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Comorbidity and multimorbidity in patients with cirrhosis, hospitalised in an internal medicine ward: a monocentric, cross-sectional study

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ABSTRACT

Objectives There are no data regarding the prevalence of comorbidity (ie, additional conditions in reference to an index disease) and multimorbidity (ie, co-occurrence of multiple diseases in which no one holds priority) in patients with liver cirrhosis. We sought to determine the rate and differences between comorbidity and multimorbidity depending on the aetiology of cirrhosis.

Design This is a subanalysis of the San MAtteo Complexity (SMAC) study. We have analysed demographic, clinical characteristics and rate of comorbidity/multimorbidity of patients with liver cirrhosis depending on the aetiology—alcoholic, infectious and non-alcoholic fatty liver disease (NAFLD). A multivariable analysis for factors associated with multimorbidity was fitted.

Setting Single-centre, cross-sectional study conducted in a tertiary referral, academic, internal medicine ward in northern Italy (November 2017–November 2019).

Participants Data from 1433 patients previously enrolled in the SMAC study were assessed; only those with liver cirrhosis were eventually included.

Results Of the 1433 patients, 172 (median age 79 years, IQR 67–84; 83 females) had liver cirrhosis. Patients with cirrhosis displayed higher median Cumulative Illness Rating Scale (CIRS) comorbidity (4, IQR 3–5; p=0.01) and severity (1.85, IQR 16.–2.0; p<0.001) indexes and lower educational level (103, 59.9%; p=0.003). Patients with alcohol cirrhosis were significantly younger (median 65 years, IQR 56–79) than patients with cirrhosis of other aetiologies (p<0.001) and more commonly males (25, 75.8%). Comorbidity was more prevalent in patients with alcohol cirrhosis (13, 39.4%) and multimorbidity was more prevalent in viral (64, 81.0%) and NAFLD (52, 86.7%) cirrhosis (p=0.015). In a multivariable model for factors associated with multimorbidity, a CIRS comorbidity index >3 (OR 2.81, 95% CI 1.14 to 6.93, p=0.024) and admission related to cirrhosis (OR 0.19, 95% CI 0.07 to 0.54, p=0.002) were the only significant associations.

Conclusions Comorbidity is more common in alcohol cirrhosis compared with other aetiologies in a hospital, internal medicine setting.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We collected prospective data from patients with liver cirrhosis admitted to an internal medicine ward and we have described the rates of, and factors associated with, comorbidity and multimorbidity in this population.
⇒ We have also divided patients according to the liver aetiology, finding that those with alcohol cirrhosis were significantly younger than patients with infectious or non-alcoholic liver disease cirrhosis and more commonly males.
⇒ The sample size was rather small, especially for some cirrhosis aetiologies, so we had to exclude some patients from our analysis.
⇒ Generalisability of our results is limited to the internal medicine setting and cannot be applied to other specialty settings, nor primary care.

INTRODUCTION

Clinical complexity is one of the most challenging issues of modern medicine, especially in internal medicine, and it originates from the interaction between the patient's own factors and other external, but contextual, factors.[1 2] Its fundamental attributes are represented by interconnectedness, non-linearity, context-sensitivity and unpredictability.[3–5] Among the most important determinants of clinical complexity, the association of multiple chronic conditions within the same patient is certainly one of the most relevant, and for some years multiple chronic conditions and clinical complexity have been identified in each other. However, subsequent studies have demonstrated that clinical complexity is something more and different compared with the mere disease associations, and it includes both biological (ie, ageing, multiple chronic conditions, frailty, mental impairment, malnutrition, dependency) and non-biological (ie, socioeconomic,

cultural, environmental, behavioural) variables.[3 6 7] Further, multiple chronic conditions can be split into two important clinical categories, namely comorbidity, which indicates the combined effects of additional conditions in reference to an index disease under study and multimorbidity, which indicates the mere co-occurrence of multiple diseases within the same individual, in which no single disease holds priority.[8 9] The distinction between comorbidity and multimorbidity may translate into substantial differences in the pathways of care.

Among various end-stage organ failure, liver cirrhosis is an example of clinical complexity and of systemic condition.[10] To mention a few disease-related manifestations, ascites, hepatic encephalopathy, cell blood count alterations, coagulopathy and gastrointestinal bleeding, all have a negative impact on both physical and mental functioning.[11] Additionally, patients with cirrhosis frequently have multiple chronic conditions,[12–14] although their impact on prognosis remains unclear,[14] and despite a distinction between comorbidity and multimorbidity has never been assessed. Besides its biological complexity, the impact of socioeconomic factors, that is, education, marital and employment status, household income, is an additional detrimental factor the effects of which appear to vary according to disease aetiology,[15 16] and to have a relevant impact on survival and overall patients' management.[15 17] In particular, different networks and trajectories of disease association might be noticed according to the specific aetiology of cirrhosis, such as chronic viral hepatitis (hepatitis B virus (HBV), hepatitis C virus (HCV) related), alcoholic liver disease, autoimmune liver disease and non-alcoholic fatty liver disease (NAFLD).[18]

On these bases, we sought to analyse a population of patients with cirrhosis admitted to an internal medicine ward, in order to highlight whether any difference exists in the rate of comorbidity, multimorbidity and other determinants of clinical complexity in relation to patients' characteristics and to the specific aetiology of liver cirrhosis.

METHODS

Study population

For the purpose of this paper, data from the San MAtteo Complexity (SMAC) study were used. The SMAC study is a large ongoing prospective research project regarding clinical complexity (NCT03439410) conducted at our Institution (IRCCS San Matteo Hospital Foundation, University of Pavia, Pavia, Italy).[19–22] The primary aim of the SMAC study is the validation of a tool for assessing clinical complexity in hospitalised patients. Several sociodemographic and clinical characteristics were collected, including age, sex, socioeconomic status, cause of admission, polypharmacy and major health outcomes (ie, in-hospital death, hospital readmissions, death at follow-up). Specifically, adult patients (age >18 years) admitted to our internal medicine ward, regardless of the cause, were consecutively enrolled from November 2017 to November 2019 by trained physicians and by a research nurse. All patients' data were collected by the trained researchers, to avoid potential biases. Terminally ill patients with an expected prognosis of less than 48 hours and denial of informed consent were the only exclusion criteria. The telephone follow-up, scheduled every 4 months for the first year after discharge and yearly thereafter for up to 5 years, is still ongoing.

Selection of patients with cirrhosis

In this study, which is a subanalysis of the SMAC study, among all enrolled patients (n=1433), we selected those with a clinical diagnosis of liver cirrhosis according to the International Classification of Diseases-9 codes (ie, 571, 571.2, 571.5, 571.6, 571.4, 571.40, 571.41, 571.49, 571.8 and 571.9). Hence, this is a cross-sectional study, in which we used data from a single time point (ie, the time of discharge of the patient). Also, the discharge letter of each patient with cirrhosis was reviewed for confirming the aetiology of the disease, according to internationally recognised guidelines and recommendations.[23–25] Among all causes of cirrhosis, we categorised patients as having alcohol, viral (either by HBV and/or HCV infection) or NAFLD cirrhosis. Patients with undetermined causes of cirrhosis or with rare causes of cirrhosis (eg, autoimmune liver disease, sclerosing cholangitis and others) were excluded. In the case of multiple aetiologies, we selected either the leading or the more lasting cause of liver injury. Liver cirrhosis was diagnosed on the basis of clinical features, laboratory characteristics, imaging (abdominal ultrasound, liver fibroscan) and liver biopsy (when available).[25] Alcohol cirrhosis was diagnosed when a history of persistent alcohol consumption/abuse was ascertained while the diagnosis of viral hepatitis relied on serology. NAFLD cirrhosis was diagnosed when all other causes of cirrhosis were ruled out, and other clear metabolic alterations were present (ie, obesity/overweight, dyslipidaemia, oral glucose intolerance or diabetes mellitus type II); in some cases, the diagnosis was also confirmed by biopsy.

Definition of comorbidity and multimorbidity

Considering its clinical features and the progressive disease course, liver cirrhosis could ideally represent a model of comorbidity or multimorbidity, both encompassing the concept of multiple chronic conditions. In this regard, recently standardised definitions for comorbidity and multimorbidity[8 9] have been introduced to distinguish patients in the context of multiple chronic conditions. As already stated, comorbidity indicates the combined effects of additional conditions in reference to an index disease under study, whereas multimorbidity indicates the mere co-occurrence of multiple diseases within the same individual, in which no single disease holds priority. Accordingly, specific novel Medical Subject Heading (MeSH) definitions have been released for indexing purposes.[8] Following these definitions, all our patients have been categorised as having either

comorbidity or multimorbidity by an expert physician who reviewed all patients' discharge letters. For example, patients having only complications of liver cirrhosis (namely cirrhosis decompensation, gastrointestinal bleeding, hepatic encephalopathy, ascites) have been categorised as being comorbid (ie, all these conditions are dependent on liver cirrhosis, which is therefore the index disease), while patients with association with other clinically relevant conditions (eg, a patient with liver cirrhosis, ischaemic heart disease, diabetes mellitus type II and chronic kidney failure) have been categorised as having multimorbidity.

Outcomes and variables

As a primary aim, we looked at the rates of comorbidity or multimorbidity and other possible determinants of clinical complexity in patients with cirrhosis, compared with the whole SMAC cohort. As a secondary aim, we compared the rate of comorbidity and multimorbidity according to the aetiology of liver cirrhosis, as well as other potential determinants of clinical complexity, including sex, body mass index (BMI), schooling (categorised into <8 or ≥8, which is the legal number of compulsory education), income (categorised into <€1000/month or ≥€1000/month), Cumulative Illness Rating Scale (CIRS) comorbidity e severity index, Edmonton Frail Scale (a score >5 indicates being frail),[26] Barthel index (a score <60 indicates dependency),[27] Short Blessed Test (a score >9 indicated cognitive impairment),[28] length of stay (LOS). The causes of admission to hospital were categorised as either related or unrelated to liver cirrhosis and were included in the multivariable analysis. Finally, we sought to determine the factors affecting the risk of having multimorbidity according to the aetiology.

Statistical analysis

Continuous data were described with the median and IQR and compared with the Mann-Whitney U test or the Kruskall-Wallis test. Categorical data were reported as counts and per cent and compared with the Fisher's exact test. Based on clinical considerations, we chose a priori a series of candidate variables, which were considered the most relevant patient clinical characteristics according to the aetiology of cirrhosis. These were checked for collinearity and were included in a logistic multivariable model. For descriptive purposes, the univariable analysis of the candidate variables was also performed. The area under the model receiver operating characteristic (ROC) curve was computed as a measure of model performance. The model calibration was assessed graphically using the calibration plot and the corresponding statistic test was computed. We did not formally calculate the sample size for this substudy, as all patients from the SMAC registry were included. However, given the overall sample of 172 patients with cirrhosis with 36 patients with comorbidity, we would be able to fit a multivariable model with up to about four predictors without overfitting, according to the 1:10 predictors to event rule. A posteriori the good calibration of our model with 6 df was assessed, as described above. The software Stata V.17 (StataCorp) was used for all computations. The study follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations for reporting.

Patient and public involvement

None.

RESULTS

Table 1 reports the baseline characteristics of the entire cohort of 172 patients with cirrhosis (median age 79 years, IQR 67–84; 83 females) compared with the other 1261 patients (median age 80 years, IQR 70–86; 685 females) included in the SMAC study. Patients with cirrhosis displayed higher CIRS comorbidity (4, IQR 3–5, p=0.01) and severity (1.85, IQR 1.6–2.0, p<0.001) indexes and lower educational level (103, 59.9%, p=0.002). No other significantly different results were noticed for sex, nutritional status, frailty, dependency, cognitive impairment, income and living alone.

Table 2 reports the main demographic and clinical characteristics of patients with liver cirrhosis according to their aetiologies. Notably, we found that patients with alcohol cirrhosis were significantly younger (median age 65 years, IQR 56–79) and more commonly males (25, 75.8%) than patients with cirrhosis of other aetiologies (p<0.001). Further, BMI was significantly higher (27.1, IQR 23.7–31.8) in patients with NAFLD cirrhosis (p<0.001). No differences among groups were noticed in terms of CIRS comorbidity and severity indexes, frailty, dependency, cognitive impairment, living alone, schooling and LOS. Regarding comorbidity and multimorbidity, we found a significant (p=0.015) difference in their prevalence among the three liver aetiologies under study (p=0.015). Particularly, comorbidity was more prevalent in patients with alcohol cirrhosis (13, 39.4%) while multimorbidity was more prevalent in viral (64, 81.0%) and NAFLD (52, 86.7%) cirrhosis.

Finally, in a multivariable model (table 3), we found that a CIRS comorbidity index >3 (OR 2.81, 95% CI 1.14 to 6.93, p=0.024) was significantly correlated with having multimorbidity. On the contrary, admission related to cirrhosis (OR 0.19, 95% CI 0.07 to 0.54, p=0.002) was inversely correlated with the presence of multimorbidity. Online supplemental figure 1 shows the good calibration of the model while online supplemental table 1 shows the univariable analysis of the candidate variables.

DISCUSSION

We here found some important differences regarding baseline clinical characteristics of patients with cirrhosis compared with the whole cohort of patients hospitalised in an academic, internal medicine ward. In particular, patients with cirrhosis had even greater CIRS indexes (comorbidity and severity) and higher rates of

Table 1 Baseline characteristics of the entire cohort of patients

	Patients with cirrhosis	Other patients*	P value
Total number of patients, n (%)	172 (12.0)	1261 (88.0)	
Age, median (IQR)	79.0 (67.0–84.0)	80.0 (70.0–86.0)	0.275
Sex, n (%)			0.079
M	89 (51.7)	576 (45.7)	
F	83 (48.3)	685 (54.3)	
CIRS Comorbidity Index, median (IQR)	4.0 (3.0–5.0)	4.0 (2.0–5.0)	0.01
CIRS Severity Index, median (IQR)	1.85 (1.6–2.0)	1.77 (1.5–1.9)	<0.001
Co-multimorbidity, n (%)			0.003
None	0 (0)	57 (4.6)	
Comorbidity	35 (20.5)	251 (20.4)	
Multimorbidity	136 (79.5)	923 (75.0)	
BMI, median (IQR)	25.1 (21.5–29.2)	24.2 (21.3–27.7)	0.057
Edmonton Frail Scale >5, n (%)			0.724
No	50 (29.1)	377 (30.6)	
Yes	122 (70.9)	854 (69.4)	
Barthel index <60, n (%)			0.508
No	134 (77.9)	956 (77.6)	
Yes	38 (22.1)	276 (22.4)	
Short blessed test >9, n (%)			0.870
No	82 (47.9)	578 (47.1)	
Yes	89 (52.1)	649 (52.9)	
Income <€1000/month, n (%)			0.935
No	89 (51.7)	641 (52.2)	
Yes	83 (48.3)	587 (47.8)	
Living alone, n (%)			0.439
No	137 (79.6)	944 (76.6)	
Yes	35 (20.4)	288 (23.4)	
Schooling <8 years, n (%)			0.032
No	69 (40.1)	590 (47.8)	
Yes	103 (59.9)	640 (52.0)	
Length of stay, median (IQR)	14.0 (9.0–20.0)	14.0 (10.0–23.0)	0.018

*This includes all the other patients enrolled in the SMAC study, with the exception of patients with cirrhosis, as explained in the text.
BMI, body mass index; CIRS, Cumulative Illness Rating Scale; SMAC, San MAtteo Complexity.

comorbidity and multimorbidity, as well as a lower educational level, despite being similarly frail and dependent, and had a similarly impaired cognitive function. These latter results were not unexpected, considering that our controls were similarly old (median age 80 years vs 78) and hospitalised. In a similar large, prospective and multicentre study, although including only patients greater than 65 years old, enrolled in internal medicine and geriatric wards, among 6193 patients, liver cirrhosis was found in 315 (5%); of these, 43% were multimorbid, 44% had cognitive impairment and 51% were disabled.[29]

This study is the first in which a distinction between comorbidity and multimorbidity in a population of hospitalised patients with a specific chronic disease was performed. Indeed, previous studies have analysed the presence of multiple chronic conditions in patients with liver disease,[12–14] but the term 'comorbidity' has been used with a different meaning, outside the current MeSH definition.[8] In these studies,[12–14] it was evident that patients with cirrhosis suffered from many other disorders, but they have not been identified as either a consequence of cirrhosis itself or its aetiological factor (ie, comorbidities) or as separate entities (ie, multimorbidity).

Regarding differences among cirrhosis aetiologies in our study, we found that viral (median age 81 years, IQR 77–85) and NAFLD (median age 78 years, IQR 65–82) patients with cirrhosis were significantly older

Table 2 Baseline characteristics of patients with cirrhosis according to the aetiology

	Alcohol (I)	Viral (II)	NAFLD (III)	P value
Total number of patients, n (%)	33 (19.2)	79 (45.9)	60 (34.9)	/
Age, median (IQR)	65 (56–79)	81 (77–85)	78 (65–82)	<0.001
				0.007 (II vs III)
				<0.001 (II vs I)
				0.005 (III vs I)
Sex, n (%)				0.008
Male	25 (75.8)	37 (46.8)	27 (45.0)	
Female	8 (24.2)	42 (53.2)	33 (55.0)	
CIRS Comorbidity Index, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–6.0)	0.314
CIRS Severity Index, median (IQR)	1.85 (1.62–1.92)	1.85 (1.62–2.0)	1.85 (1.69–2.15)	0.423
Co-multimorbidity, n (%)				0.015
Comorbidity	13 (39.4)	15 (19.0)	8 (13.3)	
Multimorbidity	20 (60.6)	64 (81.0)	52 (86.7)	
BMI, median (IQR)	23.4 (21.5–29.4)	23.5 (20.5–26.6)	27.1 (23.7–31.8)	<0.001
				<0.001 (II vs III)
				0.11 (II vs I)
				0.02 (III vs I)
Edmonton Frail Scale >5, n (%)				0.604
No	11 (33.3)	20 (25.3)	19 (31.7)	
Yes	22 (66.7)	59 (74.7)	41 (68.3)	
Barthel index <60				0.164
No	29 (87.9)	57 (72.1)	48 (80)	
Yes	4 (12.1)	22 (27.9)	12 (20)	
Income <€1000/month, n (%)				0.523
No	14 (42.4)	43 (54.4)	32 (53.3)	
Yes	19 (57.6)	36 (45.6)	28 (46.7)	
Living alone, n (%)				0.219
No	26 (78.8)	59 (74.7)	52 (86.7)	
Yes	7 (21.2)	20 (25.3)	8 (13.3)	
Schooling <8 years, n (%)				0.282
No	12 (36.4)	28 (35.4)	29 (48.3)	
Yes	21 (63.6)	51 (64.6)	31 (51.7)	
Short blessed test >9, n (%)				0.102
No	20 (60.6)	31 (39.7)	31 (51.7)	
Yes	13 (39.4)	47 (60.3)	29 (48.3)	
Length of stay, median (IQR)	12.0 (8.0–19.0)	14.0 (9.0–19.0)	14.0 (10.0–21.5)	0.423

BMI, body mass index; CIRS, Cumulative Illness Rating Scale; NAFLD, non-alcoholic fatty liver disease.

than alcohol cirrhosis patients (median age 65 years, IQR 56–79), as already demonstrated in other studies which, however, were conducted in completely different settings (eg, population level or specialty settings).[12 30 31] This translates into a higher rate of multimorbidity—that we actually found—possibly due to the stochastic accumulation of different disorders with advanced age. Conversely, in patients with alcohol cirrhosis, the higher rate of comorbidity could be interpreted as a direct consequence of alcohol abuse which is a strong and well-known risk factor for multiple organ involvement, often underlying a common psychopathological basis.[32] Additionally, in the alcohol cirrhosis group, we found a clear male predominance, while in the other groups, there was not a prominent difference with regard to biological sex, and this is consistent with previous reports.[31 33] Of note, although a higher prevalence of alcoholic cirrhosis in male patients is expected, the gap in alcohol consumption between men and women has been progressively narrowing over the last years.[34]

Admission related to cirrhosis was found to be inversely related to the presence of multimorbidity while CIRS

Table 3 Multivariable analysis for factors associated with multimorbidity

	OR	95% CI	P value
Sex			
Male	1.0 (reference)	0.64 to 4.14	0.308
Female	1.63		
Aetiology of cirrhosis			0.148
Viral	1.0 (reference)		
NAFLD	0.81	0.27 to 2.40	0.698
Alcohol	0.35	0.12 to 1.02	0.055
CIRS Comorbidity Index >3			
No	1.0 (reference)		
Yes	2.81	1.14 to 6.93	0.024
Barthel index <60			
No	1.0 (reference)	0.61 to 13.29	0.186
Yes	2.84		
Admission related to cirrhosis			
No	1.0 (reference)	0.07 to 0.54	0.002
Yes	0.19		

Model χ^2 32.23, p<0.001; area under the receiver operating curve (ROC)=0.79; calibration belt p=0.709, plot within 95% CI.
CIRS, Cumulative Illness Rating Scale; NAFLD, non-alcoholic fatty liver disease.

was directly related to multimorbidity. These correlations represent a counterproof of the validity of the classification applied for categorising patients as having either comorbidity or multimorbidity. For example, a patient with cirrhosis and many other randomly associated multiple chronic conditions (multimorbid) would be more likely to be admitted to hospital due to one of these many multiple chronic conditions compared with a patient with cirrhosis and its classical comorbidities, such as ascites, gastrointestinal bleeding or encephalopathy (comorbid). It is not surprising that, according to a recent expert consensus, the evaluation of socioeconomic factors, educational status and comorbid psychiatric illness should all be taken into account by a multidisciplinary team in alcohol cirrhosis patients.[32] In fact, a low educational level was found to be common in our alcohol cirrhosis patients, and interventions aimed at improving one's knowledge of the disease may translate into a therapeutic advantage.

LIMITATIONS

We are aware that our study has some limitations that should be mentioned. The sample size was rather small, especially for some cirrhosis aetiologies (eg, autoimmune liver disease) so we had to exclude these patients from our analysis. Hence, a wider multivariable analysis could not be made. Even if our data should be considered as preliminary in this field, a distinction between comorbidity and multimorbidity could potentially aid decision-making in patients with cirrhosis, in whom a prioritisation of the clinical problems to be solved is mandatory. Also, our data should be interpreted in the light of the specific setting of enrolment, in which patients admitted are usually older than others. Hence, our data cannot be generalised to other settings, like that of the population level or the primary care. Nevertheless, this study had some strengths, including a prospective collection of data, not administrative based, but collected during the hospitalisation by a dedicated and qualified staff of healthcare professionals who had been instructed before study commencement.[20]

Conclusion

To conclude, we have performed the first study focusing on the distinction of comorbidity and multimorbidity in a cohort of patients with a specific chronic condition. We found that patients with alcoholic cirrhosis had a high comorbidity rate, while the other aetiologies—viral and NAFLD—were mostly multimorbid due to ageing. How these characteristics may translate into distinct and personalised clinical management should be further investigated.

Contributors All authors participated in the drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version. Individual contributions are as follows: GRC designed and coordinated the study; MVL and AB drafted the manuscript; MVL, AB, GC, ASB, LP, GB and ADS organised data collection conducted the study and/or enrolled patients; CK designed and performed statistical analysis, interpreted data and revised the manuscript; GRC made the final critical revision for important intellectual content. GRC is the guarantor of the article. All authors approved the final version of the paper.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All patients provided written informed consent prior to study enrolment and the study protocol was approved by the local Ethics Committee (San Matteo Hospital Foundation; 3 July 2017, protocol number 2017/0019414). Consent for publication of data was obtained from all patients. This research was performed in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The full dataset of the study cannot be shared publicly at this stage since the SMAC study is still ongoing. Additional data can be shared on request to the authors (please contact GRC at the email address provided).

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