The multifaceted spectrum of liver cirrhosis in older hospitalised patients: Analysis of the REPOSI registry

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Abstract

Background: Knowledge on the main clinical and prognostic characteristics of older multimorbid subjects with liver cirrhosis (LC) admitted to acute medical wards is scarce.

Objectives: To estimate the prevalence of LC among older patients admitted to acute medical wards and to assess the main clinical characteristics of LC along with its association with major clinical outcomes and to explore the possibility that welldistinguished phenotypic profiles of LC have classificatory and prognostic properties.

Methods: A cohort of 6,193 older subjects hospitalised between 2010 and 2018 and included in the REPOSI registry was analysed.

Results: LC was diagnosed in 315 patients (5%). LC was associated with rehospitalisation (age–sex adjusted hazard ratio, [aHR] 1.44; 95% CI, 1.10–1.88) and with mortality after discharge, independently of all confounders (multiple aHR, 2.1; 95% CI, 1.37–3.22), but not with in-hospital mortality and incident disability. Three main clinical phenotypes of LC patients were recognised: relatively fit subjects (FIT, N = 150), subjects characterised by poor social support (PSS, N = 89) and, finally, subjects with disability and multimorbidity (D&M, N = 76). PSS subjects had an increased incident disability (35% vs 13%, $P < 0.05$) compared to FIT. D&M patients had a higher mortality (in-hospital: 12% vs 3%/1%, $P < 0.01$; post-discharge: 41% vs 12%/15%, $P < 0.01$) and less rehospitalisation (10% vs 32%/34%, $P < 0.01$) compared to PSS and FIT.

Conclusions: LC has a relatively low prevalence in older hospitalised subjects but, when present, accounts for worse postdischarge outcomes. Phenotypic analysis unravelled the heterogeneity of LC older population and the association of selected phenotypes with different clinical and prognostic features.

Keywords: liver cirrhosis, older people, mortality, hospitalisation, disability, phenotypes

Introduction

With the progressive population ageing, healthcare systems are being challenged by older patients, who nowadays represent the great majority of those acutely admitted to hospital wards. These patients typically present with multiple diseases, which are often treated by different specialists with poor integration and related proliferation of prescribed drugs [1–3]. Accordingly, the clinical presentation along with the in-hospital and post-discharge impact of diseases may be markedly different from those observed in the younger patient population [4]. Increasing knowledge in this field plays a pivotal role in order to better design tailored strategies of care able to improve health outcomes of older in-patients. Clinical characteristics and health outcomes have been widely investigated for many diseases [5–8], but specific data on older patients admitted to hospital with a diagnosis of liver cirrhosis (LC) are sparse [9–13]. LC is a worldwide challenge frequently leading to physical disability, hospitalisation and mortality, but the relatively low prevalence of LC in older in-patients (from 2% to 10%) [10, 11, 13, 14] has probably prioritised more prevalent and highly impacting diseases such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) [5, 6, 15]. Notwithstanding, results from previous studies suggest that, even if relatively less prevalent, LC is prognostically relevant, both in absolute terms and in comparison with other highly impacting diseases [9–13]. With this background and gaps of knowledge, we sought (a) to analyse the prevalence of and main clinical characteristics of LC patients in the frame of a registry of older patients hospitalised in internal medicine or geriatric wards for acute illness, (b) to comparatively investigate the association with major clinical outcomes (incident disability, in-hospital mortality, rehospitalisation and mortality up to 12 months from discharge) of LC with other highimpacting conditions such as CHF and COPD and (c) to verify whether LC patients cluster in well-distinguished phenotypic profiles and whether these phenotypes differently associate with clinical outcomes.

Methods

Data source

We used data from 'Registro Politerapia Società Italiana di Medicina Interna' (REPOSI), enrolling patients aged 65 years or more admitted to more than 100 Italian medical wards and sponsored by the Italian Society of Internal Medicine (SIMI) together with the Istituto di Ricerche Farmacologiche 'Mario Negri' and the Fondazione Ca Granda Ospedale Maggiore Policlinico, both in Milan. The study design is described in details elsewhere [1]. The full database of 6,193 patients was analysed (Figure 1). The presence of LC and other diseases was ascertained through the appropriate International Classification of Diseases (ICD) 9 codes (Supplementary Table S1), whereas the burden of comorbidities was analysed according to the Cumulative Illness Rating Scale (CIRS) [16]. The main socio-demographic and clinical characteristics were also registered and available. The Barthel Index was measured in order to assess the patient status before the acute illness leading to hospitalisation [17]. Katz's activities of daily living (ADL) were retrieved through the items of the Barthel Index, with disability defined as loss of independence in at least one of the six ADL (eating, bathing, dressing, toileting, transferring and maintaining continence) [18]. Moreover, cognitive impairment was identified by Short Blessed Test ≥10 [19] and depression by Geriatric Depression Scale (≥2) according to the short version by Hickie and Snowdon [20]. After hospital discharge, participants discharged alive (N = 5,950) were followed up after 3 and/or 12 months by a phone call (Figure 1), in order to verify the occurrence of death and rehospitalisation and any variation of the functional status. Overall, 2,537 patients (43%) could be ultimately contacted after 3 months and 1,438 (24%) after 12 months, whereas 1,975 of them (33%) were lost to follow-up (Figure 1). Incident disability was defined as the loss of one or more ADL during follow-up among patients who were independent before hospitalisation in all of six ADL.

Analytical approach

The general characteristics of the study population were presented by means of descriptive statistics. Data were shown as stratified by the presence of LC diagnosis. Comparison between groups was carried out with the Kruskal−Wallis test or chi-squared test, with Holm's correction for multiple testing when needed. The association with mortality and rehospitalisation after discharge was evaluated through Cox proportional hazard regression models and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The association with incident disability was computed through log-binomial regression models and expressed as risk ratios (RRs) with 95% CI. All models were firstly corrected for age and sex then also for low education, living alone, marital status, previous hospitalisations within 3 months, hypertension, diabetes mellitus, body mass index, CHF, COPD, LC, neoplasms, CIRS severity index (CIRS-SI), active smoking, alcohol assumption, glomerular filtration rate, disability, cognitive decline and depression. Finally, we assessed whether socio-demographic and clinical features were aggregated into distinct classes (clinical phenotypes) using the latent class analysis (LCA). We used this method to test our study hypothesis that the REPOSI population of LC patients comprises N sub-populations (classes) characterised by the co-occurrence of similar comorbidities, disabilities or social-economical features. N was fixed at 3, corresponding to the value that maximised the goodness of fit (evaluated by Bayesian information factor, BIC) of models with different class numbers (Supplementary Figure 1). Once the classes were obtained, the specific incidence of study outcomes within each clinical phenotype was computed and each other compared. Analyses were performed using R 3.6.1 software for Mac (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study population of 6,193 subjects included 315 (5%) with the diagnosis of LC (Table 1). These patients were younger than those without LC (median age 76 vs 80 years, $P < 0.001$) and more likely to be male (60% vs 48%, $P < 0.001$), married (63% vs 53%, $P < 0.001$) and former vs active alcohol users (28%/21% vs 13%/31%, $P < 0.001$). No differences were observed for cognitive, functional and mood status at hospital admission, but LC patients were more frequently hospitalised in the preceding 3 months (27% vs 19%, $P = 0.002$). Concerning comorbidities, they showed a higher prevalence of diabetes mellitus and neoplasms (mainly hepatocellular carcinoma, HCC), but a lower prevalence of all the other major comorbidities that when present accounted for a more severe clinical picture shown by a higher CIRS (Table 1). Overall, the hospital stay was shorter in LC patients (median stay of 8 vs 10 days, $P < 0.001$), with a comparable incidence of in-hospital mortality (4% vs 4%, $P = 0.73$). After a median follow-up of 90 days, the incidence of disability was similar to that observed in the non-LC population (19% vs 22%, $P = 0.54$; Figure 2). Conversely, LC patients showed an increased risk of rehospitalisation (age–sex aHR 1.44, 95% CI 1.10–1.88; Figure 2) and mortality (age–sex aHR 2.08, 95% CI 1.52–2.83; Figure 2), which was consistent also in multiple adjusted models for mortality (multiple aHR 2.1, 95% CI 1.37–3.22; Figure 2). Diagnoses of CHF and COPD were both associated with rehospitalisation, even after multiple corrections for CHF, but not with mortality (Figure 2 and Supplementary Table S2). Finally, by means of the LCA, three clinical phenotypes were identified (Figure 3 and Supplementary Table S4). The first one (relatively fit patients—FIT—but with a higher prevalence of HCC) included 150 younger patients characterised by a relatively low prevalence of comorbidities and disability, and with a nearly 50% absolute risk of HCC. The hospital admission was secondary to liver related problems in 68% of the cases, due to ascites (13%), bleeding (17%), encephalopathy (7%) or HCC (18%) (Supplementary Table S5). When the admission diagnosis was HCC (ICD9 code 155), the hospital stay was shorter [median 4 days, interquartile range (IQR) 2–9, vs 8 days, IQR 5–12, $P < 0.01$]. The second clinical phenotype (poor social support, PSS) was made up of 89 patients with a higher prevalence of poor socio-economical features—such as low income, low education, living alone, not married—when compared to the previous phenotype. The main causes of hospitalisation were liver-related (61%), but with a higher frequency of admissions for infections (12%). The third phenotype (disability and multimorbidity, D&M) included 76 patients with the highest prevalence of major comorbidities and physical

and cognitive disabilities. Compared to the other phenotypes, they were less frequently hospitalised for liver problems (46%), but more for infections, lung- or heart-related disorders. Figure 3 visually represents the characteristics of the aforementioned phenotypes according to the variables included in the LCA. All in all, PSS subjects had an increased incident disability (35% vs 13%, $P < 0.05$; Figure 3), and a similar incidence of rehospitalisation and death in comparison with FIT. D&M patients had a higher mortality (in-hospital 12% vs 3% and 1% for PSS and FIT with $P < 0.01$ in both comparisons; post-discharge 41% vs 12% and 15% for PSS and FIT with $P < 0.01$ in both comparisons; Figure 3) and less rehospitalisation (10% vs 32% and 34% for PSS and FIT with $P < 0.01$ in both comparisons; Figure 3).

Discussion

This study shows that LC has a relatively low prevalence in older subjects admitted to medical wards for acute illness, but LC patients have a more severe burden of comorbidities and worse post-discharge outcomes. The diagnosis of LC was associated with rehospitalisation as also shown for CHF and COPD, but, at variance with these diseases, LC was also associated with mortality up to 1 year from hospital discharge, independently of other confounders. Finally, LC older in-patients showed three different clinical phenotypes. The majority of them were relatively young with a low prevalence of comorbidities and physical or cognitive disability, but a higher likelihood of HCC (FIT). A few others were characterised by poor socio-economic conditions (PSS). Finally, a small but not negligible part of LC patients were older, with a high prevalence of D&M. While D&M patients had increased in-hospital and post-discharge mortality, PSS ones showed comparable mortality and rehospitalisation to FIT, but a higher incident disability. With the steady worldwide increase in the burden of chronic disease among older patients seeking hospital admission, much attention has been paid so far to highly impacting and frequent conditions such as CHF and COPD, but LC remained nearly unexplored in this context. Available studies have shown that LC affected 2–10% of patients acutely hospitalised for any cause, compared to 20–25% for CHF and COPD [6, 13, 14]. In this study, we found a 5% prevalence of LC in a representative population of older hospitalised subjects in Italy. In line with another study [14], LC was more frequently associated with diabetes mellitus and malignancy, but in approximately a fourth of the cases LC cooccurred with other major comorbidities, thus accounting for a more complex clinical scenario. Overall, we found the diagnosis of LC to be associated with a 44% increased risk of rehospitalisation and a more than double risk of dying up to 1 year after hospital discharge. To allow a more accurate interpretation of these findings, we put them in the context of other chronic resource-intensive conditions (i.e. CHF and COPD). Similarly to LC, they were associated with rehospitalisation, but none of them showed an increased risk of postdischarge mortality, which in the case of LC was independent from an extensive list of socio-demographic and clinical factors. Interestingly, we found no associations between LC (but also CHF and COPD) and in-hospital mortality and post-discharge incident disability. While the reported effect on disability is novel, the absence of influence on in-hospital mortality is in disagreement with other studies [5, 6, 10, 13]. The different setting and statistical measures used, along with the specific population characteristics, may partially explain this difference. Moreover, with the exception of a single study [6], the younger age of the previously studied populations may explain the major impact of a specific diagnosis over all the other clinical variables, compared to older cohorts in which the global health status may play a more relevant role. Similarly, patient-level factors (such as frailty, sarcopenia, cognitive status, but not morbidities) have been already advocated to influence the occurrence of disability after hospital discharge. In an attempt to profile hospitalised older subjects with LC on the basis of their socio-demographic and clinical features, we identified three main phenotypes. FIT patients were mainly those hospitalised for liver-related problems (ascites, encephalopathy, bleeding or HCC). When admitted with a diagnosis of liver malignancy (HCC), some of them showed a significantly shorter hospital stay, so that it is realistic to assume that they included a number of patients admitted with the goal of undergoing locoregional procedures for HCC. Compared to FIT, PSS patients had a higher rate of admissions

for infections and a higher incident disability. Finally, D&M patients were generally admitted for liver-related, but also heart- and lung-related problems, due to the increased prevalence of these organ comorbidities. Accordingly, they showed the highest in-hospital and postdischarge mortality, but on the other hand a lower rehospitalisation, probably explained by a mortality selection bias. Thus, recognising these phenotypes might help to foresee healthcare needs and to plan care at discharge. For instance, PSS patients might be the object of dedicated interventions designed to prevent the onset of disability, while assessing the respective roles of LC and other chronic diseases in conditioning the rehospitalisation of D&M patients might find an in depth assessment of their medical status. Thus, these patients seem to be the optimal target of a comprehensive geriatric assessment, a procedure largely shown to benefit many categories of older patients, but, as far as we know, insofar untested in LC patients. This study has some limitations. First, being solely based on ICD-9 codes, some bias related to coding mistakes and inaccurate diagnosis cannot be excluded. Particularly, ICD9 codes allowed to disclose LC aetiology in only the 30% of subjects, highlighting alcoholic disease as the most common cause, accounting for the 20.1% of all LC subjects. Even though these data are in line with previous reports [9, 12], the present study cannot be intended to provide data on LC aetiology in Italian older in-patients, because assessing the aetiology of selected diseases was out of the scope of REPOSI study. Second, owing to the limited dataset of the register, disease-specific clinical stages were unavailable for LC (Child-Pugh class), but also for CHF (New York Heart Association—NYHA—classification) and COPD (Global Initiative for COPD—GOLD—classification), so that we could not correct the analysis for these factors. Third, follow-up data were not available for 33% of the baseline population. However, these subjects did not significantly differ from the population included in the analysis (Supplementary Table S3), so that it is unlikely that selection bias may have affected our results. Due to the fact that our register was not specifically designed and powered to detect differences in the subgroups considered, some data should be considered with caution, particularly that stemming from small numbers. Finally, being derived from a cohort of hospitalised subjects, these results should not be generalised to the population of LC out-patients. This study has also some strengths, mainly the reallife setting and the representative sample of older medical in-patients in Italy. Moreover, it represents the largest study comparatively investigating the impact of LC along with CHF and COPD on post-discharge outcomes up to 12 months, and clinical phenotypes of LC older in-patients were described for the first time. In conclusion, this study adds to our knowledge of LC in the acute care setting by showing that the LC older population is heterogeneous and that selected phenotypes associate with different clinical and prognostic features. This should allow to identify health status trajectories not currently evident based on a classical analysis of the LC population.

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Table 1. Socio-demographic and clinical features of hospitalised older patients with or without a diagnosis of LC

	REPOSI population without LC	REPOSI patients with LC	P
N	5,878	315 (5%)	-
Demographic, social and anthropometric features			
Age (years), median (IQR)	80 (74–85)	76 (71–81)	<0.001
Sex (male), n (%)	2,837 (48%)	190 (60%)	<0.001
Smoke (former/active), n (%)	2,102 (37%)/495 (9%)	111 (37%)/32 (11%)	0.498
Alcohol consumption (former/active), n (%)	712 (13%)/1,738 (31%)	86 (28%)/64 (21%)	<0.001
Education level (years), median (IQR)	5 (5–8)	5 (5–8)	0.66
Living alone, n (%)	1,330 (24%)	53 (18%)	0.013
Marital status (married), n (%)	3,031 (53%)	193 (63%)	<0.001
Low income, n (%)	3,818 (72%)	216 (76%)	0.152
BMI (Kg/m2), median (IQR)	25.8 (5)	25.6 (4.5)	0.507
Comorbidities			
Diabetes mellitus, n (%)	1,647 (28%)	114 (36%)	0.002
Arterial hypertension, n (%)	4,566 (78%)	193 (61%)	<0.001
Hypercholesterolemia, n (%)	355 (6%)	2 (1%)	<0.001
CHF, n (%)	1,377 (23%)	35 (11%)	<0.001
IHD, n (%)	1,294 (22%)	35 (11%)	<0.001
COPD, n (%)	1,368 (23%)	55 (17%)	0.02
Atrial fibrillation, n (%)	1,535 (26%)	39 (12%)	<0.001
Cerebro-vascular disease, n (%)	1,398 (24%)	32 (10%)	<0.001
Neoplasms, n (%)	1,144 (19%)	116 (37%)∗	<0.001
CKD, n (%)	1,674 (29%)	88 (28%)	0.859
Genito-urinary disorders, n (%)	1,441 (25%)	61 (19%)	0.041
Musculo-skeletal disease, n (%)	2,031 (35%)	78 (25%)	<0.001
CNS disorders, n (%)	1,467 (25%)	64 (20%)	0.069
Psychiatric disorders, n (%)	1,388 (24%)	39 (12%)	<0.001
CIRS-CI > 3 (median), n (%)	2,129 (36%)	137 (43%)	0.013
CIRS-SI > 1.6 (median), n (%)	2,699 (46%)	184 (58%)	<0.001

Hospital admission parameters

Disability, n (%) 2,957 (51%) 161 (51%) 0.997

Cognitive impairment, n (%) 2,178 (42%) 129 (44%) 0.52

Depressive symptoms, n (%) 1,995 (42%) 119 (44%) 0.477

Previous hospitalisation (within 3 months), n (%) 1,131 (19%) 84 (27%) 0.002

Hospital discharge parameters

Length of hospital stay (days), median (IQR) 10 (7–15) 8 (6–13) <0.001

Discharge destination (other ward/home/home in

critical conditions), n (%)

500 (9%)/4,972 (86%)/64 (1%) 18 (6%)/276 (89%)/3 (1%) 0.34

In-hospital mortality, n (%) 229 (4%) 14 (4%) 0.734

Follow-up

Follow-up time (days), median (IQR) 90 (90–365) 90 (90–95) <0.001

Lost at follow-up, n (%) 1,887 (32%) 88 (28%) 0.138

Incident disability, n (%) 364 (22%) 16 (19%) 0.539

Rehospitalisation, n (%) 747 (20%) 59 (28%) 0.007

Deaths, n (%) 467 (12%) 44 (21%) <0.001

Comparison carried out with chi-squared or Kruskal−Wallis test, as appropriate. ∗102 on 116 (88%) patients with neoplasms had hepatocellular carcinoma. SD,

standard deviation; BMI, body mass index; IHD, ischemic heart disease; CNS, central nervous system; CIRS, cumulative illness rating, scale; CI, comorbidity

index; CKD, chronic kidney disease.

Figure 1. Flow diagram of subjects included in the analyses for the overall REPOSI population and for the sub-cohort of subjects with LC. ∗ Out of 1,739 subjects and 84 LC subjects independent in ADL at hospital admission and with available FU data. Sbjs, subjects.

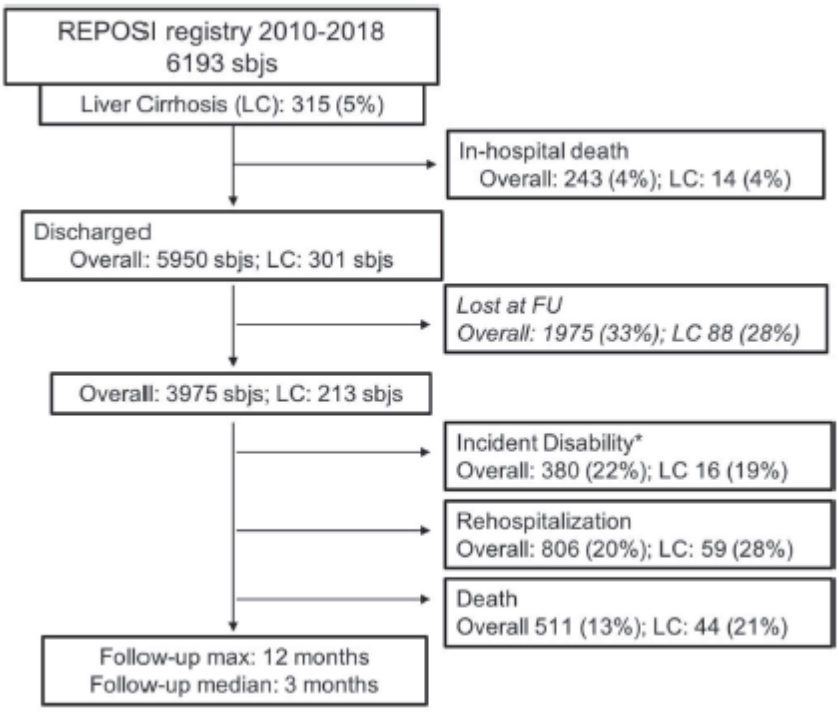

Figure 2. Association between the diagnoses of LC, CHF and COPD and study outcomes. Multiple adjusted models corrected for age, sex, living alone, low education, marital status, previous hospitalisation within 3 months, hypertension, diabetes mellitus, body mass index (BMI), CHF, COPD, LC, neoplasms, CIRS-SI, active smoking, alcohol assumption, glomerular filtration rate (GFR), baseline disability, cognitive decline and depression. Disabled subjects at baseline excluded from the analysis of incident disability. RR: risk ratio; HR, hazard ratio; CI, confidence intervals; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease

In-Hospital Mortality	**RR**	**95%CI**
Liver Cirrhosis age-sex adj	1.38	0.76-2.28
Liver Cirrhosis multiple adj	0.55	0.13-1.51
CHF age-sex adj	1.29	0.98-1.7
CHF multiple adj	1.28	0.8-2.01
COPD age-sex adj	1.17	0.87-1.54
COPD multiple adj	1.29	0.8-2.04
Incident Disability	**RR**	**95%CI**
Liver Cirrhosis age-sex adj	0.93	0.54-1.48
Liver Cirrhosis multiple adj	0.73	0.36-1.32
CHF age-sex adj	1.17	0.91-1.48
CHF multiple adj	0.83	0.6-1.13
COPD age-sex adj	1.26	0.99-1.6
COPD multiple adj	1.06	0.78-1.41
Rehospitalization	**HR**	**95%CI**
Liver Cirrhosis age-sex adj	1.44	1.1-1.88
Liver Cirrhosis multiple adj	1.17	0.81-1.68
CHF age-sex adj	1.43	1.22-1.68
CHF multiple adj	1.39	1.14-1.7
COPD age-sex adj	1.32	1.12-1.54
COPD multiple adj	1.15	0.94-1.41
Mortality	**HR**	**95%CI**
Liver Cirrhosis age-sex adj	2.08	1.52-2.83
Liver Cirrhosis multiple adj	2.1	1.37-3.22
CHF age-sex adj	1.12	0.92-1.37
CHF multiple adj	1.17	0.89-1.54
COPD age-sex adj	0.92	0.75-1.13
COPD multiple adj	0.88	0.66-1.17

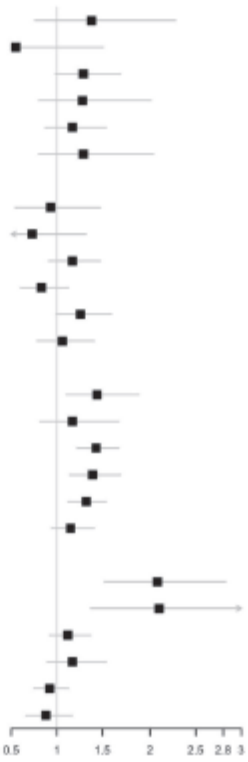

Figure 3. The clinical phenotypes of subjects with LC admitted to medical wards along with the specific incidence of adverse health outcomes. (Left panel) Characterisation of the clinical phenotypes according to the prevalence of the different variables included in the LCA. The lines represent the prevalence difference between each clinical phenotype and that with the lowest observed prevalence (reported as value label beside y-axis). (Right panel) Incidence of in-hospital mortality, disability, rehospitalisation and death up to 12 months from hospital discharge across different clinical phenotypes. Comparison between groups carried out with chi-squared test with Holm's correction for multiple comparisons. IHD, ischemic heart disease; CVD, cardiovascular disease; CKD, chronic kidney disease.