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Determinants of clinical complexity in hospitalised cirrhotic patients

Running head: liver cirrhosis and co-multimorbidity

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Abstract

Objectives: There are no data regarding the prevalence of comorbidity (i.e., additional conditions in reference to an index disease) and multimorbidity (i.e., 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 co-multimorbidity depending on the aetiology of cirrhosis. **Design:** This is a sub-analysis of the SMAC study (prospective study, internal medicine ward). We have analysed demographic and clinical characteristics of patients with liver cirrhosis depending on the aetiology - alcoholic, infectious, and non-alcoholic fatty liver disease (NAFLD). The prevalence and risk factors for comorbidity and multimorbidity were assessed. **Setting**: Single-centre study conducted in a tertiary referral, academic, internal medicine ward in northern Italy. **Participants**: Data from 1451 patients previously enrolled in the SMAC study were assessed; only those with liver cirrhosis were eventually included. **Results:** Of the 1451 patients, 187 (median age 78 years, IQR 66-84; 88 females) had liver cirrhosis. Patients with cirrhosis displayed higher Cumulative Illness Rating Scale (CIRS) comorbidity (p=0.003) and severity (p<0.001) indexes, and lower educational level (p=0.002). Patients with alcohol cirrhosis were significantly younger than patients with cirrhosis of other aetiologies (p<0.001) and more commonly males. Comorbidity was more prevalent in patients with alcohol cirrhosis and multimorbidity more prevalent in viral and NAFLD cirrhosis (p=0.015). In a multivariable model for factors associated with multimorbidity, a CIRS comorbidity index >3 (OR 2.81, p=0.024) and admission related to cirrhosis (OR 0.19, p=0.002) were the only significant associations. **Conclusions:** Patients with liver cirrhosis had a higher disease burden and a lower educational level compared to other patients. The different patterns of co- and multimorbidity might translate into different pathways of care.

Keywords: ageing; alcohol; chronic liver disease; multimorbidity.

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 for the first time 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 to the primary care.

Introduction

Clinical complexity (CC) 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 CC, the association of multiple chronic conditions (MCC) within the same patient is certainly one of the most relevant, and for some years MCC and CC have been identified in each other. However, subsequent studies have demonstrated that CC is something more and different compared to the mere disease associations, and it includes both biological (i.e., ageing, MCC, frailty, mental impairment, malnutrition, dependency) and non-biological (i.e., socioeconomic, cultural, environmental, behavioural) variables.[3,6,7]

Among various end-stage organ failure, liver cirrhosis is an example of CC and of systemic condition.[8] 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.[9] Additionally, patients with cirrhosis frequently have MCC,[10-12] although their impact on prognosis remains unclear.[12] Besides its biological complexity, the impact of socioeconomic factors, i.e., education, marital and employment status, household income, is an additional detrimental factor the effects of which appear to vary according to disease aetiology,[13,14] and to have a relevant impact on survival and overall patients' management.[13,15] In particular, different networks and trajectories of disease association might be noticed according to the specific aetiology of cirrhosis, such as chronic viral hepatitis (HBV-, HCV-related), alcoholic liver disease, autoimmune liver disease, and non-alcoholic fatty liver disease (NAFLD).[16]

On these bases, we sought to analyse a population of cirrhotic patients admitted to an internal medicine ward, in order to highlight whether any difference exists in the rate of MCC

and other determinants of CC in relation to patients' characteristics and to the specific aetiology of liver cirrhosis.

Methods

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.[17-20] 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. Patients with a prognosis <48 hours and denial of informed consent were the only exclusion criteria. The telephone follow-up, scheduled for up to five years, is still ongoing.

In the present study, which is a sub-analysis of the SMAC study, among all enrolled patients (n. 1451), we selected those with a clinical diagnosis of liver cirrhosis according to the International Classification of Diseases (ICD) 9 codes (i.e., 571, 571.2, 571.5, 571.6, 571.4, 571.40, 571.41, 571.49, 571.8, 571.9). Also, the discharge letter of each cirrhotic patient was reviewed for confirming the aetiology of the disease. Applying these criteria, 187 cirrhotic patients (median age 78 years, IQR 66-84; 88 females) were identified.

Among all causes of cirrhosis, we categorised patients as having alcohol, viral (either by HBV and/or HCV infection), or NAFLD cirrhosis. For comparison among liver aetiologies, we excluded patients with undetermined or rare causes of cirrhosis, namely primary biliary cholangitis (n=1), cryptogenic or undetermined cirrhosis (n=12), Budd-Chiari syndrome (n=1), and polycystic liver disease with advanced liver failure (n=1). In the "undetermined" aetiology group, we have also included cases in which a single aetiology, among many, was not possible to ascertain. In case of multiple aetiologies, we selected either the leading or the more lasting cause of liver injury.

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 MCC. In this regard, recently standardised definitions for comorbidity and multimorbidity have been introduced to distinguish patients in the context of MCC.[20-22] In particular, 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.[21] Following these definitions, all our patients have been categorised as having either comorbidity or multimorbidity. For example, patients having only complications of liver cirrhosis (namely cirrhosis decompensation, gastrointestinal bleeding, hepatic encephalopathy, ascites) have been categorised as being comorbid, while patients with association with other conditions have been categorised as having multimorbidity.

As a primary aim, we looked at possible determinants of CC in cirrhotic patients, compared to the whole SMAC cohort, as well as the overall rates of co- or multimorbidity. 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 CC, including sex, BMI, schooling, income, Cumulative Illness Rating Scale (CIRS) comorbidity e severity index, resilience, Edmonton Frail Scale, Barthel index, Short Blessed Test (SBT), 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.

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). The consent for publication of data was also obtained by all patients. This research was performed in accordance with the Declaration of Helsinki. There were no uneducated participants in this study. 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 upon request to the authors.

Statistical analysis

Continuous data were described with the median and interquartile range (IQR) and compared with the Mann Whitney U test or the Kruskall Wallis test. Categorical data were reported as counts and percent and compared with the Fisher 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. The area under the model 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. The software Stata 17 (StataCorp, College Station, TX, USA) was used for all computations. The study follows the STROBE recommendations for quality assurance.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Table 1 reports the baseline characteristics of the entire cohort of 187 cirrhotic patients compared to the other 1264 patients included in the SMAC study. Patients with cirrhosis

displayed higher CIRS comorbidity (p=0.003) and severity (p<0.001) indexes, higher rate of comorbidity (p=0.001), lower educational level (p=0.002), and higher length of stay (p=0.025). No other significantly different results were noticed for sex, nutritional status, frailty, dependency, cognitive impairment, income, and living alone. Thereafter, 15 cirrhotic patients were excluded, as having rarer or undetermined aetiologies, and the subsequent analyses will therefore focus on 172 patients.

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 and more commonly males than patients with cirrhosis of other aetiologies (p<0.001). As expected, BMI was significantly higher 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 length of stay. Regarding the rates of comorbidity and multimorbidity, we found a statically significant difference among the three groups (p=0.015), being comorbidity more prevalent in patients with alcohol aetiology and multimorbidity more prevalent in viral and NAFLD cirrhosis.

Finally, in a multivariable model looking at factors affecting the risk of having multimorbidity (Table 3), we found that a CIRS comorbidity index >3 (OR 2.81, p=0.024) was significantly correlated, while the admission related to cirrhosis (OR 0.19, p= 0.002) was significantly and inversely correlated with this outcome.

Discussion

Patients with liver cirrhosis, due to their systemic clinical involvement,[8,9] the frequent association with MCC,[10-12] polypharmacy,[11] and the possible interference of extra-biological factors,[11,13,14] certainly represent a prototype of CC. Concerning clustering of MCC, the

recent possibility to label patients as having co- or multimorbidity[20-22] could potentially translate into a different clinical management.[23,24]

We herein found some important differences regarding baseline clinical characteristics of cirrhotic patients compared to the whole cohort of patients hospitalised in an academic, internal medicine ward. In particular, cirrhotic patients had an even greater CIRS indexes (comorbidity and severity) and higher rates of co- 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 multicentric 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.[25]

The present 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 MCC in patients with liver disease,[10-12] but the term “comorbidity” has been used with a different meaning, outside the current MeSH definition.[21] In these studies,[10-12] 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 aetiologic factor (i.e., comorbidities) or as separate entities (i.e., 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) cirrhotic patients were significantly older than alcohol cirrhosis patients (median age 65 years, IQR 56-79), as already demonstrated in other studies.[10,26,27] 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.[28] 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.[27,29] 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.[30]

Admission related to cirrhosis was found to be inversely related to the presence of multimorbidity, while CIRS was directly related to multimorbidity. These correlations represent a counterproof of the validity of the classification applied for categorizing patients as having either co- or multimorbidity. For example, a patient with cirrhosis and many other randomly associated MCC (multimorbid) would be more likely to be admitted to hospital due to one of these many MCC compared to 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.[28] 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 (e.g., 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 co- and multimorbidity could potentially aid decision-making in cirrhotic patients, 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 in others. 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.[18]

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.

Data availability statement

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 upon request to the authors (please contact Prof. Gino Roberto Corazza at the email address provided).

Ethics statements

Patient consent for publication

Acquired by all patients before enrolment.

Ethics approval

The study protocol was approved by the local Ethics Committee (San Matteo Hospital Foundation; 3 July 2017, Protocol number 2017/0019414). This research was performed in accordance with the Declaration of Helsinki. There were no uneducated participants in this study.

Competing interests

The authors report no conflict of interest.

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Authors contributions

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 follow: GRC designed and coordinated the study; MVL and AB drafted the manuscript; all authors 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. All authors approved the final version of the paper.

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None.

Abbreviations: CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; LOS, length of stay; MCC, multiple chronic conditions; MeSH, medical subject heading; NAFLD, non-alcoholic fatty liver disease; SBT, Short Blessed Test; SMAC, San MAtteo Complexity.

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Table 1. Baseline characteristics of the entire cohort of patients.

	Cirrhotic patients	*Other patients	p value
Total number of patients, n (%)	187 (12.9)	1264 (87.1)	
Age, median (IQR)	78.0 (66.0-84.0)	80.0 (70.0-86.0)	0.351
Sex, n (%)			0.071
M	99 (52.9)	579 (45.8)	
F	88 (47.1)	685 (54.2)	
CIRS comorbidity index, median (IQR)	4.0 (3.0-5.0)	4.0 (2.0-5.0)	0.003
CIRS severity index, median (IQR)	1.8 (1.6-2.0)	1.7 (1.5-1.9)	<0.001
Co- multimorbidity, n (%)			0.001
None	0 (0)	57 (4.6)	
Comorbidity	42 (22.7)	250 (20.3)	
Multimorbidity	143 (77.3)	927 (75.1)	
BMI, median (IQR)	25.2 (21.5-29.3)	24.2 (21.3-27.7)	0.056
Edmonton >5, n (%)			1.0
No	57 (30.5)	377 (30.5)	
Yes	130 (69.5)	857 (69.5)	
Barthel <60, n (%)			0.706
No	148 (79.1)	957 (77.5)	
Yes	39 (20.9)	278 (22.5)	
SBT >9, n (%)			1.0
No	88 (47.3)	580 (47.2)	
Yes	98 (52.7)	650 (52.8)	
Income <1000 €/mon, n (%)			0.814
No	96 (51.3)	644 (52.3)	
Yes	91 (48.7)	587 (47.7)	
Living alone, n (%)			0.514
No	148 (79.1)	948 (76.8)	
Yes	39 (20.9)	287 (23.2)	
Schooling <8, n (%)			0.023
No	73 (39.0)	592 (48.0)	
Yes	114(61.0)	641 (52.0)	
LOS median (IQR)	14.0 (9.0-20.0)	15.0 (10.0-23.0)	0.025

*This includes all the other patients enrolled in the SMAC study, with the exception of cirrhotic patients, as explained in the text. Abbreviations: BMI, Body Mass Index; CIRS, Cumulative Illness Rating Scale; SBT, Short Blessed Test; LOS, long of stay.

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 >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 <60				0.164
No	29 (87.9)	57 (72.1)	48 (80)	
Yes	4 (12.1)	22 (27.9)	12 (20)	
Income <1000 €/mon, 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, n (%)				0.282
No	12 (36.4)	28 (35.4)	29 (48.3)	
Yes	21 (63.6)	51 (64.6)	31 (51.7)	
SBT >9, n (%)				0.102
No	20 (60.6)	31 (39.7)	31 (51.7)	
Yes	13 (39.4)	47 (60.3)	29 (48.3)	
LOS median (IQR)	12.0 (8.0-19.0)	14.0 (9.0- 19.0)	14.0 (10.0-21.5)	0.423

Abbreviations: BMI, Body Mass Index; CIRS, Cumulative Illness Rating Scale; SBT, Short Blessed Test; LOS, length of stay.

Table 3. Multivariable analysis for factors associated with multimorbidity.

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

Model Chi^2 36.77, p-value<0.001; area under the ROC curve=0.81; calibration belt p=0.615, plot within 95% CI. Abbreviations: Cumulative Illness Rating Scale, CIRS; NAFLD, non-alcoholic fatty liver disease.

STROBE Statement—checklist of items that should be included in reports of observational studies
Paper: Determinants of clinical complexity in hospitalized cirrhotic patients by Lenti MV et al.

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	6-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-8
		(*b*) Report category boundaries when continuous variables were categorized	6-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

Running head: liver cirrhosis and co-multimorbidity

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Abstract

Objectives: There are no data regarding the prevalence of comorbidity (i.e., additional conditions in reference to an index disease) and multimorbidity (i.e., 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 co-multimorbidity depending on the aetiology of cirrhosis. **Design:** This is a sub-analysis of the SMAC study. We have analysed demographic, clinical characteristics, and rate of co-/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 (Novembre 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 patients, 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 patients, 75.8%). Comorbidity was more prevalent in patients with alcohol cirrhosis (13 patients, 39.4%) and multimorbidity more prevalent in viral (64 patients, 81.0%) and NAFLD (52 patients, 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 1.14-6.93, p=0.024) and admission related to cirrhosis (OR 0.19, 95% CI 0.07-0.54, p=0.002) were the only significant associations.

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

Keywords: ageing; alcohol; chronic liver disease; multimorbidity.

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 for the first time 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 to the 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 to the mere disease associations, and it includes both biological (i.e., ageing, multiple chronic conditions, frailty, mental impairment, malnutrition, dependency) and non-biological (i.e., 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, i.e., 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 (HBV-, 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 cirrhotic patients 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 hospitalized patients. Several sociodemographic and clinical characteristics were collected, including age, sex, socioeconomic status, cause of admission, polypharmacy, and major health outcomes (i.e., 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, so do 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 five years, is still ongoing.

Selection of cirrhotic patients

In the present study, which is a sub-analysis 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 (ICD) 9 codes (i.e., 571, 571.2, 571.5, 571.6, 571.4, 571.40, 571.41, 571.49, 571.8, 571.9). Hence, this is a cross-sectional study, in which we used data in a single timepoint (i.e., the time of discharge of the patient). Also, the discharge letter of each cirrhotic patient 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 (e.g., autoimmune liver disease, sclerosing cholangitis, others) were excluded. In 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 (i.e., 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 (i.e., all these conditions are dependent on liver cirrhosis, which is therefore the index disease), while patients with association with other clinically relevant conditions (e.g., a patient with liver cirrhosis, ischemic heart disease, diabetes mellitus type II, and chronic kidney failure) have been categorised as having multimorbidity.

Aims of the study and variables included

As a primary aim, we looked at the rates of co- or multimorbidity and other possible determinants of clinical complexity in cirrhotic patients, compared to 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, 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 (SBT; 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 and ethics considerations

Continuous data were described with the median and interquartile range (IQR) and compared with the Mann Whitney U test or the Kruskall Wallis test. Categorical data were reported as counts and percent and compared with the Fisher 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. The area under the model 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 sub-study, as all patients from the SMAC registry were included. However, given the overall sample of 1433 patients and 172 cirrhotic patients, we were able to fit a multivariable model with up to 17 predictors without overfitting. The software Stata 17 (StataCorp, College Station, TX, USA) was used for all computations. The study follows the STROBE recommendations for quality assurance.

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). The consent for publication of data was also obtained by all patients. This research was performed in accordance with the Declaration of

Helsinki. 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 upon request to the authors.

Patient and public involvement

None.

Results

Table 1 reports the baseline characteristics of the entire cohort of 172 cirrhotic patients (median age 79 years, IQR 67-84; 83 females) compared to 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 patients, 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 patients, 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 length of stay. 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 patients, 39.4%), while

multimorbidity was more prevalent in viral (64 patients, 81.0%) and NAFLD (52 patients, 86.7%) cirrhosis.

Finally, in a multivariable model (Table 3) we found that a CIRS comorbidity index >3 (OR 2.81, 95% CI 1.14-6.93, p=0.024) was significantly correlated with having multimorbidity. On the contrary, admission related to cirrhosis (OR 0.19, 95% CI 0.07-0.54, p=0.002) was inversely correlated with the presence of multimorbidity.

Discussion

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

The present 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 aetiologic factor (i.e., comorbidities) or as separate entities (i.e., 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) cirrhotic patients were significantly older 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 (e.g., population level or specialistic 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 was directly related to multimorbidity. These correlations represent a counterproof of the validity of the classification applied for categorizing patients as having either co- 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 to 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 (e.g., 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 co- and multimorbidity could potentially aid decision-making in cirrhotic patients, 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 in 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.

Data availability statement

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 upon request to the authors (please contact Prof. Gino Roberto Corazza at the email address provided).

Ethics statements

Patient consent for publication

Acquired by all patients before enrolment.

Ethics approval

The study protocol was approved by the local Ethics Committee (San Matteo Hospital Foundation; 3 July 2017, Protocol number 2017/0019414). This research was performed in accordance with the Declaration of Helsinki. There were no uneducated participants in this study.

Competing interests

The authors report no conflict of interest.

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Authors contributions

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 follow: 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. All authors approved the final version of the paper.

Acknowledgements

None.

Abbreviations: CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; LOS, length of stay; MeSH, medical subject heading; NAFLD, non-alcoholic fatty liver disease; SBT, Short Blessed Test; SMAC, San MAtteo Complexity.

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Table 1. Baseline characteristics of the entire cohort of patients.

	Cirrhotic patients	*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 >5, n (%)			0.724
No	50 (29.1)	377 (30.6)	
Yes	122 (70.9)	854 (69.4)	
Barthel <60, n (%)			0.508
No	134 (77.9)	956 (77.6)	
Yes	38 (22.1)	276 (22.4)	
SBT >9, n (%)			0.870
No	82 (47.9)	578 (47.1)	
Yes	89 (52.1)	649 (52.9)	
Income <1000 €/mon, 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, n (%)			0.032
No	69 (40.1)	590 (47.8)	
Yes	103 (59.9)	640 (52.0)	
LOS 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 cirrhotic patients, as explained in the text. Abbreviations: BMI, Body Mass Index; CIRS, Cumulative Illness Rating Scale; SBT, Short Blessed Test; LOS, lenght of stay.

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 >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 <60				0.164
No	29 (87.9)	57 (72.1)	48 (80)	
Yes	4 (12.1)	22 (27.9)	12 (20)	
Income <1000 €/mon, 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, n (%)				0.282
No	12 (36.4)	28 (35.4)	29 (48.3)	
Yes	21 (63.6)	51 (64.6)	31 (51.7)	
SBT >9, n (%)				0.102
No	20 (60.6)	31 (39.7)	31 (51.7)	
Yes	13 (39.4)	47 (60.3)	29 (48.3)	
LOS median (IQR)	12.0 (8.0-19.0)	14.0 (9.0- 19.0)	14.0 (10.0-21.5)	0.423

Abbreviations: BMI, Body Mass Index; CIRS, Cumulative Illness Rating Scale; SBT, Short Blessed Test; LOS, length of stay.

Table 3. Multivariable analysis for factors associated with multimorbidity.

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

Model Chi^2 36.77, p-value<0.001; area under the ROC curve=0.81; calibration belt p=0.615, plot within 95% CI. Abbreviations: Cumulative Illness Rating Scale, CIRS; NAFLD, non-alcoholic fatty liver disease.

STROBE Statement—checklist of items that should be included in reports of observational studies
Paper: Determinants of clinical complexity in hospitalized cirrhotic patients by Lenti MV et al.

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	6-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-8
		(*b*) Report category boundaries when continuous variables were categorized	6-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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Comorbidity and multimorbidity in cirrhotic patients 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 (i.e., additional conditions in reference to an index disease) and multimorbidity (i.e., 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 co-multimorbidity depending on the aetiology of cirrhosis.

Design: This is a sub-analysis of the SMAC study. We have analysed demographic, clinical characteristics, and rate of co-/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 (Novembre 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 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 1.14-6.93, p=0.024) and admission related to cirrhosis (OR 0.19, 95% CI 0.07-0.54, p=0.002) were the only significant associations.

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

Keywords: ageing; alcohol; chronic liver disease; multimorbidity.

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 to 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 to the mere disease associations, and it includes both biological (i.e., ageing, multiple chronic conditions, frailty, mental impairment, malnutrition, dependency) and non-biological (i.e., 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, i.e., 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 (HBV-, 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 cirrhotic patients 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 hospitalized patients. Several sociodemographic and clinical characteristics were collected, including age, sex, socioeconomic status, cause of admission, polypharmacy, and major health outcomes (i.e., 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, so do 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 five years, is still ongoing.

Selection of cirrhotic patients

In the present study, which is a sub-analysis 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 (ICD) 9 codes (i.e., 571, 571.2, 571.5, 571.6, 571.4, 571.40, 571.41, 571.49, 571.8, 571.9). Hence, this is a cross-sectional study, in which we used data in a single timepoint (i.e., the time of discharge of the patient). Also, the discharge letter of each cirrhotic patient 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 (e.g., autoimmune liver disease, sclerosing cholangitis, others) were excluded. In 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 (i.e., 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 (i.e., all these conditions are dependent on liver cirrhosis, which is therefore the index disease), while patients with association with other clinically relevant conditions (e.g., a patient with liver cirrhosis, ischemic 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 co- or multimorbidity and other possible determinants of clinical complexity in cirrhotic patients, compared to 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, 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 (SBT; 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 interquartile range (IQR) and compared with the Mann Whitney U test or the Kruskall Wallis test. Categorical data were reported as counts and percent and compared with the Fisher 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 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 sub-study, as all patients from the SMAC registry were included. However, given the overall sample of 172 cirrhotic patients 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 six degrees of freedom was assessed, as described above. The software Stata 17 (StataCorp, College Station, TX, USA) was used for all computations. The study follows the STROBE recommendations for reporting.

Ethical considerations

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.

Patient and public involvement

None.

RESULTS

Table 1 reports the baseline characteristics of the entire cohort of 172 cirrhotic patients (median age 79 years, IQR 67-84; 83 females) compared to 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 length of stay. 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 1.14-6.93, p=0.024) was significantly correlated with having multimorbidity. On the contrary, admission related to cirrhosis (OR 0.19, 95% CI 0.07-0.54, p=0.002) was inversely correlated with the presence of multimorbidity. Supplementary Figure 1 shows the good calibration of the model, while Supplementary Table 1 shows the univariable analysis of the candidate variables.

DISCUSSION

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

The present 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 aetiologic factor (i.e., comorbidities) or as separate entities (i.e., 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) cirrhotic patients were significantly older 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 (e.g., population level or speciality 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 was directly related to multimorbidity. These correlations represent a counterproof of the validity of the classification applied for categorizing patients as having either co- 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 to 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 (e.g., 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 co- and multimorbidity could potentially aid decision-making in cirrhotic patients, 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 in 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.

Data availability statement

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 upon request to the authors (please contact Prof. Gino Roberto Corazza [gr.corazza@smatteo.pv.it]).

Ethics approval and consent to participate

The study protocol was approved by the local Ethics Committee (San Matteo Hospital Foundation; 3 July 2017, Protocol number 2017/0019414). This research was performed in accordance with the Declaration of Helsinki. Participants provided written informed consent.

Competing interests

The authors report no competing interests.

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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 follow: 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. All authors approved the final version of the paper.

Abbreviations: CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; LOS, length of stay; MeSH, medical subject heading; NAFLD, non-alcoholic fatty liver disease; SBT, Short Blessed Test; SMAC, San MAtteo Complexity.

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Supplementary Figure legend

Supplementary Figure 1. Calibration plot for the multivariable logistic model for multi/co-morbidity. The red line of perfect calibration is included in the grey confidence band indicating a good calibration of the model.

Table 1. Baseline characteristics of the entire cohort of patients

	Cirrhotic patients	*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 cirrhotic patients, as explained in the text. Abbreviations: BMI, Body Mass Index; CIRS, Cumulative Illness Rating Scale.

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 (%)	14 (42.4)			0.523
No	19 (57.6)	43 (54.4)	32 (53.3)	
Yes		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 (%)	12 (36.4)			0.282
No	21 (63.6)	28 (35.4)	29 (48.3)	
Yes		51 (64.6)	31 (51.7)	
Short Blessed Test >9, n (%)	20 (60.6)			0.102
No	13 (39.4)	31 (39.7)	31 (51.7)	
Yes		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

Abbreviations: BMI, Body Mass Index; CIRS, Cumulative Illness Rating Scale.

Table 3. Multivariable analysis for factors associated with multimorbidity

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

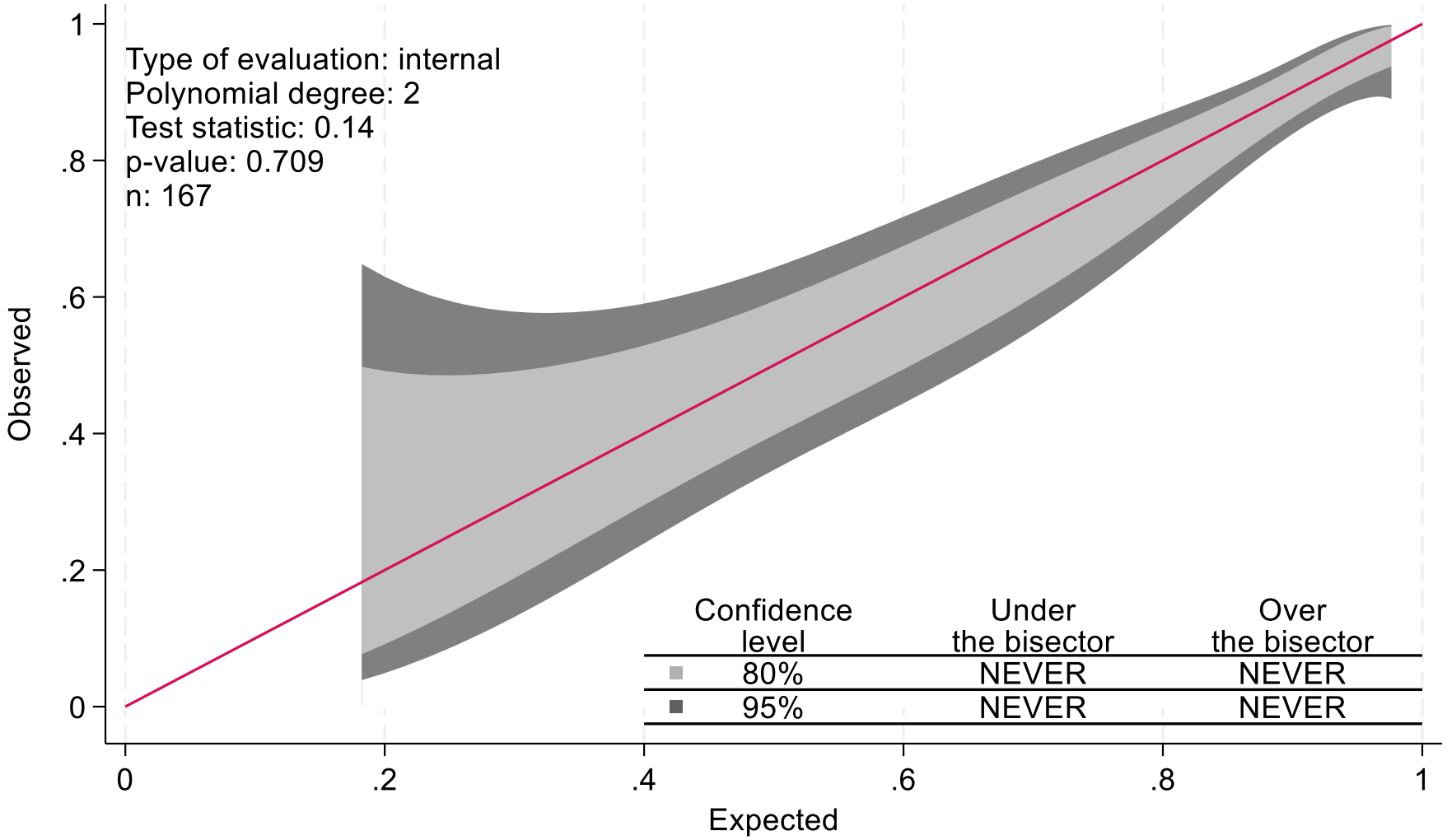
Model Chi^2 32.23, p-value<0.001; area under the ROC curve=0.79; calibration belt p=0.709, plot within 95% CI.

Abbreviations: Cumulative Illness Rating Scale, CIRS; NAFLD, non-alcoholic fatty liver disease.

Supplementary Table 1. Univariable analysis of the candidate variables.

	Comorbidity, n (%)	Multimorbidity, n (%)	p-value
Sex			0.027
Male	29 (29.0)	71 (71.0)	
Female	14 (16.1)	73 (83.9)	
Aetiology of cirrhosis			0.015
Viral	15 (19.0)	64 (81.0)	
NAFLD	8 (13.3)	52 (86.7)	
Alcohol	13 (39.4)	20 (60.6)	
CIRS comorbidity index >3			0.066
No	22 (29.3)	53 (70.7)	
Yes	21 (18.8)	91 (81.2)	
Barthel index <60			0.019
No	39 (26.5)	108 (73.5)	
Yes	4 (10.0)	36 (90.0)	
Admission related to cirrhosis			<0.001
No	24 (16.1)	125 (83.9)	
Yes	18 (56.3)	14 (43.7)	

Supplementary Figure 1



STROBE Statement—checklist of items that should be included in reports of observational studies
Paper: Determinants of clinical complexity in hospitalized cirrhotic patients by Lenti MV et al.

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	6-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-8
		(*b*) Report category boundaries when continuous variables were categorized	6-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.