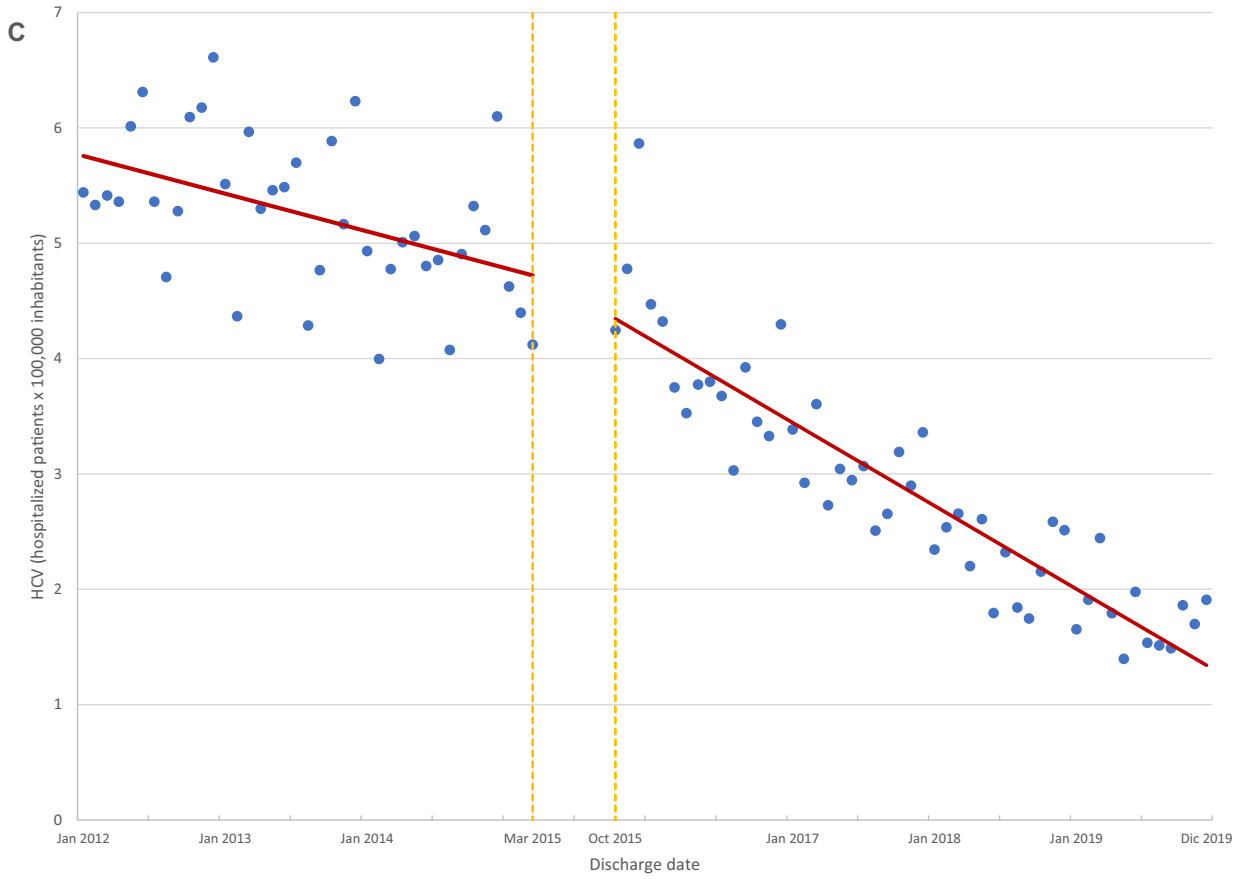


FIGURE 2 | (Continued)

the significant decrease in the overall hospitalisation rates of younger patients diagnosed with cirrhosis without mention of alcohol and the substantial reduction in hospitalisation rates in younger and older cohorts diagnosed with HCV-related cirrhosis could suggest an overall significant impact of DAAs on reducing liver-related hospitalisations. The mean age of our study population of the patients admitted to the hospital was older compared to a study from the United States, which showed HCV-related hospitalisations over the period 2000–2019 predominantly occurring among persons aged 45–64 years Persons aged 55–64 experienced a 132.9% increase in HCV-related hospitalisation rates, while persons aged 35–44 and 45–54 experienced a 47% and 43.7% decrease in HCV-related hospitalisation rates, respectively, coinciding with the release of the DAAs [11]. Despite different HCV epidemiology in between Italy and United States, these similar results underline that HCV elimination in younger ages is associated in the short term with a significant reduction of liver complications and hospitalisation rates.

A significant reduction was observed for HCC hospitalisations in patients younger than 60 years. Overall findings of this study showed a decrease in liver cancer-related hospitalisation rates, though it was not statistically significant until 4 years after the introduction of DAAs (p-value = 0.066). Unfortunately, older age can lead to longer-term viral replication, which can result in more severe liver complications. Although improved liver function has been observed in patients with no liver disease complications after stopping DAAs, for patients with severe liver damage and cirrhosis complications who have achieved viral eradication, impediments still exist. Particularly for older patients, cancer, portal vein thrombosis, or other complications are reduced but not abolished after viral eradication [26–28]. By a National Health Services (NHS) perspective. patients with advanced cirrhosis treated with DAAs are still at risk of liver failure and liver cancer with all the consequent direct costs [29].

Data of this study indicating the significant decrease of HCV-related hospitalisations are in accordance with data from the ECALITA (Evolution of IndiCAtion in LIver transplantation in ITAly) registry. The waiting list for HCV-related cirrhosis decreased from 35.9% during the period 2004–2011 to 12.1% during the period 2015–2020. On the contrary the waiting list for the HCV-related HCC increased from 8.5% to 26.7%, for HBV-related cirrhosis remained almost unchanged (13.2% and 12.4%), while those for HBV-related HCC increased from 4.0% to 11.6% [30].

As seen in Table 2 and in Figure 3, hospitalisations for cirrhosis with mention of alcohol did not show a significant decreasing trend over the study period in both pre and post-intervention periods. Findings from a survey conducted in 2014 showed that risky alcohol intake plays a role in more than one-fifth of chronic liver disease cases in Italy, particularly impacting older patients and those with more advanced disease [31]. Data from the ECALITA registry showed ALD-related cirrhosis to be decreased from 16.9% to 12.9% while ALD-related HCC increased from 1.9% to 3.9% [30]. Patients with alcohol abuse frequently have hospitalisations for competitive comorbidities in addition

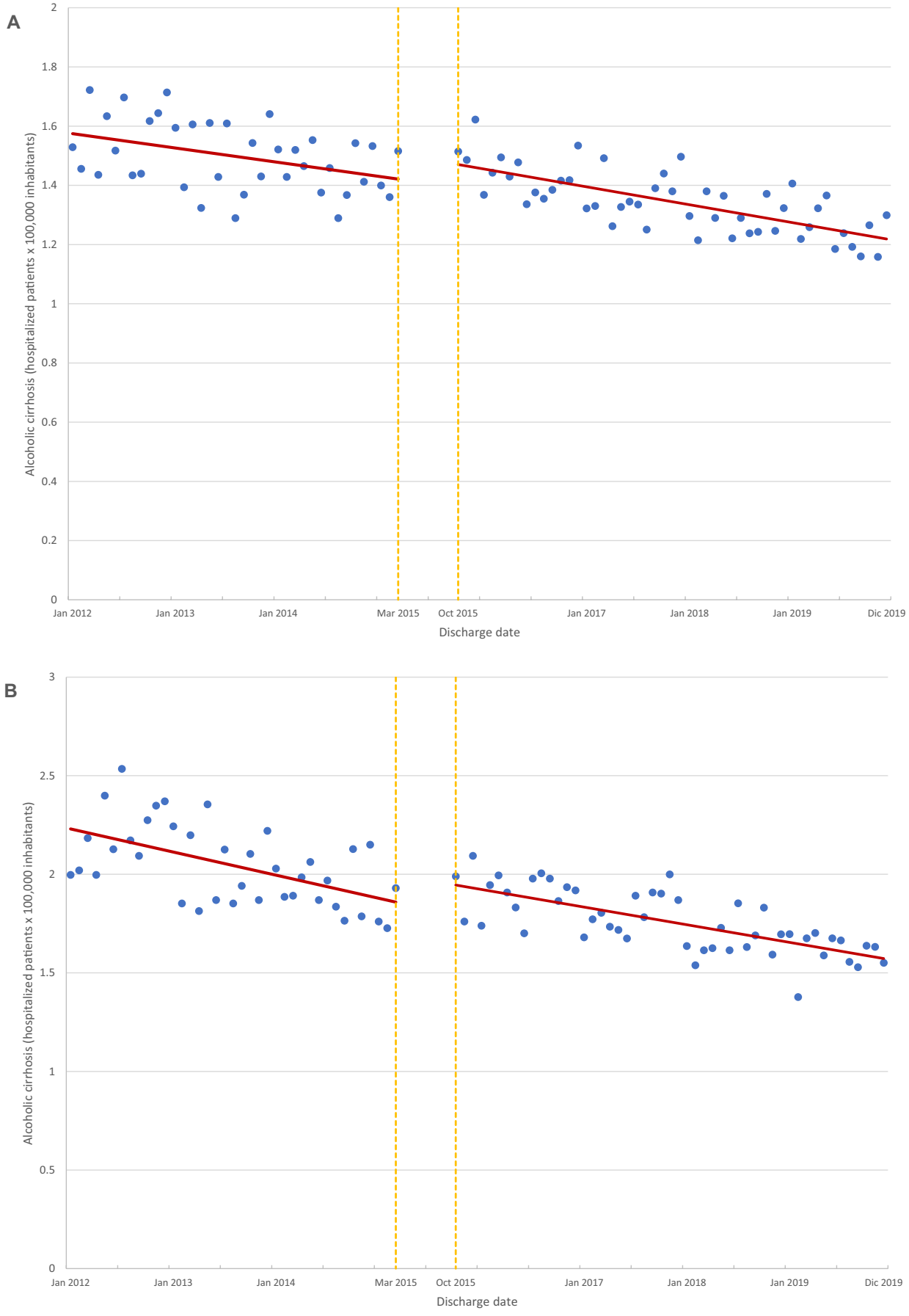


FIGURE 3 | Interrupted time series of hospitalisation for cirrhosis with mention of alcohol. (A) Overall; (B) age 40–59 years, (C) age ≥ 60 years.

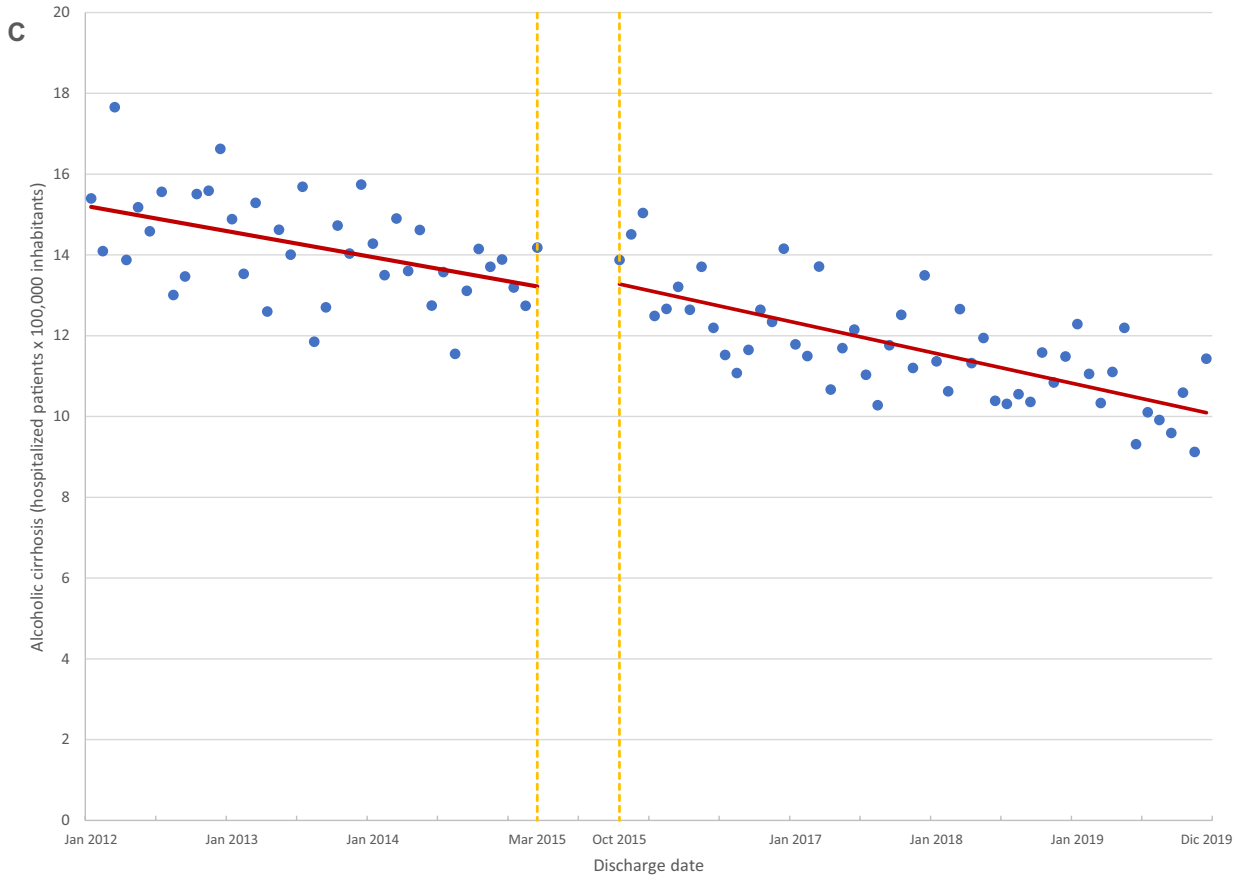


FIGURE 3 | (Continued)

TABLE 2 | Annual hospitalisation rates (per 100,000 residents) for cirrhosis and liver cancer from 2012 to 2019 in Italy.

Year	Cirrhosis with no mention of alcohol	Liver cancer	Cirrhosis with mention of alcohol	HCV and cirrhosis and/or HCC
2012	39.7	18.9	18.8	5.7
2013	37.2	18.0	17.8	5.5
2014	35.7	17.6	17.5	5.2
2015	35.7	17.6	17.3	4.9
2016	32.7	16.8	17.0	4.2
2017	29.2	16.6	16.4	3.4
2018	26.6	15.1	15.5	2.6
2019	24.4	14.6	15.1	2.1

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

to liver complications and this could potentially explain the decreasing trend of liver related hospitalisations over time. However, the increase of alcohol related HCC waiting list indicates that alcohol should be considered as an important risk factor of HCC and its related hospitalisations in Italy.

Lastly, based on projections in this study, HCC and cirrhosis without mention of alcohol hospitalisation rates are expected to be minimal (2.0 per 100,000 residents) by 2032. Additionally, a 65% reduction in HCV-related morbidity is anticipated by 2026 (Figure S1). This data confirms our previous assumptions and underline an important evidence for national and global health policies [32]. Investing in screening and linkage to care to treat HCV infection brings short-term individual and societal benefits and long-term economic benefits by avoiding hospitalisations related to HCV liver disease complications.

4.1 | Strengths and Limitations

The main strength of this study is the utilisation of hospitalisation data. Italy has universal access to healthcare with no insurance or socioeconomic restrictions on treatment eligibility or hospitalisation access. This limits bias due to insurance, prescriber type, substance use and hepatic fibrosis restrictions, which could influence hospitalisation rates. More so, given the significant burden of liver cirrhosis due to hepatitis C in Italy, compared to other European countries, and the treatment of a substantial number of individuals with HCV since 2015, the analysis of the hospitalisation trends for HCV liver cirrhosis or liver cancer in Italy was feasible and meaningful. This analysis could be helpful for countries where HCV chronic infection have affected mainly key populations and younger age groups. The potential impact of the DAAs in these countries is probably not visible now; it could be shown over longer period of their use.

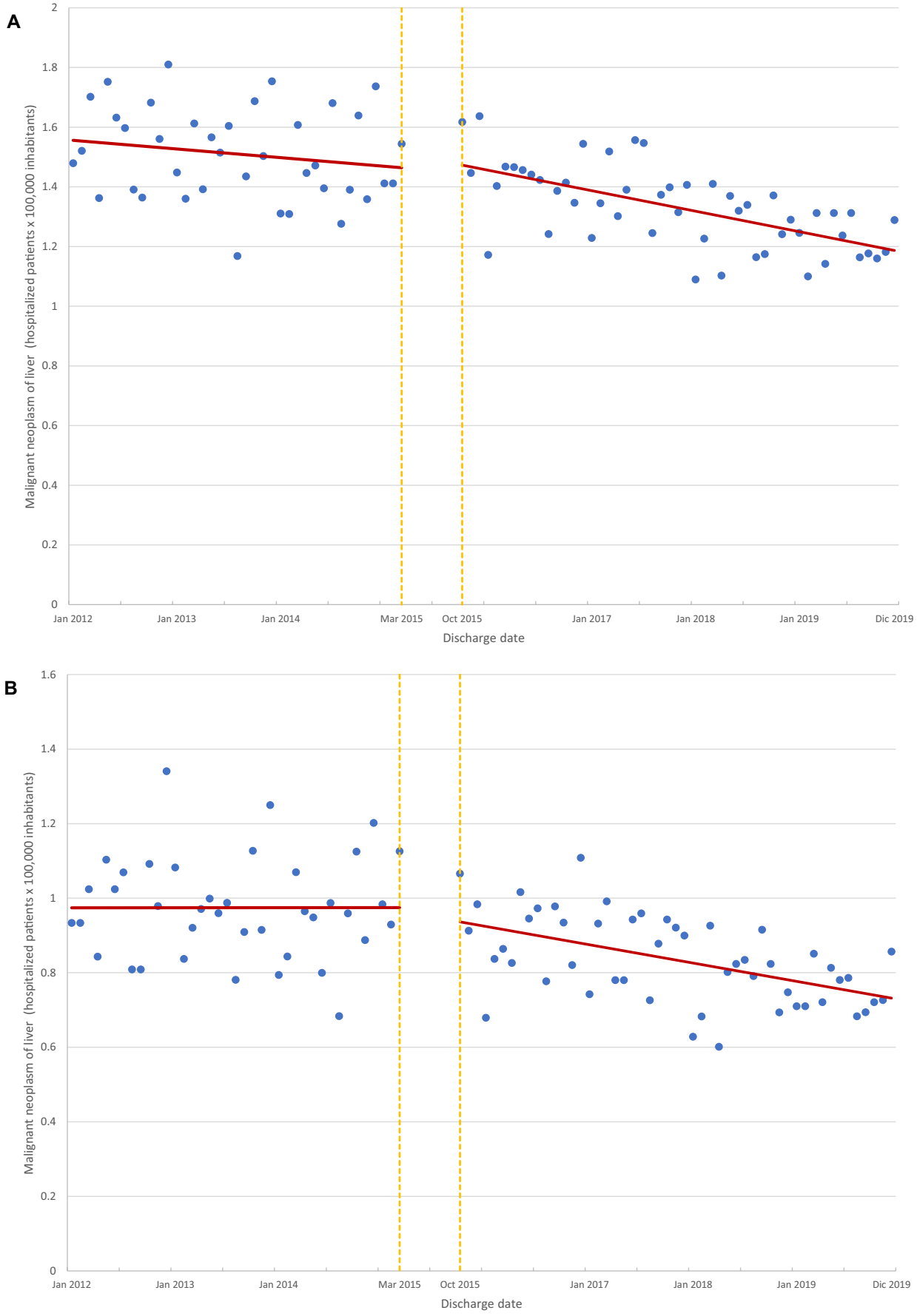


FIGURE 4 | Interrupted time series for hospitalisation for HCC.

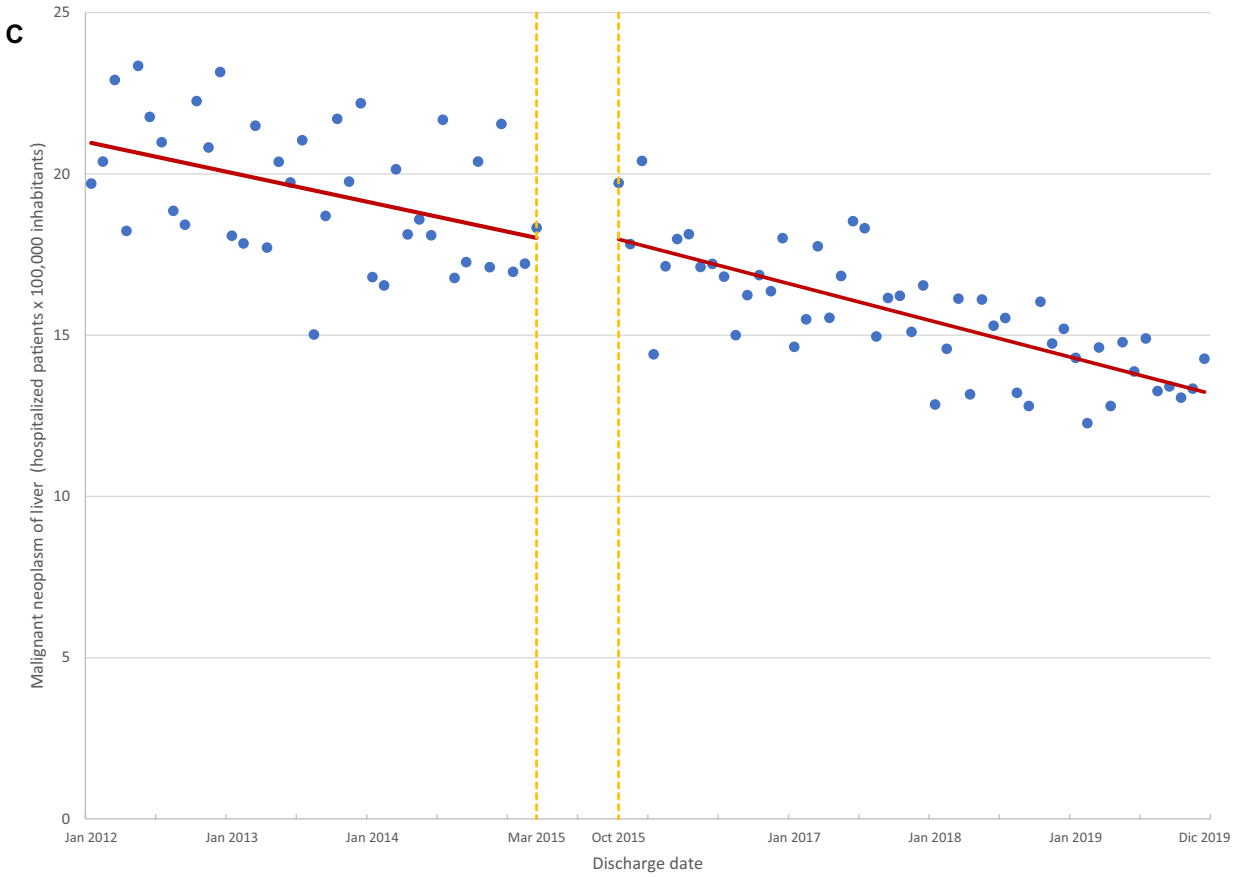


FIGURE 4 | (Continued)

Lastly, because multiple hospitalisations for an individual patient were excluded, the impact of hospital readmissions was minimised, with each hospitalisation counting once as a new hospitalisation.

This study has several limitations. Though HDRs include the main complications of liver cirrhosis and HCC, the HCV aetiology in hospitalised patients could be underreported. In addition, there is no identification code for metabolic disfunction-associated steatotic liver disease (MASLD), and several hospitalisations classified as cirrhosis without mention of alcohol could be related to MASLD complications. To limit this bias, we analysed both trends of HCV related liver cirrhosis and HCC and the hospitalisations trend of those without mention of alcohol. The hospitalisation trends in both groups analysed were similar. Although the inclusion of MASLD in the group of cirrhosis without mention of alcohol, the HCV prevalence in liver cirrhosis and HCC, during the year from 2012 to 2019, was the highest compared with other risk factors of liver disease in Italy.

We could not evaluate the 65% reduction in HCV related mortality which is one of the targets of HCV elimination. The HCV morbidity projections, based on hospitalisation reduction trend could be only used as surrogate data to support that Italy is on track to achieve the HCV mortality targets by 2030, as similarly reported by a study conducted in the Veneto Region and modelled in a previous study in Italy [32, 33]. However, this trend do not take into account the potential increasing rate of hospitalisations due to MASLD, which need to be better characterised in the codes used for hospital discharges and mortality rates.

Lastly, this analysis focuses only on liver-related hospitalisations and likely underestimates the overall HCV-related hospitalisation burden due to frequent extrahepatic manifestations of HCV infection, reported to be frequent also in patients in care in Italy, enrolled in the PITER cohort [22, 23, 25, 34].

5 | Conclusion

The significant decrease in the incidence of cirrhosis without mention of alcohol highlights the impact that DAAs has on reducing HCV liver-related hospitalisations in Italy.

Expanded access to DAA treatment is needed before severe liver disease is diagnosed to decrease HCV-related hospitalisations and liver-related mortality further. Not only could this prevent more transmission, but it could reduce the healthcare and financial burdens associated with HCV-related hospitalisations and ultimately eliminate hepatitis C as a public health threat in Italy.

Author Contributions

Conceptualization, F.S.M. and L.A.K.; methodology, P.S.; software, P.S.; validation, A.M., S.R. and C.S.; formal analysis, P.S., C.S. and A.M.;

investigation, F.S.M., P.S and L.A.K.; resources, P.S., A.M., F.S.M. and L.A.K.; data curation, P.S.; writing – original draft preparation, F.S.M., P.S. and L.A.K.; writing – review and editing, F.S.M., P.S., C.S., A.M., S.R. and L.A.K. supervision, F.S.M., P.S., C.S., A.M., S.R. and L.A.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The health administrative databases which are the data sources of this study are not publicly available and the authors do not have permission to share them; the unidentifiable aggregated data will be available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.