Prognostic implications of comorbidity patterns in critically ill COVID-19 patients: A multicenter, observational study

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Summary

Background The clinical heterogeneity of COVID-19 suggests the existence of different phenotypes with prognostic implications. We aimed to analyze comorbidity patterns in critically ill COVID-19 patients and assess their impact on in-hospital outcomes, response to treatment and sequelae.

Methods Multicenter prospective/retrospective observational study in intensive care units of 55 Spanish hospitals. 5866 PCR-confirmed COVID-19 patients had comorbidities recorded at hospital admission; clinical and biological parameters, in-hospital procedures and complications throughout the stay; and, clinical complications, persistent symptoms and sequelae at 3 and 6 months.

Findings Latent class analysis identified 3 phenotypes using training and test subcohorts: low-morbidity (n=3385; 58%), younger and with few comorbidities; high-morbidity (n=2074; 35%), with high comorbid burden; and renal-morbidity (n=407; 7%), with chronic kidney disease (CKD), high comorbidity burden and the worst oxygenation profile. Renal-morbidity and high-morbidity had more in-hospital complications and higher mortality risk than low-morbidity (adjusted HR (95% CI): 1.57 (1.34-1.84) and 1.16 (1.05-1.28), respectively). Corticosteroids, but not tocilizumab, were associated with lower mortality risk (HR (95% CI) 0.76 (0.63-0.93)), especially in renal-morbidity and high-morbidity. Renal-morbidity and high-morbidity showed the worst lung function throughout the follow-up, with renal-morbidity having the highest risk of infectious complications (6%), emergency visits (29%) or hospital readmissions (14%) at 6 months (p<0.01).

Interpretation Comorbidity-based phenotypes were identified and associated with different expression of in-hospital complications, mortality, treatment response, and sequelae, with CKD playing a major role. This could help clinicians in day-to-day decision making including the management of post-discharge COVID-19 sequelae.

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Research in context

Evidence before this study

COVID-19 has a broad range of manifestations, from fully asymptomatic to a severe life-threatening illness requiring admission to the intensive care unit (ICU). Early studies have identified the individual prognostic value of older age, male sex, and several chronic conditions, including obesity, hypertension, diabetes, chronic obstructive pulmonary disease, cancer, chronic kidney disease (CKD) and immunosuppression status. Stepping further, some studies have tried to identify COVID-19 phenotypes based on complex sets of data including sociodemographic variables, baseline comorbidities, signs and symptoms during the acute phase, functional and biological parameters and chest radiological features. However, these studies have two key drawbacks: (i) they have a limited sample size or are based on too complex sets of data not easily available to clinicians worldwide, which limits generalizability; (ii) they do not assess the impact of COVID-19 phenotypes on prognosis, response to treatment and sequelae, which is required for a truly comprehensive assessment of the relevance of the identified phenotypes.

Added value of this study

The present study differs from the aforementioned in being based exclusively on the baseline comorbidity patterns of a large multicenter sample of critically ill patients and assessing how different comorbidity backgrounds influence clinical outcome, response to available treatment, risk of different complications, mortality, and sequelae. As expected, two of the identified phenotypes corresponded to a low-comorbidity and a high-comorbidity group of patients, which is no news for clinicians. However, we found a third phenotype characterized by the presence of CKD, which had the worst prognosis at all stages (throughout hospitalization and when considering post-discharge sequelae). Moreover, even amongst patients in the low-comorbidity phenotype, having CKD was associated with in-hospital mortality, which confirms the key role of CKD on COVID-19 prognosis. All these findings were independent of patient's age.

Implications of all the available evidence

Critically ill COVID-19 patients can be grouped into different comorbidity-based phenotypes with prognosis implications independently of patient's age, and doing this could help clinicians in day-to-day decision making including the management of post-discharge sequelae. Our research presents a straightforward means of phenotyping patients based solely on previous comorbidities, and provides data on what to expect from each group of patients in terms of in-hospital complications and mortality, response to standard treatment, and the prevalence of sequelae and their progressive remission up to six months after discharge.

Introduction

COVID-19 has a broad range of manifestations, from fully asymptomatic to a severe life-threatening illness requiring admission to the intensive care unit (ICU).[1,2] Great efforts have been devoted to characterizing severe COVID-19 patients and identifying key prognostic variables. In this regard, early studies have identified the prognostic value of older age, male sex, and several chronic conditions, including obesity, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cancer, chronic kidney disease (CKD), and immunosuppression status.[3–5] The heterogeneity of comorbidity patterns in such patients could be related to different clinical phenotypes that could show distinct prognoses, responses to treatment and sequelae. Therefore, the results of an in depth analysis of comorbidity patterns could have implications for clinical practice.

To date, several studies have aimed to identify phenotypes among hospitalized COVID-19 patients based on sociodemographic variables, baseline comorbidities, signs and symptoms during the acute phase, and the results of complementary tests, such as biological parameters in the blood test[6–9] or chest radiological features.[8,10] Most interestingly, several studies have focused on patients admitted to the ICU that are those at a higher risk of experiencing severe complications and sequelae.[11–17] However, no comprehensive study has yet identified the comorbidity patterns of critically ill COVID-19 patients and assessed its independent impact on prognosis, response to treatment and sequelae.

Therefore, the current study aims to use data from the CIBERESUCICOVID study[18] to analyze comorbidity patterns in critically ill COVID-19 patients and assess their impact on in-hospital parameters and outcomes, response to treatment and sequelae.

Methods

Study design

CIBERESUCICOVID is a multicenter prospective/retrospective observational study of critically ill COVID-19 patients admitted to the ICUs of 55 Spanish hospitals and registered in ClinicalTrials.gov with identifier NCT04457505. CIBERESUCICOVID started in May 2020 by collecting retrospective data of patients admitted to participating ICUs before May 2020 and continued prospectively from then onward (data collection is still ongoing). The data for the current analyses correspond to consecutive COVID-19 patients admitted to 55 Spanish ICUs from February 2020 to December 2021.

Study population

All included patients were admitted to the ICU due to the severity of COVID-19. COVID-19 diagnosis was confirmed by a positive nasopharyngeal swab polymerase chain reaction (PCR) test for SARS-CoV-2. Patients lacking baseline or discharge data were excluded from the current analyses. Patients transferred to other hospitals during or after ICU admission, receiving palliative care, or with severe mental disability precluding pulmonary function tests after discharge, were excluded from the follow-up. Given the nature of our study and the targeted participants, no Patient and Public Involvement was possible.

Measures

Baseline variables were collected at hospital admission and included sociodemographic, anthropometric and lifestyle variables as well as comorbidities registered in electronic medical records (see "Methods. Collection of chronic conditions" in the online supplement). In addition, the following variables were collected at the time of ICU admission and throughout the ICU stay: clinical (vital signs and symptoms) and biological parameters (blood test and blood gas test), including estimations of the glomerular filtration rate obtained using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation[19]; procedures performed before and during the ICU stay, including use of invasive mechanical ventilation (IMV), hemodialysis or hemofiltration, and pharmacological treatment (inotropes/vasopressors, antivirals); in-hospital complications such as infections (coinfections or nosocomial infections), thrombotic events, heart failure, myocarditis/pericarditis, delirium, shock and hemorrhages; and characteristics of the hospital stay (length of stay, length of ICU, and mortality). Finally, post-discharge data included persistent symptoms (fatigue, cardiac complications, and infectious complications), hospital readmissions (emergency visits and hospital admissions), late clinical complications (infections, thrombotic events, atrial fibrillation and heart failure), sequelae at 3 and 6 months, assessed by a thoracic CT scan (radiological normalization, persistent infiltrates, Interstitial lung disease, pulmonary embolism, fibrous tracts, emphysema and other alterations), functional respiratory test (FVC, FEV_1, FEV_1 to FVC ratio and D_{LCO}) and quality-of-life questionnaire.

Primary outcome

In-hospital mortality was considered as the primary outcome, including all causes of death. Time to event was calculated from ICU admission to death or discharge. This was assessed primarily according to comorbidity phenotypes, but also according to treatment, multimorbidity subphenotypes, and individual comorbidities in a low-morbidity sub-population.

Secondary outcomes

The following secondary outcomes were considered: in-hospital complications; hospital re-admissions at 3 and 6 months after discharge; and complications and sequelae at 3 and 6 months after discharge.

Ethics and data protection

The study was designed and conducted in compliance with the Declaration of Helsinki and national and international law on data protection. Each of the participating hospitals obtained approval from their ethics boards. Informed consent was obtained from all participants or their relatives when possible, and in cases when this was unfeasible, an informed consent waiver was authorized by the ethics board. All data were pseudonymized and stored in a REDCap database hosted in the Centro de Investigación Biomédica en Red (CIBER), Madrid, Spain. The study coordinators ensured integrity and timely completion of data collection.

Identification of comorbidity patterns

Potentially relevant comorbidities (n=17) were included to identify morbidity patterns within the CIBERESUCICOVID population. To identify morbidity patters and evaluate its reproducibility, the study cohort was divided (ratio 1:1) into training (n = 2933) and test (n = 2933) subcohorts using simple random sampling. Morbidity patterns were first identified in the training cohort using Latent class analysis (LCA).[20] The number of latent classes was determined using the parsimony criteria based on the minimum value of the Bayesian

information criterion measure from 0 to 10 latent classes. To assess the reproducibility of the identified latent classes, an independent latent class analysis was applied to the test cohort fixing the number of classes to the number obtained in the training cohort. Latent class identified in both cohorts (training and test) were compared. Finally, we carried out a latent class analysis on the whole CIBERESUCICOVID cohort (training and test altogether). Average posterior probabilities above 70% were considered as an optimal fit.[21] Each patient was assigned to one class according to his or her highest computed probability of membership. The Global cohort was used to evaluate primary and secondary outcomes. Prevalence of comorbidities and clinical data at ICU admission were graphically represented for each cluster. The continuous variables of clinical data at ICU admission were standardized. Given that a latent class grouped patients with a high morbidity burden, it was decided to apply a latent class analysis to this population to identify patterns of multimorbidity.

Statistical analyses

All descriptive and inferential analyses were performed using the whole CIBERESUCICOVID cohort and based on the phenotypes obtained using the whole cohort. Descriptive statistics were used to summarize the characteristics of the study population. Absolute and relative frequencies were used for qualitative data. The means (sd) and medians (25^{th}–75^{th} percentile) were estimated for quantitative variables with normal and non-normal distributions, respectively. Normal distributions were assessed by the Shapiro–Wilk test. Clinical data, at UCI admission, were compared between phenotypes using ANOVA (or Kruskall-Wallis test for variables with non-normal distribution) for continuous variables and chi-squared test (or Fisher-Freeman-Halton exact test when the expected frequencies were less than 5 in some cell) for qualitative.

Primary outcome was defined as in-hospital mortality. The effect of comorbidity phenotypes on the risk of in-hospital mortality was assessed using Cox model adjusted for confounding factors such as age and sex. Additionally, a Fine-Gray's competing risk model was performed to control for potential overestimation of in-hospital mortality risk when considering discharge as censored information.[22,23] The same analysis were perform in multimorbidity phenotypes. Furthermore, the impact of the most broadly used pharmacological treatment for COVID-19, tocilizumab and corticosteroids, on in-hospital mortality was evaluated according to comorbidity phenotypes, including phenotype and drug interaction terms.

The odds of having hospital complications were assessed for each comorbidity and phenotype using logistic regression models adjusted for age and sex, with a low-morbidity phenotype as a reference. The Odds ratios and confidence intervals were graphically represented with a forest plot. Hospital complications were also assessed according to multimorbidity patterns. Linear or logistic regression models were used as appropriate to assess the risk of sequelae, taking into account confounding factors associated with lung damage prior to SARS-CoV-2 infection (age, sex, chronic lung disease and asthma). Additionally, since one of the latent classes grouped patients with low morbidity burden, the impact of individual comorbidities on in-hospital mortality was evaluated in this population using Cox model adjusted for confounding factors such as age and sex.

Missing values were not imputed and models included complete cases. Tables and figures present the number of evaluable patients in each comparison. The main findings of the previous analyzes were represented in graphical abstract.

R statistical software, version 4.0.1 (R Project for Statistical Computing), was used for all analyses.

Role of the funding source

Funding sources had no role in the study's design, conduct, and reporting.

Results

Phenotypes based on comorbidities

Three statistically and clinically significant comorbidity phenotypes were identified in the training cohort (n = 2933) and then validated in the test cohort (n = 2933) (Table 1 and eFigure 1). The baseline characteristics were similar between subcohorts (eTable1). The final classification of patients was performed by LCA on the global cohort (Figure 1A). LCA model showed an optimal fit with a mean posterior probabilities of class membership of 84%.[21] The first phenotype, named low-morbidity, included 3385 (57.7%) patients characterized by a low comorbidity burden (median [p_{25}; p_{75}] of 1 [0; 2] comorbidity), with obesity (29.9%) as the most prevalent comorbidity and a younger age than the other phenotypes. The second phenotype, high-morbidity, included 2074 (35.3%) patients with a high comorbidity burden (median of 3 [3; 4] comorbidities), with hypertension (87.6%), diabetes (52.2%), other metabolic disorders (47.3%) and obesity (44.8%) being the most frequent comorbidities. The third phenotype, named renal-morbidity, included 407 (6.9%) patients with previous chronic kidney disease and a very high comorbidity burden (median of 5 [4; 6] comorbidities). Table 2 and Figure 1A show the main characteristics of the phenotypes at hospital admission. Reported Symptoms before hospital admission were similar in all phenotypes (eFigure 2). A Flowchart of the study including the initial number of evaluable patients, patients

	Training cohort			Test cohort		
	Low-morbidity n = 1488 *n(%)*	High-morbidity n = 1256 *n(%)*	Renal-morbidity n = 189 *n(%)*	Low-morbidity n = 1729 *n(%)*	High-morbidity n = 997 *n(%)*	Renal-morbidity n = 207 *n(%)*
Comorbidities						
Obesity	368 (24.7%)	619 (49.3%)	66 (34.9%)	520 (30.1%)	441 (44.2%)	71 (34.3%)
Hypertension	237 (15.9%)	1074 (85.5%)	174 (92.1%)	381 (22.0%)	892 (89.5%)	197 (95.2%)
Diabetes mellitus (Type I / II)	51 (3.43%)	574 (45.7%)	99 (52.4%)	92 (5.32%)	536 (53.8%)	106 (51.2%)
Chronic heart disease	14 (0.94%)	310 (24.7%)	70 (37.0%)	49 (2.83%)	241 (24.2%)	69 (33.3%)
Chronic renal disease	10 (0.67%)	0 (0.00%)	186 (98.4%)	18 (1.04%)	10 (1.00%)	199 (96.1%)
Chronic moderate liver disease	8 (0.54%)	12 (0.96%)	4 (2.12%)	11 (0.64%)	15 (1.50%)	8 (3.86%)
Chronic mild liver disease	28 (1.88%)	39 (3.11%)	10 (5.29%)	16 (0.93%)	39 (3.91%)	11 (5.31%)
Chronic neurological disease	36 (2.42%)	111 (8.84%)	17 (8.99%)	69 (3.99%)	71 (7.12%)	17 (8.21%)
Chronic pulmonary disease	55 (3.70%)	203 (16.2%)	47 (24.9%)	69 (3.99%)	167 (16.8%)	41 (19.8%)
Asthma	109 (7.33%)	63 (5.02%)	11 (5.82%)	109 (6.30%)	62 (6.22%)	7 (3.38%)
Dementia	7 (0.47%)	10 (0.80%)	4 (2.12%)	5 (0.29%)	13 (1.30%)	1 (0.48%)
Rheumatic disease	44 (2.96%)	90 (7.17%)	9 (4.76%)	44 (2.54%)	58 (5.82%)	20 (9.66%)
Gastrointestinal/pancreatic disorders	68 (4.57%)	122 (9.71%)	26 (13.8%)	83 (4.80%)	96 (9.63%)	29 (14.0%)
Endocrine disorders	103 (6.92%)	126 (10.0%)	23 (12.2%)	113 (6.54%)	103 (10.3%)	28 (13.5%)
Metabolic disorders	147 (9.88%)	492 (39.2%)	62 (32.8%)	173 (10.0%)	488 (48.9%)	82 (39.6%)
Malnutrition	3 (0.20%)	5 (0.40%)	2 (1.06%)	4 (0.23%)	5 (0.50%)	4 (1.93%)
Genitourinary disorders	46 (3.09%)	113 (9.00%)	21 (11.1%)	48 (2.78%)	103 (10.3%)	22 (10.6%)
Hematology disorders	58 (3.90%)	78 (6.21%)	18 (9.52%)	64 (3.70%)	67 (6.72%)	23 (11.1%)
Malignant neoplasm	46 (3.09%)	57 (4.54%)	11 (5.82%)	44 (2.54%)	56 (5.62%)	10 (4.83%)
Solid organ transplantation	4 (0.27%)	3 (0.24%)	44 (23.3%)	8 (0.46%)	0 (0.00%)	49 (23.7%)
Bone marrow transplant	3 (0.20%)	0 (0.00%)	0 (0.00%)	3 (0.17%)	0 (0.00%)	0 (0.00%)
Human Immunodeficiency Virus	7 (0.47%)	5 (0.40%)	2 (1.06%)	12 (0.69%)	6 (0.60%)	1 (0.48%)
Immunological disorders	18 (1.21%)	26 (2.07%)	14 (7.41%)	33 (1.91%)	21 (2.11%)	12 (5.80%)

***Table 1*: Comorbidity phenotypes identified in the training and test subcohorts.**

included in the LCA model and patients available for the primary outcome analysis can be found on the online supplement (eFigure 3).

Baseline characteristics of the cohort

The main baseline characteristics of the 5866 patients in the cohort are summarized in Table 2. Briefly, the median [p_{25}; p_{75}] age was 63 [54; 71] years, 29.6% were women, and 63.4% were never smokers. The median number of comorbidities was 2 [1; 3], with the most frequent comorbidities being hypertension (50.4%), obesity (35.5%) and diabetes mellitus (24.9%).

Severity and key parameters at ICU admission

The majority of patients presented acute respiratory distress syndrome (ARDS) at ICU admission (95.9%), with a median PaO_2 to FiO_2 ratio of 113 [82; 163]. Despite all phenotypes having similar elapsed times from symptom onset to ICU admission (median of 9 [7; 12] days), renal-morbidity and high-morbidity patients had higher APACHE and SOFA scores than patients with the low-morbidity phenotype (Figure 1B and eTable 2). Patients with the renal-morbidity phenotype showed worse oxygenation than patients in the other clusters (Figure 1B and eTable 2) but were less prone to having IMV at the time of ICU admission than patients with the low-morbidity phenotype (171 (42%) vs. 1733 (51.2%), adjusted OR (95% CI) of 0.58 (0.47 to 0.72)), while patients in the high-morbidity phenotype had the highest rates of IMV at ICU admission (1166 (56.2%)). Finally, each of the phenotypes showed a characteristic profile in the blood test (Figure 1C and eTable 2).

In-hospital complications and mortality

Specific complication profiles were observed for each phenotype after adjustment for confounding factors (Figure 2A and eTable 3). Renal-morbidity and high-morbidity phenotypes had a greater number of in-hospital complications than the low-morbidity phenotype. Both phenotypes showed a greater incidence of myocardial infarction and ischemia, heart failure, acute kidney injury and anemia. The renal-morbidity phenotype showed a greater incidence of other cardiovascular complications, such as cardiac arrest, noninfectious shock and bleeding. The high-morbidity phenotype had a

Figure 1. Identification of comorbidity phenotypes in the whole CIBERESUCICOVID cohort using Latent Class Analysis. A) Prevalence of comorbidities according to phenotypes. B) Disease severity parameters at ICU admission according to phenotypes. C) Laboratory parameters according to phenotypes. The values in B and C have been standardized.

greater incidence of bacterial pneumonia, other infections and septic shock. Finally, the low-morbidity phenotype showed a greater incidence of disseminated intravascular coagulation (DIC) and pulmonary embolism.

Regarding in-hospital mortality, both renal-morbidity and high-morbidity phenotypes had higher in-hospital mortality risk than the low-morbidity phenotype, with adjusted HRs (95% CIs) of 1.57 (1.34 to 1.84) and 1.16 (1.05 to 1.28), respectively (Figure 2B). This was confirmed in a competing risks analysis (eFigure 4).

Effect of tocilizumab and corticosteroids on mortality

Tocilizumab was not associated with a reduction in the risk of mortality in any phenotype (eTable 4). Conversely, corticosteroids showed an overall significant reduction in mortality risk, with this reduction being stronger in the high-morbidity and renal-morbidity phenotypes although the later not reaching statistical significance in a test for interaction (eTable 4).

Mid-term sequelae: structural and functional lung impairment

Hospital readmissions, complications and sequelae (including lung structural and functional impairment), adjusted by factors associated with lung damage prior to infection (age, sex, chronic lung disease and asthma), are shown in eTable 5. Half of the patients reported persistent limiting fatigue at 3 and 6 months after discharge. All phenotypes showed a high presence of pulmonary functional and morphological sequelae at 3 months that persisted over time. Overall, patients with the renal-morbidity phenotype showed worse values than the other phenotypes at the 3 and 6-month follow-up (eTable 5).

Multimorbidity subphenotypes and its impact on mortality

Given that all patients with the high-morbidity phenotype had two or more comorbidities and 77.5% had three or more comorbidities, a study of multimorbidity

	ALL n = 5866 *Median [p_{25};p_{75}] or n(%)*	Low-morbidity n = 3385 *Median [p_{25};p_{75}] or n(%)*	High-morbidity n = 2074 *Median [p_{25};p_{75}] or n(%)*	Renal-morbidity n = 407 *Median [p_{25};p_{75}] or n(%)*	*p value*	n
Sociodemographic data						
Sex, *woman*	1732 (29.6%)	1043 (30.8%)	569 (27.5%)	120 (29.5%)	**0.031**	5859
Age, *years*	63.0 [54.0;71.0]	60.0 [50.0;68.0]	67.0 [61.0;73.0]	68.0 [60.5;74.0]	**<0.001**	5866
Smoking history					**<0.001**	5386
Non smoker	3416 (63.4%)	2171 (70.3%)	1036 (54.2%)	209 (54.4%)		
Current	324 (6.02%)	171 (5.53%)	121 (6.33%)	32 (8.33%)		
Former	1646 (30.6%)	748 (24.2%)	755 (39.5%)	143 (37.2%)		
Alcohol consumption					**<0.001**	5320
Non consumer	5027 (94.5%)	2930 (95.8%)	1760 (93.3%)	337 (89.9%)		
Current	194 (3.65%)	94 (3.07%)	83 (4.40%)	17 (4.53%)		
Former	99 (1.86%)	35 (1.14%)	43 (2.28%)	21 (5.60%)		
Drug use					0.141	5420
Non consumer	5370 (99.1%)	3067 (98.8%)	1924 (99.5%)	379 (99.2%)		
Current	25 (0.46%)	18 (0.58%)	6 (0.31%)	1 (0.26%)		
Former	25 (0.46%)	19 (0.61%)	4 (0.21%)	2 (0.52%)		
Comorbidities						
Obesity	2085 (35.5%)	1012 (29.9%)	930 (44.8%)	143 (35.1%)	**<0.001**	5866
Hypertension	2955 (50.4%)	765 (22.6%)	1817 (87.6%)	373 (91.6%)	<0.001	5866
Diabetes mellitus (Type I / II)	1458 (24.9%)	162 (4.79%)	1083 (52.2%)	213 (52.3%)	<0.001	5866
Chronic heart disease	753 (12.8%)	69 (2.04%)	543 (26.2%)	141 (34.6%)	**<0.001**	5866
Chronic renal disease	423 (7.21%)	29 (0.86%)	0 (0.00%)	394 (96.8%)	<0.001	5866
Chronic moderate liver disease	58 (0.99%)	19 (0.56%)	26 (1.25%)	13 (3.19%)	**<0.001**	5866
Chronic mild liver disease	143 (2.44%)	49 (1.45%)	73 (3.52%)	21 (5.16%)	**<0.001**	5866
Chronic neurological disease	321 (5.47%)	110 (3.25%)	177 (8.53%)	34 (8.35%)	**<0.001**	5866
Chronic pulmonar disease	582 (9.92%)	123 (3.63%)	372 (17.9%)	87 (21.4%)	**<0.001**	5866
Asthma	361 (6.15%)	219 (6.47%)	123 (5.93%)	19 (4.67%)	0.314	5866
Dementia	40 (0.68%)	15 (0.44%)	20 (0.96%)	5 (1.23%)	**0.019**	5866
Rheumatic disease	265 (4.52%)	107 (3.16%)	129 (6.22%)	29 (7.13%)	**<0.001**	5866
Gastrointestinal/ pancreatic disorders	424 (7.23%)	153 (4.52%)	215 (10.4%)	56 (13.8%)	**<0.001**	5866
Endocrine disorders	496 (8.46%)	212 (6.26%)	232 (11.2%)	52 (12.8%)	**<0.001**	5866
Metabolic disorders	1444 (24.6%)	312 (9.22%)	981 (47.3%)	151 (37.1%)	**<0.001**	5866
Malnutrition	23 (0.39%)	8 (0.24%)	8 (0.39%)	7 (1.72%)	**0.001**	5866
Genitourinary disorders	353 (6.02%)	95 (2.81%)	213 (10.3%)	45 (11.1%)	**<0.001**	5866
Hematology disorders	308 (5.25%)	122 (3.60%)	145 (6.99%)	41 (10.1%)	**<0.001**	5866
Malignant neoplasm	224 (3.82%)	87 (2.57%)	114 (5.50%)	23 (5.65%)	**<0.001**	5866
Solid organ transplantation	108 (1.84%)	13 (0.38%)	0 (0.00%)	95 (23.3%)	**<0.001**	5866
Bone marrow transplant	6 (0.10%)	6 (0.18%)	0 (0.00%)	0 (0.00%)	0.165	5866
Human Immunodeficiency Virus	33 (0.56%)	19 (0.56%)	11 (0.53%)	3 (0.74%)	0.819	5866
Immunological disorders	124 (2.11%)	54 (1.60%)	43 (2.07%)	27 (6.63%)	**<0.001**	5866

***Table 2*: Characteristics of patients at hospital admission according to phenotypes in the whole CIBERESUCICOVID cohort.**
Continuous and categorical variables were compared between groups using Kruskall-Wallis test and Chi-squared test, respectively.

patterns was performed using a second step of LCA. Six multimorbidity subphenotypes were identified: (i) hypertension and chronic lung disease; (ii) hypertension and diabetes; (iii) hypertension and chronic heart disease; (iv) hypertension and other metabolic disorders; (v) diabetes and other metabolic disorders; and (vi) hypertension and others (Figure 3A and eTable 6). Significant differences on in-hospital mortality risks were found when taking subphenotype IV (hypertension and other metabolic disorders) as a reference, as shown in Figure 3B. Similar results were obtained when using competing risks model (eTable 7).

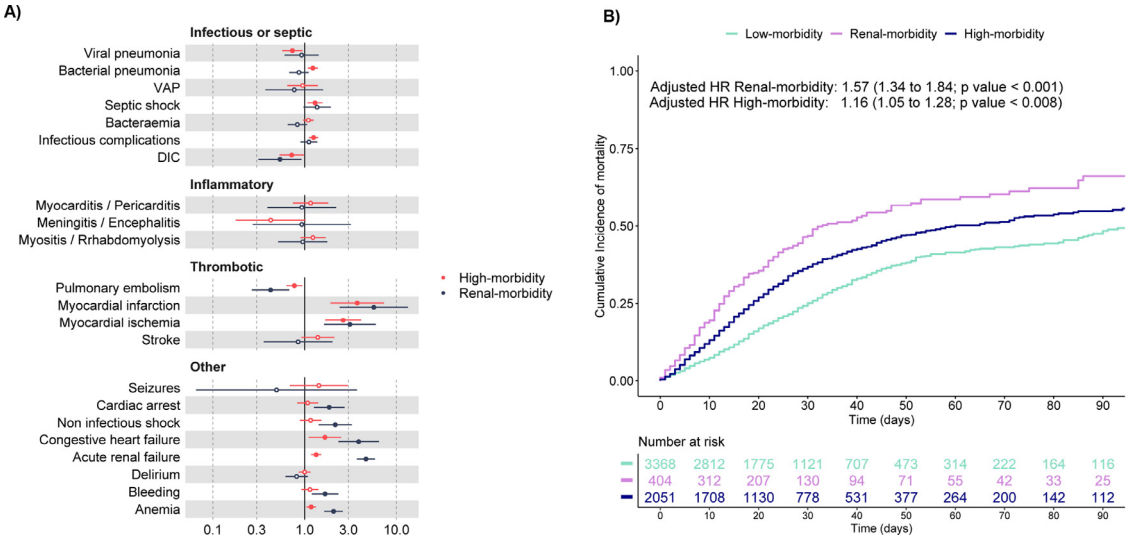

Figure 2. Hospital prognosis according to morbidity phenotypes in the whole CIBERESUCICOVID cohort. A) Comparison of the risk of having in-hospital complications between phenotypes. B) In-hospital mortality according to morbidity phenotypes using Cox model. Cox regression model with phenotypes as predictor, and age and sex as confounding factors. Low-morbidity phenotype was used as reference group. Cox model showed a c-statistic of 0.65. 43 patients were excluded from this analysis because of mismatches in the dates of ICU admission and hospital discharge. A total of 808, 784 and 200 patients died during hospitalization in the low-morbidity, high-morbidity and renal-morbidity phenotypes, respectively.

Impact of individual comorbidities in a low-morbidity population

The population of patients in the low-morbidity phenotype was best suited for the study of the individual impact of each comorbidity on the risk of intubation and mortality, which is shown in Figure 4. On the one hand, CKD, malignant neoplasm and diabetes were significantly associated with in-hospital mortality. On the other hand, obesity was associated with a higher risk of intubation (but not mortality).

Discussion

The analysis of the baseline comorbidity patterns of a large cohort of critically ill COVID-19 patients allowed the identification of well-characterized phenotypes with an impact on prognosis, response to treatment mid-term sequelae. Three statistically and clinically significant phenotypes were identified: (i) low-morbidity, including younger patients with few comorbidities; (ii) high-morbidity, including patients with two or more comorbidities; and (iii) renal-morbidity, including patients with CKD and additional comorbidities. As expected, patients with the low-morbidity phenotype reported lower ICU mortality than high-morbidity and renal-morbidity patients. Moreover, an in-depth analysis of the role of specific comorbidities in each of the phenotypes highlighted the key impact of CKD and, to a lesser extent, chronic lung disease in the course of severe COVID-19. Figure 5 shows a visual overview of the study and its main results.

The current study has some key strengths that enhance its value compared with previous literature. First, we performed an in-depth analysis of the independent impact of comorbidity patterns prior to SARS-CoV-2 infection on the prognosis of critically ill COVID-19 patients, considering in-hospital outcomes and sequelae and thus being useful for the planning of therapeutic strategies and post-discharge controls. Second, the study is based on a large multicentric cohort of critically ill COVID-19 patients. Third, it includes a broad set of parameters and variables at different time points of the COVID-19 course, including data before ICU admission, during ICU admission, and up to 6 months after discharge. This, for instance, allowed us to provide some insight into the effectiveness of treatment or the impact of phenotypes on sequelae. Finally, all data were thoroughly revised and validated in contrast to registry-based studies. Despite these strengths, some limitations must be acknowledged. First, the study was limited by its observational design. Second, although phenotypes were internally validated using training and test subcohorts, no formal external validation in a completely independent cohort was available. Third, the conditional independence assumption for LCA did not hold after assessing local dependence based on standardized bivariate residuals. However, other indicators such as the high average posterior class probabilities, the clinical interpretability of the latent classes and their reproducibility allowed us to believe in the validity of the identified latent classes. Fourth, data on the administration timing and dose of pharmacological treatments was not

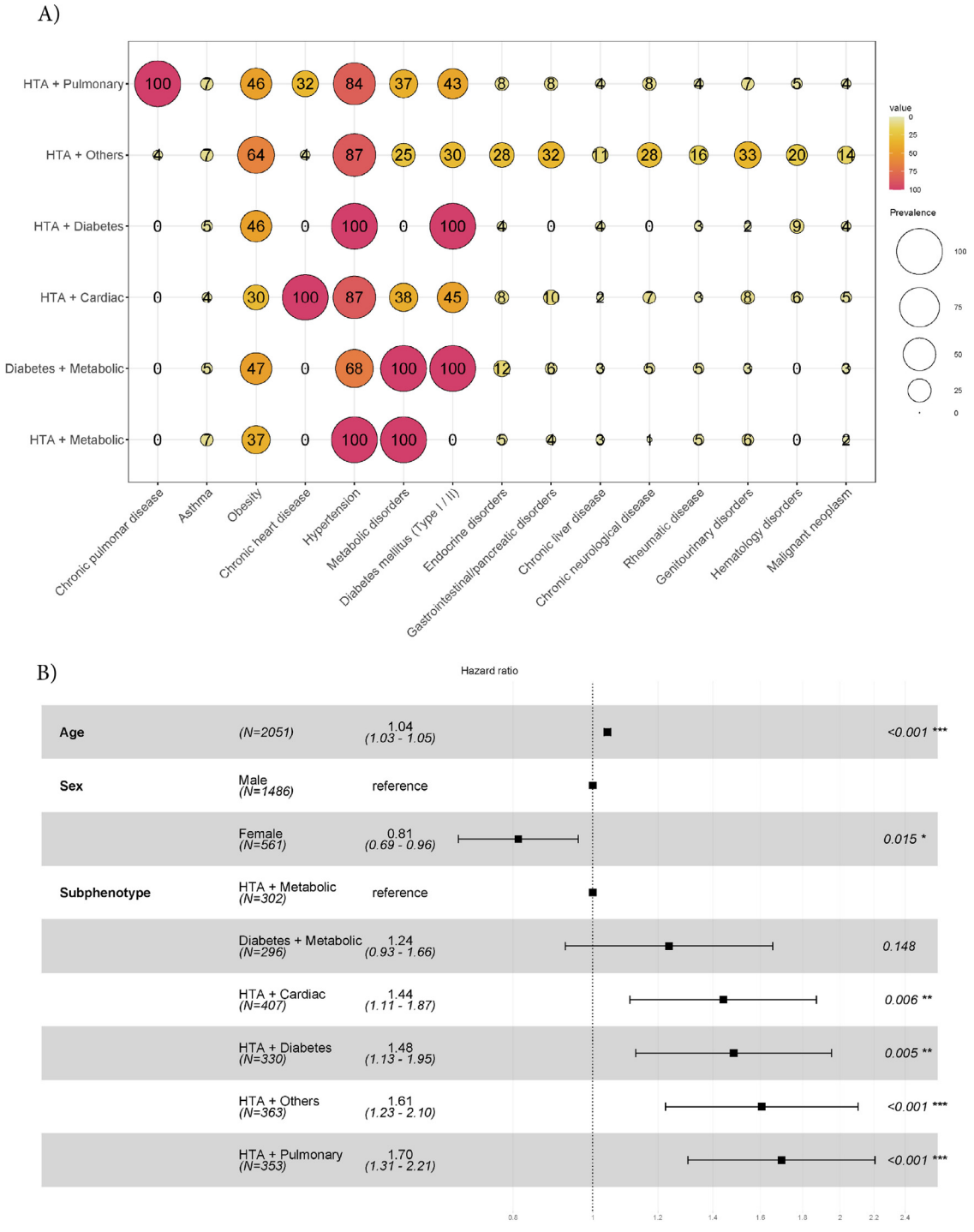

Figure 3. Multimorbidity patterns in patients with high comorbid burden. A) Prevalence of comorbidities according to subphenotypes. B) Impact of subphenotypes on in-hospital mortality. Cox regression model with subphenotypes as predictor, and age and sex as confounding factors. Significance levels were indicate as * if p value<0.05, ** if p value<0.01 and *** if p value<0.001. Cox model showed a c-statistic of 0.63.

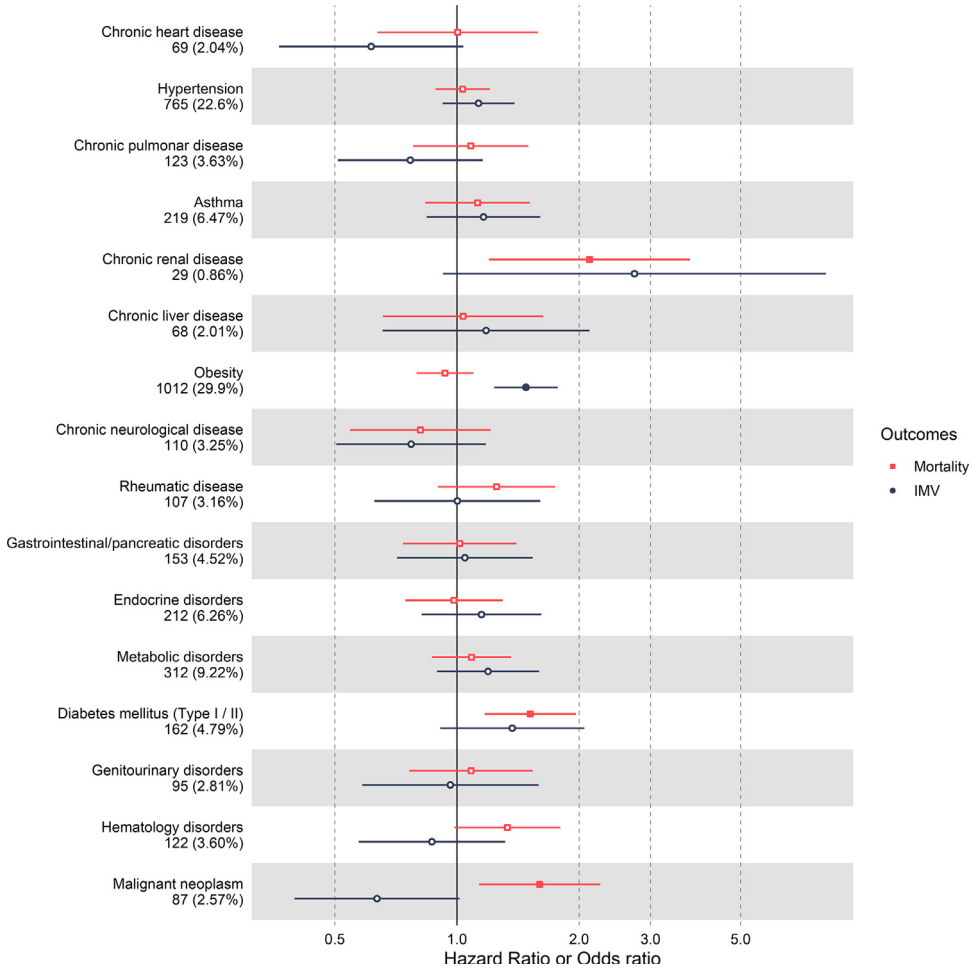

Figure 4. Impact of individual comorbidities of patients with low comorbid burden on in-hospital mortality and invasive mechanical ventilation (IMV). Logistic regression models were used to assess the association between comorbidities and IMV risk. Cox proportional hazards models were used to assess mortality risk. All models were adjusted for age and sex. The n (%) of subjects having each comorbidity is reported.

available. Fifth, a potential impact of therapeutic effort limitation cannot be ruled out, especially in the most difficult moments of the pandemic. Moreover, therapeutic strategies, which changed through the course of the pandemic, could have affected the measures of some of the reported biologic and clinical parameters. Sixth, the date of complications during hospital stay was not recorded, this precluded the use of mortality as a competing risk for complications. Seventh, the subphenotypes' cluster analysis among high-morbidity patients could not be internally validated due to constraints in the number of available subjects. Eighth, the number of patients with baseline CKD was not big enough to allow for subgroup analyses, especially considering CKD patients that had undergone a solid organ transplantation. Ninth, potentially relevant variables such as ethnicity were not recorded and could not be potentially used in adjusted models. Finally, the number of patients included in the analyses of sequelae was necessarily limited, and the available data were scarce. Nevertheless, the authors considered it key to provide as much data as available, especially linking the acute phase and mid-term follow-up, as this kind of study is scarce in the literature.

To date, studies aiming to derive phenotypes of hospitalized COVID-19 patients have been based on previous comorbidities,[6–8,15] COVID-19 signs and symptoms,[8,9,11,12,16,17] variables from blood tests,[8,11,13–17] and chest radiologic features[8,10] in an attempt to identify groups of patients with distinct risks of ICU admission, need for mechanical ventilation, and risk of experiencing clinical complications or death. Among those focused on critically ill patients,[11–17] most studies identified two or three phenotypes corresponding to different degrees of severity with a role of intense inflammation when defining the most severe phenotype. The

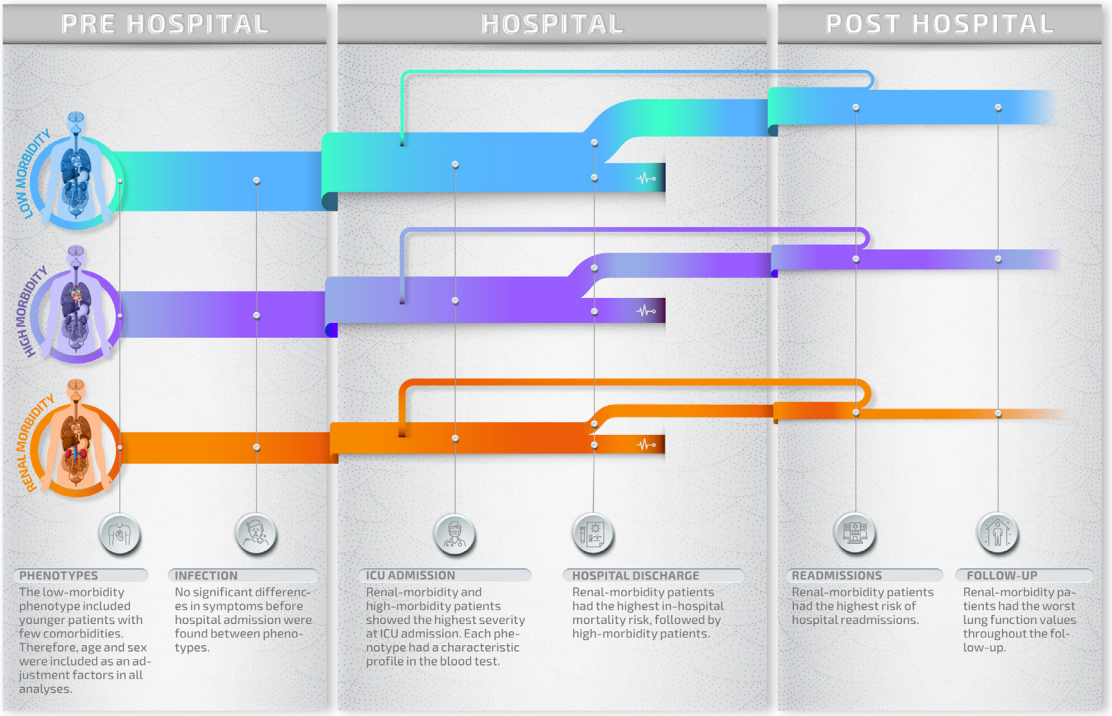

Figure 5. Graphical abstract. Identification of phenotypes and impact on prognosis. Phenotypes identified in the whole CIBERESUCI-COVID cohort by means of Latent Class Analysis based on 17 potentially relevant comorbidities and validated internally using training and test sub-cohorts. The width of the flow lines in each of the phenotypes is proportional to the number of subjects in each time point (all lines are proportional within each phenotype). The width of the flow lines is not proportional between phenotypes (for instance, the renal-morbidity phenotype flow has been over-represented in the sake of a better data visualization). Key characteristics of each phenotype: Low-morbidity (n=3385; 58%), younger patients with few comorbidities; High-morbidity (n=2074; 35%), patients with high comorbid burden; Renal-morbidity (n=407; 7%), patients with chronic kidney disease, high comorbidity burden and the worst oxygenation profile.

present study differs from the aforementioned studies in being based exclusively on the baseline comorbidity patterns of critically ill patients and assessing how different comorbidity backgrounds influence clinical outcome, response to available treatment, risk of different complications, mortality, and sequelae.

Previous research focusing on the comorbidity burden of hospitalized COVID-19 patients has identified hypertension, diabetes, obesity, COPD, active cancer and CKD as having an impact on prognosis and clinical outcome.[3–5] The present cluster analysis and subsequent deepened analyses of the role of comorbidities in each phenotype highlighted the key role of CKD. Subjects with baseline CKD, regardless of comorbidity burden, experienced the worst in-hospital outcome in terms of complications, either infectious or related to myocardial infarction and ischemia, and total in-hospital mortality. Even in the low-morbidity phenotype, patients with CKD experienced significantly higher in-hospital mortality than those with other or no comorbidities. The impact of baseline CKD on the prognosis of COVID-19 could be explained by the effects of kidney failure on general immunity, including intestinal barrier dysfunction, difficulties associated with maintaining the acid-base balance, systemic inflammation and immunodeficiency.[24] In contrast, acute renal failure, caused directly by SARS-CoV-2 in the renal parenchyma or secondary to hemodynamic instability, inflammatory cytokines or the consequences of ICU therapies,[25] could be seen as a marker of global vascular damage caused by the infection and thus imply inherent prognostic value throughout the acute phase.

Regarding other comorbidities, on the one hand, analyses in the low-comorbidity phenotype showed that only diabetes and active malignancies were associated with higher mortality rates. On the other hand, the analysis of multimorbidity patterns among patients with the high-morbidity phenotype identified subphenotypes with the highest burden of metabolic diseases as having the best prognosis as opposed to those with pulmonary comorbidities or a wide spectrum of chronic diseases added to hypertension. Prior studies reported that patients with chronic lung disease, especially COPD patients, appear to have a predisposition to suffer from severe forms of disease.[26–28] This has been related to a higher expression of ACE-2 receptors in the bronchial

epithelium,[29] especially in smokers,[30,31] and with the impairment of the immune response.[32] However, these mechanisms seem insufficient to fully explain this result. Perhaps, our findings reporting the poor prognosis of chronic lung disease in the context of a high comorbidity burden highlight the need for the concurrence of other factors not related to lung impairment that act as key contributors to adverse outcomes in these subjects, either by increasing cell infection or by worsening immune response impairment.

A comparison of key biological parameters between phenotypes showed no significant differences regarding the severity of respiratory insufficiency at ICU admission, based on PaO_2/FIO_2, and the degree of inflammation, based on C reactive protein. In contrast, significantly higher levels of markers of coagulation activation, such as D dimer, were found in the high-morbidity and renal-morbidity phenotypes. This could imply a higher degree of microthrombosis, which has been related to an increased risk of in-hospital mortality.[33,34]

As expected, patients with the high-morbidity and renal-morbidity phenotypes experienced the highest burden of infectious and thrombotic complications. In this sense, these patients experienced more cardiovascular events, either ischemic heart disease or myocardial infarction, most probably due to prior subclinical coronary plaques being aggravated by coagulation disorder and endothelial damage induced by the virus. In contrast, patients with the low-morbidity phenotype showed higher pulmonary embolism and disseminated intravascular coagulation. Despite uncertainties regarding the cause of pulmonary embolism, either local thrombosis complications in the gateway of the virus infection or deep vein thrombosis,[35] it is likely that its higher incidence is observed by the absence of other competing risks, such as cardiovascular events, leading to the need for ICU admission. Disseminated intravascular coagulation is likely caused by viral sepsis, especially in subjects struggling to clear the virus, and would not be related to the comorbidity burden.

Corticosteroids, especially dexamethasone[36] and tocilizumab,[37] have both been widely used for the treatment of COVID-19. Focusing on corticosteroids, the current study showed an overall positive effect on mortality, which was stronger in the high-morbidity and renal-morbidity phenotypes (although only the former reached statistical significance in a test for interaction). This contrasts with results by Sinha et al. showing a benefit of corticosteroids only in hyperinflammatory phenotype patients.[16] When looking at tocilizumab, no effect on mortality was found in any of the phenotypes. This contrasts with previously reported results showing effectiveness if used in the first days of ICU admission.[38,39] Unfortunately, information on treatment timing was not available in the current study.

In a wide systematic review on persistent post-acute sequelae of COVID-19 (PASC), Groff et al.[40] reported that more than half of COVID-19 survivors experienced PASC six months after recovery. Our study, focused on ICU patients, shows several relevant findings. First, in line with Groff et al., half of the patients, regardless of their comorbidity phenotype, experience persistent fatigue at 3 and 6 months after discharge. Second, patients with the high-morbidity and renal-morbidity phenotypes showed worse lung function than those with the low-morbidity phenotype, with renal-morbidity patients showing the worst results. However, the overall presence of impaired pulmonary function at 3 months after discharge was high in all phenotypes and only the renal-morbidity phenotype showed substantial differences in terms of diffusion impairment at 3 and 6 months after discharge, which could suggest a differential activation of harmful mechanisms in patients with the renal-morbidity phenotype (at least at the lung level). Finally, the risk of experiencing infectious complications, emergency visits or hospital readmissions was significantly higher in renal-morbidity patients than in those with the low-morbidity phenotype, with patients with the high-morbidity phenotype falling in between the two.

To conclude, this study identified three well-defined phenotypes in critically ill COVID-19 patients, based on previous comorbidities and with a key role of CKD, and related them to in-hospital complications and mortality, response to standard treatment, and the prevalence of sequelae and their progressive remission up to 6 months after discharge. This highlights the importance of comorbidity patterns and especially CKD in COVID-19, and could help clinicians in day-to-day decision making including the management of post-discharge sequelae.

Contributors

Conceptualization (IDB, JdB, GT, FB), data curation (IDB, CG-P, AM-M), formal analysis (IDB), funding acquisition (AT, FB), investigation (all), methodology (IDB, JdB, GT, AT, FB), project administration (AT, FB), supervision (AT, FB), writing – original draft (IDB, JdB, GT), and writing – review & editing (all). Iván D. Benítez and Jordi de Batlle have directly accessed and verified the underlying data. Ferran Barbé was responsible for the decision to submit the manuscript.

Data sharing statement

An anonymized, de-identified version of the dataset can be made available upon reasonable request to allow results to be reproduced. A two-year embargo time since time of publication will be in place.

Declaration of interests

None declared.

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Transparency statement
The leading authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data availability statement

Excerpts of relevant data can be available from the corresponding author on reasonable request. However, a two years embargo is foreseen to allow authors to fully complete their analysis and publication plans.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100422.

References

1 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395. https://doi.org/10.1016/S0140-6736(20)30183-5.
2 Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk factors for severe disease and efficacy of treatment in patients infected with COVID-19: a systematic review, meta-analysis, and meta-regression analysis. *Clin Infect Dis*. 2020;71:2199–2206.
3 Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med*. 2020;180:1081–1089.
4 Gupta RK, Harrison EM, Ho A, et al. Development and validation of the ISARIC 4C deterioration model for adults hospitalised with COVID-19: a prospective cohort study. *Lancet Respir Med*. 2021;9. https://doi.org/10.1016/S2213-2600(20)30559-2.
5 Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. *JAMA - J Am Med Assoc*. 2020;323. https://doi.org/10.1001/jama.2020.5394.
6 Wang X, Jehi L, Ji X, Mazzone PJ. Phenotypes and subphenotypes of patients With COVID-19: a latent class modeling analysis. *Chest*. 2021;159:2191–2204.
7 Lusczek ER, Ingraham NE, Karam BS, et al. Characterizing COVID-19 clinical phenotypes and associated comorbidities and complication profiles. *PLoS One*. 2021;16:1–18.
8 Gutiérrez-Gutiérrez B, del Toro MD, Borobia AM, et al. Identification and validation of clinical phenotypes with prognostic implications in patients admitted to hospital with COVID-19: a multicentre cohort study. *Lancet Infect Dis*. 2021;21:783–792.
9 Rubio-Rivas M, Corbella X, Mora-Luján JM, et al. Predicting clinical outcome with phenotypic clusters in covid-19 pneumonia: an analysis of 12,066 hospitalized patients from the spanish registry semi-covid-19. *J Clin Med*. 2020;9:1–19.
10 Robba C, Battaglini D, Ball L, et al. Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. *Respir. Physiol. Neurobiol*. 2020;279. https://doi.org/10.1016/j.resp.2020.103455.
11 Azoulay E, Zafrani L, Mirouse A, Lengliné E, Darmon M, Chevret S. Clinical phenotypes of critically ill COVID-19 patients. *Intensive Care Med*. 2020;46:1651–1652.
12 Bos LDJ, Sjoding M, Sinha P, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts. *Lancet Respir Med*. 2021;2600. https://doi.org/10.1016/s2213-2600(21)00365-9.
13 Chen H, Zhu Z, Su N, et al. Identification and prediction of novel clinical phenotypes for intensive care patients with SARS-CoV-2 pneumonia: an observational cohort study. *Front Med*. 2021;8:1–9.
14 Dupont T, Caillat-Zucman S, Fremeaux-Bacchi V, et al. Identification of distinct immunophenotypes in critically ill coronavirus disease 2019 patients. *Chest*. 2021;159. https://doi.org/10.1016/j.chest.2020.11.049.
15 Rodríguez AH, Ruiz-Botella M, Martín-Loeches I, et al. Deploying unsupervised clustering analysis to derive clinical phenotypes and risk factors associated with mortality risk in 2022 critically ill patients with COVID-19 in Spain. *Crit Care*. 2021;25:1–15.
16 Sinha P, Furfaro D, Cummings MJ, et al. Latent class analysis reveals COVID-19-related ARDS subgroups with differential responses to corticosteroids. *Am J Respir Crit Care Med*. 2021:1–65.
17 Vasquez CR, Gupta S, Miano TA, et al. Identification of distinct clinical subphenotypes in critically ill patients with COVID-19. *Chest*. 2021;160. https://doi.org/10.1016/j.chest.2021.04.062.
18 Torres A, Arguimbau M, Bermejo-Martín J, et al. CIBERESUCICOVID: a strategic project for a better understanding and clinical management of COVID-19 in critical patients. *Arch. Bronconeumol*. 2021;57. https://doi.org/10.1016/j.arbres.2020.10.021.
19 Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. *N Engl J Med*. 2021;385. https://doi.org/10.1056/nejmoa2102953.
20 Bandeen-roche K, Miglioretti DL, Zeger SL, Rathouz PJ. Latent variable regression for multiple discrete outcomes. *J Am Stat Assoc*. 1997;92. https://doi.org/10.1080/01621459.1997.10473658.
21 NAGIN D. Group-based modeling of development. 2005. Chapter 5. DOI:10.4159/9780674041318.
22 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133. https://doi.org/10.1161/CIRCULATIONAHA.115.017719.
23 Noordzij M, Leffondré K, Van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant*. 2013;28. https://doi.org/10.1093/ndt/gft355.
24 Kurts C, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. *Nat Rev Immunol*. 2013;13:738–753.
25 Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. *Intensive Care Med*. 2020;46. https://doi.org/10.1007/s00134-020-06153-9.
26 Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55. https://doi.org/10.1183/13993003.00547-2020.Suppl.
27 Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. *PLoS One*. 2020;15. https://doi.org/10.1371/journal.pone.0233147.
28 Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med*. 2020;201. https://doi.org/10.1164/rccm.202002-0445OC.
29 Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur. Respir. J*. 2020;55. https://doi.org/10.1183/13993003.00688-2020.
30 Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco smoking increases the lung gene expression of ACE2, the Receptor of SARS-CoV-2. *Am. J. Respir. Crit. Care Med*. 2020;201. https://doi.org/10.1164/rccm.202003-0693LE.
31 Zhang H, Rostami MR, Leopold PL, et al. Expression of the SARS-CoV-2 ACE2 receptor in the human airway epithelium. *Am J Respir Crit Care Med*. 2020;202. https://doi.org/10.1164/rccm.202003-0541OC.
32 Bhat TA, Panzica L, Kalathil SG, Thanavala Y. Immune dysfunction in patients with chronic obstructive pulmonary disease. *In: Annals of the American Thoracic Society*. 2015. https://doi.org/10.1513/AnnalsATS.201503-126AW.
33 Ye W, Chen G, Li X, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. *Respir Res*. 2020;21. https://doi.org/10.1186/s12931-020-01428-7.
34 Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic values of serum ferritin and d-dimer trajectory in patients with covid-19. *Viruses*. 2021;13. https://doi.org/10.3390/v13030419.
35 Suh YJ, Hong H, Ohana M, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. *Radiology*. 2021;298. https://doi.org/10.1148/RADIOL.2020203557.
36 Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19 — preliminary report. *N Engl J Med*. 2020. https://doi.org/10.1101/2020.06.22.20137273.
37 Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised,

controlled, open-label, platform trial. *Lancet*. 2021;397. https://doi.org/10.1016/S0140-6736(21)00676-0.

38 Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181. https://doi.org/10.1001/jamainternmed.2020.6252.

39 The REMAP-CAP Investigators*. Interleukin-6 receptor antagonists in critically ill patients with covid-19. *N Engl J Med*. 2021;384:1491–1502.

40 Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection. *JAMA Netw Open*. 2021;4. https://doi.org/10.1001/jamanetworkopen.2021.28568.