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Burden of compensated and decompensated cirrhosis: real world data from an Italian population-based cohort study

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Abstract. – OBJECTIVE: To quantify the annual healthcare resource utilization, costs and mortality rate for a large cohort of Italian patients with compensated (CC) and decompensated cirrhosis (DC).

PATIENTS AND METHODS: A population-based cohort study was conducted through the data-linkage of mortality for all-cause, hospitalizations and outpatient drugs and service databases of the Campania Region. All adults hospitalized with cirrhosis diagnosis (2007-2015) were grouped in CC and DC (prevalent patients) on January 1, 2016 and followed for 1-year. Incident patients with DC (2015) were also retrieved and followed from discharge date up to 1-year. Negative binomial regression was used to estimate Incidence Rate Ratios (IRRs) for predictors of all-cause hospitalizations. Costs were evaluated from the Italian National Health Service perspective and expressed in euro patient/year.

RESULTS: A total of 21,433 prevalent cirrhotic patients (57.1% CC and 42.9% DC) and 1,371 incident patients with DC were identified. During a 1-year, 21.5% of prevalent patients with CC were admitted for acute events, 26.8% of those with DC and 55.4% of incident patients with DC. Ascites (IRR=1.71;95% CI: 1.37-2.14) and hepatic encephalopathy (IRR=1.35; 95% CI: 1.04-1.77) at index admission were strong predictors of hospitalizations in incident DC patients. The 1-year mortality rate was respectively 5.8% and 10.1% for prevalent patients with CC and DC and 35.6% for incident patients with DC. Direct costs amounted to 3,194€ patient/year for the prevalent CC group and 4,001€ patient/year for the DC group and 13,806 € patient/year for incident individuals with DC.

CONCLUSIONS: The burden of cirrhosis dramatically differs between CC and DC patients, especially after the first decompensation episode. Ascites and hepatic encephalopathy at index admission were strong predictors of hospitalizations in incident DC patients.

Key Words:
Liver disease, Decompensation, Direct costs, Mortality, Hospitalization.

Abbreviations

CC: compensated cirrhosis; CIs: confidential intervals; CM: comorbidities; COPD: chronic obstructive pulmonary disease; DC: decompensated cirrhosis; DH: day-hospital; DRG: diagnosis related group; EVB: esophageal variceal bleeding; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDR: hospital discharge records; HE: hepatic encephalopathy; ICD-9-CM: International Classification of Diseases: Ninth Revision: Clinical Modification; IQR: interquartile range; IRRs: Incidence Rate Ratios; NHS: National Health Service; SD: standard deviation.

Introduction

Cirrhosis is the result of different chronic liver diseases that lead to necroinflammation and

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fibrogenesis. According to the Global Burden of Disease Study, cirrhosis caused 1.2% of global disability-adjusted life years and 2.4% of total deaths in 2017, worldwide[1].

Cirrhosis is distinguished between compensated and decompensated stages with different features, prognoses, and predictors of death[2,3]. The natural history is characterized by an initial asymptomatic phase, referred to as compensated cirrhosis (CC). The progression to a decompensated phase is signed by the first occurrence of portal hypertension, hepatorenal syndrome, ascites, esophageal variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (HE) and jaundice[4,5]. Transition from a compensated to a decompensated stage occurs at a rate of 5-7% per year[3]. Once decompensation develops, the hospital stay days and the mortality rate dramatically increase[1,3]. Indeed, without proper management of complications and consequent liver transplantation, <50% of patients with decompensated cirrhosis (DC) survive for 5 years[6].

In Italy, cirrhosis remains one of the main chronic diseases although the mortality rate has continuously decreased from 1.7 deaths/10,000 inhabitants in 2003 to 0.9 in 2014 (-48.7%)[7]. Hepatitis virus C (HCV) infection continues to be the most common aetiological factor observed in Italian cirrhotic patients. However, the role of HCV infection on the burden of cirrhosis is significantly decreasing over time in Italy[8]. The economic impact of cirrhosis is still relevant and the hospitalizations are the main source of healthcare-related expenditure[8]. Moreover, cirrhosis and its complications can also affect the outcome of non-liver related comorbidities requiring hospitalizations[9]. Therefore, the knowledge of the overall economic impact of this progressive and complex disorder, attributable to both liver- and non-liver related causes, is essential for decision makers to plan resource allocation and appropriate preventive strategies. Furthermore, it is important to assess the burden of disease, distinctly for CC and DC, both from clinical and economic point of view. To date, in Italy, few studies have been focusing on this topic.

The purpose of this study is to estimate the healthcare resource utilization, costs and mortality over 1-year, for patients with CC or DC, and to assess the predictors of hospitalizations in an Italian region with high HCV endemicity. The secondary aim is to assess the cirrhosis impact on outcomes and costs during the first year after the onset of DC.

Patients and Methods

Data Source

A population-based cohort study was conducted using several healthcare administrative databases of the Campania Region (about 5.8 million inhabitants, 9.7% of the Italian population). Information on mortality for all-cause, outpatient drugs, hospital discharge records (HDRs) and outpatient service databases were integrated through a deterministic record-linkage technique. Briefly, regional mortality database collects information about the date and the cause of death based on the codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). HDR database includes information on discharge date, day-hospital (DH) or ordinary admission, primary diagnosis and up to 5 secondary diagnoses and diagnosis related group (DRG) tariffs. Outpatient drugs database contains information on the prescriptions reimbursed by the National Health Service (NHS) referred to drugs prescribed by specialists[10]. Outpatient Service database includes information about laboratory tests, diagnostic procedures and specialist visits.

All data were linked through the unique individual identification code properly anonymized respecting the subject's privacy. The healthcare administrative databases are routinely used for epidemiological and administrative purposes[11,12]. The research adhered to the tenets of the Declaration of Helsinki.

Study Population

For the primary aim, we included all residents of the Campania Region, aged 18 and older, with a primary or secondary diagnosis of cirrhosis (ICD-9 codes 571.2, 571.5, 571.6) in HDRs between January 1, 2007 and December 31, 2015[13]. Cirrhotic patients were assigned to CC or DC groups in January 1, 2016 (index date) as follows. The DC group included patients who had at least one hospitalization with a primary or secondary diagnosis of portal hypertension (ICD-9 code 572.3), hepatorenal syndrome (572.4), ascites (789.5x), esophageal variceal bleeding (456.0 and 456.2), spontaneous bacterial peritonitis (567.23), HE (572.2) and jaundice (782.4)[14]. The CC group included individuals with a primary or secondary diagnosis of cirrhosis but without any complication used to define the DC group. We followed the prevalent patients with CC or DC from index date until death or December 31, 2016, whichever occurred first (Figure 1).

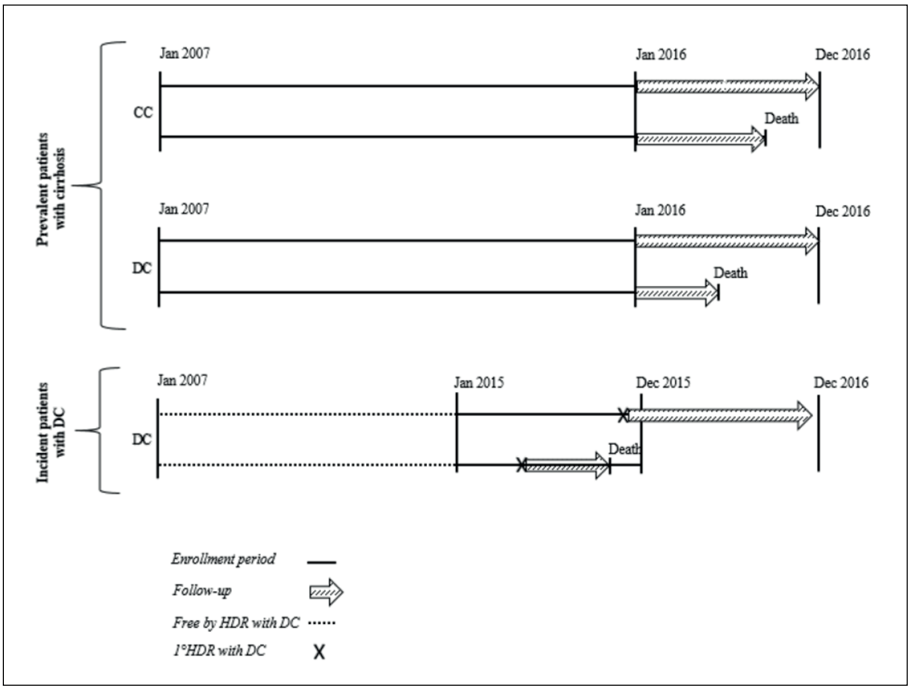

Figure 1. Study design. CC, compensated cirrhosis; DC, decompensated cirrhosis. HDR, Hospital Discharge Record.

For the secondary aim, we identified adult cirrhotic individuals who were discharged with a primary or secondary diagnosis of DC event during the 2015 calendar year. To analyse only new cases, we excluded all individuals who had at least one hospitalization with an ICD9 code for DC before the discharge date (index date) (N=17,618). Subjects who died at the index date were also excluded (N=108). Incident DC patients were followed from the index date up to 1-year or until death, whichever occurred first (Figure 1).

Outcomes

The study outcomes were the annual healthcare resource utilization, direct costs and 1-year mortality rate for all-cause in the prevalent CC and DC patients as well as in incident DC patients.

Covariates

Age was calculated at the index date and categorized in three groups (18-65, 65-74 and 75 years and older).

The presence of diagnosis of portal hypertension, hepatorenal syndrome, ascites, esophageal variceal bleeding, spontaneous bacterial peritonitis, HE and jaundice were identified in HDRs, in any diagnostic fields, between 2007 and 2015, for prevalent DC patients and, at the index date, for incident DC patients. Hepatitis B virus (HBV) and HCV infection, hepatocellular carcinoma (HCC), esophageal variceal bleeding and non-liver comorbidities (CMs) were assessed using ICD9-CM codes reported in HDRs, in any diagnostic fields, between 2007 and 2015 in prevalent cirrhotic patients (CC and DC) and, between January 1, 2007 and the index date in incident patients with DC (**Supplementary Table I**). The non-liver CMs included diabetes, hypertension, cardiovascular diseases, cerebrovascular diseases, anaemia, renal disease, peripheral vascular diseases, cancer (excluding HCC), chronic obstructive pulmonary disease (COPD) and psychiatric disorders. Moreover, patients were categorized on the basis of non-liver CMs number (0, 1 and ≥2 CMs).

Healthcare Resource Utilization Analyses

Hospitalization resource utilization was assessed by evaluating the number of hospitalizations and cumulative length of stay. The number of hospitalizations was calculated as the sum of ordinary admissions within a 1-year follow-up period. We defined as cumulative length of stay the total number of days in which the patient remained in the hospital during the follow-up period.

Costs were analysed from the perspective of the Italian NHS and quantified using the amount of money that the NHS reimbursed to care pro-

viders. We calculated the total healthcare expenditure per person-year (in euros) including cirrhosis-related and comorbidities-related care. Direct costs were divided into three main categories: hospitalizations, outpatient drugs and outpatient services. The hospitalization costs were calculated using the CMS-DRG version-24 grouping algorithm[15]. Outpatient drugs were quantified according to current prices; direct-acting antiviral agents, specifically used for HCV treatment, were not included in the analysis. Outpatient service costs were derived from national tariffs. Finally, to account for shorter follow-up periods due to deaths, time at risk was calculated in days from the index date to the date of death (or 365 days otherwise) and transformed into years. Direct costs were reported as mean per patient/year.

Statistical Analysis

Data were summarized using percentages for categorial variables and mean and standard deviations (SD), median and interquartile range (IQR) for continuous variables. We used χ^2 tests to compare categorical variables and analysis of variance to compare continuous variables. Negative binomial regression was used to estimate Incidence Rate Ratios (IRRs) for predictors of all-cause hospitalizations, because preliminary exploration of hospitalization count data revealed that the variance was not equal to the mean of the distribution. To evaluate the predictors associated with the risk of hospitalization for acute event we only referred to ordinary admissions, therefore DH were excluded. Separate models were performed for prevalent patients with CC and DC, and incident DC patients. Models were adjusted for age groups, sex, esophageal variceal without bleeding, HBV and HCV infection, HCC, non-liver CMs groups and, only in patients with DC (prevalent or incident), for portal hypertension, hepatorenal syndrome, ascites, esophageal variceal bleeding, spontaneous bacterial peritonitis, HE and jaundice. The results were shown as adjusted IRRs with 95% confidential intervals (CIs), with $p<0.05$ indicating statistical significance. All analyses are conducted using SPSS software (version 23.0).

Results

Characteristics of Study Population

On January 1, 2016 a total of 21,433 prevalent cirrhotic patients (57.8% male and 57.9% older than 65 years) in the Campania Region were identified (451/100,000 inhabitants) (Table I). Of these, 42.9% (9,197 patients of 21,433) experienced at least one decompensated condition before the index date. Ascites was the most common complication (50.5%), followed by portal hypertension (35.9%) and HE (31.3%). Compared with the CC group, a significantly higher proportion of subjects with DC had HCC, whereas the proportion of individuals with HBV and HCV infection was significantly higher in the CC group compared to the DC group. Both in groups CC and DC, almost 70% of patients had at least one non-liver CM and 43.4% two or more (Table I). The most common non-liver CM was hypertension (35.0%) followed by diabetes (27.4%) and cardiovascular diseases (24.3%) (**Supplementary Table II**).

During the 2015 calendar year, 1,371 alive incident DC patients at discharge were identified; 60.0% were male and 61.3% were older than 65 years (Table I). Of them, 56.2% reported ascites, 27.1% portal hypertension, 16.2% esophageal variceal bleeding and 15.8% HE.

Healthcare Resource Utilization and Costs

During 1-year follow-up, the proportion of patients admitted for acute event was 23.8% (21.5% in the CC group and 26.8% in the DC group, $p<0.0001$), increased to 55.4% in incident DC patients (Table II). Overall, it has been estimated an average of 0.4 hospitalization per patient/year (0.4 in group CC and 0.5 in group DC, $p<0.0001$) while it was 1.2 in incident DC patients. The median cumulative length of hospital stay was longer for prevalent DC patients compared to those with CC (11.0 *vs.* 8.0, $p<0.0001$); while it was 13.0 days (IQR 21) for incident DC patients. The 1-year mortality rate was totally 7.6% (5.8% for group CC group and 10.1% for group DC, $p<0.0001$); 35.6% of incident DC patients died within the first year after index hospitalization (Table II).

Table III reports the adjusted IRRs for all-cause hospitalizations. The presence of esophageal varices without bleeding, HCV infection, HCC and the number of non-liver CMs were all associated with the increasing risk of hospitalization both in the prevalent CC and DC patients. Among the prevalent DC patients, the risk of hospitalizations significantly increased among individuals with previous ascites, portal hypertension, esophageal variceal bleeding, and

Table I. Demographic and clinical characteristics of study population.

	Prevalent patients with cirrhosis				Incident DC patients (N = 1,371) %
	Overall (N = 21,433) %	CC group (N = 12,236) %	DC group (N = 9,197) %	*p*-value	
Male gender	57.8	57.2	58.5	0.065	60.0
Age groups					
18-65	42.1	42.1	42.1	0.191	38.7
66-74	25.3	25.8	24.7		28.5
≥ 75	32.6	32.1	33.1		32.8
Ascites	21.7	-	50.5	-	56.2
Portal hypertension	15.4	-	35.9	-	27.1
Hepatic encephalopathy	13.4	-	31.3	-	15.8
EV without bleeding	11.6	6.4	18.5	< 0.0001	8.5
EV with bleeding	9.7	-	22.5	-	16.2
Jaundice	3.1	-	7.3	-	3.9
Hepatorenal syndrome	1.0	-	2.4	-	2.3
SBP	0.9	-	2.0	-	2.0
HBV infection	4.7	5.1	4.2	0.002	2.9
HCV infection	24.5	26.9	21.2	< 0.0001	22.1
HCC	14.2	13.6	15.1	0.002	20.4
Liver trasplant	3.8	2.4	5.6	< 0.0001	0.6
Number of non-liver CMs					
0	31.3	32.2	30.2	0.004	27.9
1	25.3	24.7	26.1		26.6
≥ 2	43.4	43.1	43.8		45.5

CC, compensated cirrhosis; CM, comorbidities; DC, decompensated cirrhosis; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SBP, spontaneous bacterial peritonitis.

spontaneous bacterial peritonitis. Regarding the incident DC patients, we found that ascites (adjusted IRR=1.71; 95% CI: 1.37-2.14), HE (adjusted IRR=1.35; 95% CI: 1.04-1.77) and HCC (adjusted IRR=1.27; 95% CI: 1.03-1.56) were strong predictors of hospitalizations. In addition, the risk of hospitalization increased in patients with 1 and ≥2 non-liver CMs compared to those without non-liver CMs (Table III).

Finally, a total annual expenditure of €72.8 million was spent for the care of cirrhotic patients in the Campania Region, representing a mean cost of 3,535€ patient/year (3,194€ per patient/year for group CC and 4,001€ per patient/year for group DC) (Figure 2 and **Supplementary Table III**). Direct costs amounted to 13,806 € per patient/year for incident patients with DC, accounting for a total healthcare spending of €13.8 million (Figure 2 and **Supplementary Table III**). Hospitalizations represented 62.4% of total costs in the prevalent patients with cirrhosis (58.3% in the CC group and 66.8% in the DC

Table II. Hospital resource utilization and mortality during 1-year follow-up.

	Prevalent patients with cirrhosis				Incident patients with DC (N = 1,371)
	Overall (N = 21,435)	CC group (N = 12,238	DC group (N = 9,197)	*p*-value	
Admitted patients for acute events, n (%)	5,098 (23.8)	2,634 (21.5)	2,464 (26.8)	< 0.0001	760 (55.4%)
Hospitalizations for acute event, mean±SD	0.4 ± 1.1	0.4±0.9	0.5 ± 1.2	< 0.0001	1.2±1.6
Cumulative length of stay, median (IQR)	10.0 (16)	8.0 (14)	11.0 (19)	< 0.0001	13.0 (21)
Patients died within one year, n (%)	1,633 (7.6)	710 (5.8)	923 (10.1)	< 0.0001	488 (35.6%)

CC, compensated cirrhosis; CM, comorbidities; DC, decompensated cirrhosis; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SBP, spontaneous bacterial peritonitis.

Table III. Adjusted Incidence Rate Ratios (IRRs) for all-cause hospitalizations.

	Prevalent patients with cirrhosis		Incident DC patients IRRs (CI 95%)
	CC IRRs (CI 95%)	DC IRRs (CI 95%)	
Male gender (ref female)	1.12 (1.04-1.20)‡	1.04 (0.96-1.12)	1.40 (1.18-1.66)§
Age groups (ref 18-65)			
66-74	1.07 (0.97-1.17)	0.97 (0.88-1.06)	1.04 (0.85-1.27)
≥ 75	1.00 (0.91-1.10)	0.66 (0.60-0.73)§	0.95 (0.77-1.16)
Ascites†	-	1.37 (1.27-1.48)§	1.71 (1.37-2.14)§
Portal hypertension†	-	1.36 (1.26-1.47)§	0.89 (0.71-1.11)
Hepatic encephalopathy†	-	1.07 (0.99-1.16)	1.35 (1.04-1.77)‡
EV with bleeding†		1.33 (1.22-1.45)§	0.99 (0.77-1.24)
EV without bleeding†	1.33 (1.16-1.51)§	1.68 (1.54-1.84)§	0.99 (0.74-1.29)
Jaundice†	-	0.96 (0.83-1.12)	0.91 (0.59-1.40)
Hepatorenal syndrome†	-	0.45 (0.34-0.60)§	0.37 (0.17-0.82)‡
SBP	-	1.43 (1.14-1.80)‡	1.50 (0.87-2.59)
HBV infection†	1.05 (0.90-1.24)	1.21 (1.01-1.44)‡	1.08 (0.67-1.73)
HCV infection†	1.19 (1.10-1.29)§	1.50 (1.38-1.63)§	1.05 (0.86-1.27)
HCC†	1.65 (1.50-1.81)§	1.36 (1.23-1.50)§	1.27 (1.03-1.56)‡
Liver trasplant†	0.47 (0.35-0.62)§	0.46 (0.38-0.55)§	1.92 (0.65-5.76)
Number of non-liver CMs (Ref 0)			
1	1.42 (1.28-1.59)§	1.56 (1.39-1.73)§	1.29 (1.03-1.61)‡
≥ 2	2.78 (2.53-3.05)§	2.80 (2.53-3.08)§	2.03 (1.64-2.51)§

CC, compensated cirrhosis; CI, confidence interval; CM, comorbidities; DC, decompensated cirrhosis; EV, esophageal varices; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SBP, spontaneous bacterial peritonitis. †Reference category, No clinical condition (i.e., ascites vs. no ascites). ‡$p < 0.05$, §$p < 0.0001$.

group); drugs and outpatient service contributed to 26.1% and 11.5%, respectively (Figure 3). In incident DC patients, 84.5% of overall costs was due to hospitalizations, whereas drugs and outpatient service accounted for 13.0% and 3.8%, respectively (Figure 3).

Discussion

To the best of our knowledge, this is the first Italian population-based study aimed to quantify the impact on outcome, healthcare resource utilization and costs of cirrhosis over 1-year, distinct-

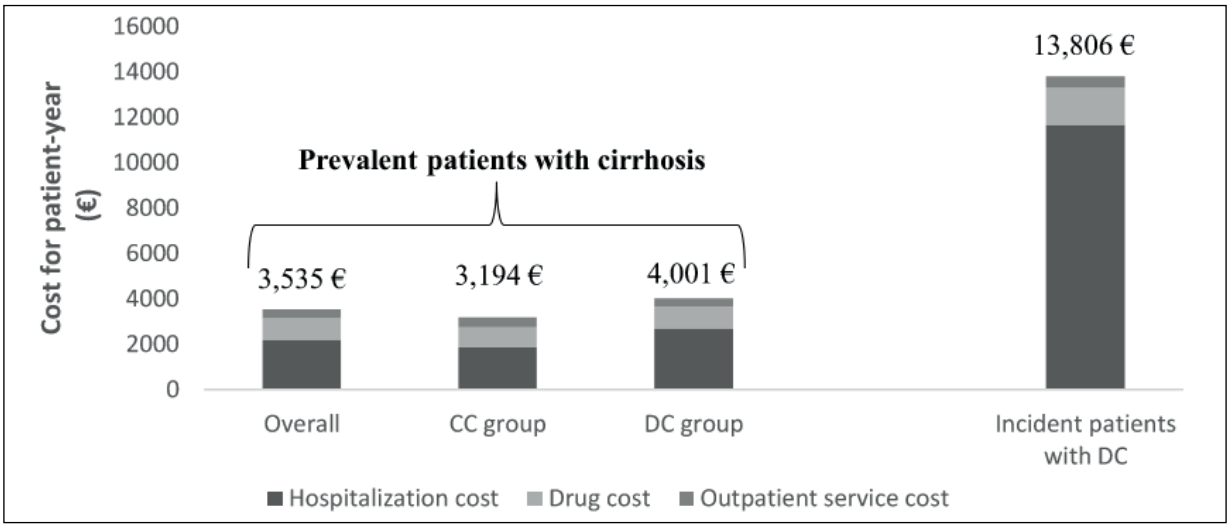

Figure 2. Mean annual costs (€) per patient with cirrhosis by type of healthcare resource.

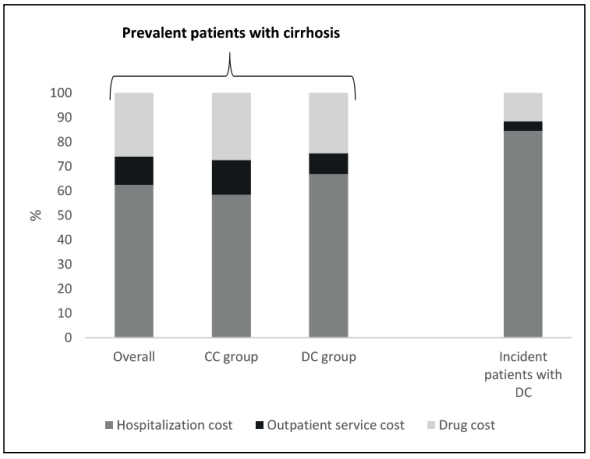

Figure 3. Distribution of costs in patients with cirrhosis by type of healthcare resource.

ly for compensated and decompensated stage. Several studies[16,17] have already estimated the economic burden of cirrhosis in many countries since the high morbidity and mortality associated with this disease, but only few analyses assessed the healthcare expenditure distinctly for CC and DC. Our study provides basic data that could be beneficial for prioritizing health services. In particular, the economic burden of new DC cases highlights the need of new therapeutic strategies aimed to primary prevention of decompensation in order to maximize the potential health economic saving.

First, we found that a total medical expenditure of €73 million euro has been spent for cirrhotic patients in the 2016 calendar year. Direct costs had a significant increasing trend from patients with CC (€3,194/patient-year) to those with DC (€4,001/patient-year). After the onset of decompensation, the direct costs rose up to €13,000/patient-year. Hospitalizations were the cost drivers in both prevalent patients with CC (58.3%) and DC (66.8%), accounting for up to 80% in incident cases with DC. Similar to our findings, a recent cost-analysis based on 34,740 cirrhotic patients in Catalonia found the highest healthcare expenditure for patients with a recent DC compared to those with a previous decompensation and to those with CC[17]. The authors reported that the hospitalizations were the main source of expenditure followed by drugs. A recent Italian study revealed that in patients admitted for cirrhosis and its complications, the hospitalization costs were about 1.5 times higher than those related to patients admitted for other chronic disease such as congestive heart failure or COPD[8].

The increasing economic burden from CC to DC stage is the reflection of the highest hospitalization rates in DC patients. Indeed, our results showed that the proportion of patients admitted for all-cause over 1-year was 21.5% and 26.8% in prevalent patients with CC and DC respectively, whereas the proportion increased to 55.4% during the first year following decompensation. In line with previous studies, the majority of patients with DC were admitted for cirrhosis-related complications (66% and 74% of individuals with prevalent and incident DC, respectively)[18]. The evaluation of factors associated to higher risk of hospitalization may provide useful information to reduce economic losses. The presence of non-liver CMs was associated to a higher risk of hospitalization in both groups of prevalent CC and DC patients, compared to those without non-liver CMs. In particular, the risk of hospitalization increased about 1.5 and 2.8 folds in presence of 1 and ≥2 non-liver CMs, respectively. Conversely, the impact of non-liver CMs is lower in incident patients with DC. These findings confirmed that chronic comorbid conditions play an important role in patients with cirrhosis and negatively affect the prognosis of cirrhotic patients[16]. McDonald et al[19] reported a substantial burden of inpatient resources among Scottish HCV-diagnosed patients with DC, but also from admissions associated with non-liver CMs. In line with our results, the authors showed that the impact of non-liver CMs on inpatient burden increased with the time since the first DC admission. Among incident patients with DC we also found that ascites and HE at index admission were strong predictors of hospitalizations. Therefore, targeted interventions are needed to decrease the rates of hospitalization in the high-risk populations. Previous population-based studies highlighted ascites and HE as predictor for readmissions based on both 30-day and time to readmission analyses[13,18,20]. Volk et al[21] showed that among the 165 re-admissions for DC within 30 days of first discharge, nearly one quarter could have been prevented by better patient understanding of their medication regimen or by more intensive outpatient monitoring. This could be particularly relevant for patients who develop HE, as the adherence to therapy and the awareness of previous HE could probably help to reduce its recurrence[22].

Finally, our results confirmed that the mortality dramatically differs between prevalent patients with CC and DC and incident DC patients. We

found that the 1-year mortality rate was 7.0%, approximately 2 times higher in patients with DC compared to those with CC (10.1% *vs.* 5.8%). The mortality rate dramatically increased after the first episode of decompensation (35.6%). In accordance with our results, the Catalonia study reported an overall 1-year mortality of 6.7%[17]; mortality rate was nearly 4.5 times higher in patients with a recent decompensation compared to those with CC and 2.5 times higher compared to those who had not gone into decompensation for at least one year. In comparison with previous reports on the natural history of cirrhosis, even in the later stages of the 20th century, the probability of dying for decompensation-related causes is still high[3]. Indeed, we found that the highest mortality rates were recorded for patients discharged for ascites (45.7%) and HE (40.0%) (data not shown). Our findings are consistent with prior evidence that identified the presence and the type of complications as strong predictors of 1-year mortality[23,24]. Similarly to ours, a Danish population-based study on alcoholic cirrhosis provided estimates for the 1-year mortality in patients with ascites around 30-50% (depending on whether ascites was alone or in association with esophageal variceal bleeding) and around 60% for patients with HE[23].

Our data should be interpreted in the context of some limitations mainly due to the use of administrative data. First of all, data were retrieved from a large administrative database that did not provide laboratory and instrumental information on patients, so the cirrhosis severity could not be calculated by means of MELD or Child-Pugh scores. Furthermore, data about socioeconomic status (patient income and educational level), which could play a role in the increasing risk of hospitalization, were not available. Second, this study relies on ICD9-CM codes recoded on HDRs for establishing diagnoses; therefore, undercoding or miscoding may have caused misclassification bias. Third, the study does not capture all direct costs from the perspective of the Italian NHS, such as GPs visits and outpatient drugs prescribed by GPs were not available. However, this limitation means that the study is likely to have underestimated the economic burden of cirrhosis on Italian NHS. Finally, our findings may have limited generalizability since they are derived from a single Italian region with high HCV endemicity. It is likely that the etiologies of cirrhosis vary among different populations. Nonetheless, previous studies confirmed our risk factors for hospitalization and resource utilization in other populations with various aetiologies[23]. Despite these limitations, our findings have important implications. Indeed, our data provide estimates of healthcare resource utilization and costs distinctly for CC and DC patients and identify hospitalization drivers in these vulnerable populations over 1-year. Furthermore, unlike many studies analysed only in-hospital mortality, we also estimated patients who died outside of the hospital.

Conclusions

This study highlights those interventions to prevent morbidity and mortality in cirrhotic patients, especially in presence of decompensation stage, are urgently needed. Patients with cirrhosis represent a complex population that can benefit by a systematic multidisciplinary and patient-centred approach. Therefore, the decision makers' efforts should be targeted to define "territorial care models" based on preventive strategies and interventions to improve the quality of care and to delay the progression of disease aiming to a proper allocation of resource.

Conflict of Interest

Simona Cammarota, Anna Citarella and Marianna Fogliasecca are employees of LinkHealth Health Economics, Outcomes & Epidemiology s.r.l., which has received grants from several entities (research institutes, pharmaceutical companies, universities) for performance of epidemiology and health economics studies. Dr. Bernardo Toraldo, belonging to the company "Alfasigma Italia", is also co-author of the manuscript. We state that Dr. Toraldo did not exert any active role in the study design and analysis. Before submission, all co-authors approved the manuscript. All other authors disclose no conflicts of interest.

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Authors' Contribution

Conceptualization, S.C., A.C., E.C., V.C.; data curation, S.C., A.C., M.F., A.V.; formal analysis, S.C., A.C.; methodology, S.C., A.C., E.C., V.R.; supervision, V. C., E.C.; validation, S.C., A.C., E.C., V.C.; visualization, F.F.B., V.M., U.T.; writing – original draft, S.C., A.C.; writing – review & editing, S.C., A.C., B.T., V.M.

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