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ORIGINAL ARTICLE

Clinical presentation, therapeutic approach, and outcome of young patients admitted for COVID-19, with respect to the elderly counterpart

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Abstract
There is limited information on the presenting characteristics, prognosis, and therapeutic approaches of young patients hospitalized for coronavirus disease 2019 (COVID-19). We sought to investigate the baseline characteristics, in-hospital treatment, and outcomes of a wide cohort < 65 years admitted for COVID-19. Using the international multicenter HOPE-COVID-19 registry, we evaluated the baseline characteristics, clinical presentation, therapeutic approach, and prognosis of patients < 65 years discharged (deceased or alive) after hospital admission for COVID-19, also compared with the elderly counterpart. Of the included 5746 patients, 2676 were < 65 and 3070 ≥ 65 years. All risk factors and several parameters suggestive of worse clinical presentation augmented through increasing age classes. In-hospital mortality rates were 6.8% and 32.1% in the younger and older cohort, respectively ($p < 0.001$). Among young patients, mortality, access to ICU and treatment with IMVwere positively correlated with age. Contrariwise, over 65 years of age this trend was broken so that only the association between age and mortality was persistent, while the rates of access to ICU and IMV started to decline. Younger patients also recognized specific predictors of case fatality, such as obesity and gender. Age negatively impacts on mortality, access to ICU and treatment with IMV in patients < 65 years. In elderly patients only case fatality rate keeps augmenting in a stepwise manner through increasing age categories, while therapeutic approaches become more conservative. Besides age, obesity, gender, history of cancer, and severe dyspnea, tachypnea, chest X-ray bilateral abnormalities, abnormal level of creatinine and leucocyte among admission parameters seem to play a central role in the outcome of patients younger than 65 years.

Keywords Coronavirus disease 2019 · SARS-CoV-2 infection · Intensive care unit · Invasive mechanical ventilation

Abbreviations

CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
ECMO	Extracorporeal mechanical oxygenation
eGFR	Estimated Glomerular Filtration Rate
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
PCR	Polymerase-chain-reaction
ROC	Receiver-operating characteristic
SIRS	Systemic inflammatory response syndrome

Introduction

SARS-CoV-2, the novel coronavirus that causes coronavirus disease 2019 (COVID-19), was first reported in China in late December 2019. Since then, due to the rapid and global spread of the disease, WHO declared a pandemic indicating

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over 118,000 cases in over 110 countries around the world on March 11th, 2020 [1]. COVID-19 is characterized by high morbidity andhigh mortality among hospitalized patients. Initial reports have also highlighted the association between age and disease severity and/or case fatality [2]. Despite mortality has been proved to increase with decades, data from large registries about prognosis and therapeutic approaches of the younger patients are still lacking.

Here, we sought to investigate the baseline clinical characteristics, the predictors of adverse outcomes, the in-hospital treatment, and the outcome of a wide cohort of patients younger than 65 years admitted for COVID-19.

Methods

Study design and population

This was a retrospective analysis of data from all consecutive patients discharged (deceased or alive) after hospital admission for confirmed or highly suspected SARS-CoV-2 infection and accrued in the multicenter international HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry. Briefly, the HOPE-COVID-19 Registry is an international initiative without conflicts of interest, designed as a "real-world" all-comers retrospective cohort registry, with voluntary participation and no financial remuneration. The study was performed according the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by Ethics Research Committee from the Hospital Clínico San Carlos (Madrid, Spain) (20/241-E) and the Spanish Agency for Medicines and Health Products classification (EPA-0D). Written informed consent was waived because of the anonymized nature of the registry and the health alarm situation generated by the pandemia. There were no exclusion criteria, except for patients' explicit refusal to participate. A list of participating hospitals, investigators, collaborators, the study protocol, and the Research Ethic Commitee (REC) approval report are available online (https://hopeprojectmd.com). The study was registered online at clinicaltrials.gov (NCT04334291). An on line anonymized database was available in electronic format to be filled in by each participating center (https://hopeprojectmd.com). All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data provided.

Data extraction

Epidemiological, clinical, and outcome data were extracted from electronic medical records. Patients' data were anonymously collected in a locked, password-protected website. Demographic information included age, sex, race, weight, and height. Coexisting conditions included any lung disease (chronic obstructive pulmonary disease [COPD], asthma, restrictive or interstitial pulmonary disease), any immunosuppressed condition (immunosuppressant use, a preexisting immunologic condition, or ongoing chemotherapy for cancer disease), current or remote history of smoking, history of hypertension, diabetes mellitus, dyslipidemia, or underlying cardiovascular disease (coronary artery disease, heart failure, valvular disease, and cardiac arrhythmia). Home medications, recorded at the time of hospital admission, included any antiplatelet/anticoagulation therapy, use of betablockers, ARBs or ACE inhibitors, inhaled betaagonist or glucocorticoids, benzodiazepines, and antidepressants.

Data regarding admission signs and symptoms (dyspnea, tachypnea, fever, cough, dysgeusia, hypo/anosmia, sorethroat, vomiting, diarrhea, arthromyalgia), initial laboratory tests and instrumental diagnostic exams (chest X-ray), inpatient medications (glucocorticoids, chloroquine, antiviral drugs, antibiotics, tolicizumab or similar, interferon or similar, ACE or ARBs, and anticoagulants), non-pharmacological treatments (Intensive Care Unit [ICU] care, oxygen therapy, high-flow nasal cannula therapy, non-invasive or invasive mechanical ventilation [IMV], prone position, extracorporeal mechanical oxygenation [ECMO] or other support), in-hospital adverse events such as mortality or clinically relevant complications (respiratory insufficiency, heart failure, renal failure, pneumonia [uni or bilateral], sepsis, systemic inflammatory response syndrome [SIRS], clinically relevant bleeding, hemoptysis, and embolic events), and discharge data were extracted for all patients.

Definitions and outcomes analysis

For the present analysis, the focus was mainly on the patients aged 18 to 64 years, according to the WHO definition of elderly as individuals aged 65 years or more [3]. Age assessment was made at the time of the hospital admission. The primary endpoint of the study was death from any cause occurring during hospital stay; secondary endpoints were access to ICU and IMV. The study endpoints were also analyzed in the rest of the registry population, which included patients aged 65 or older.

Patients were considered to have confirmed infection by a positive result on high-throughput sequencing or real-time reverse transcriptase polymerase-chain-reaction (PCR) assay of nasal or pharyngeal swab specimens; patients with compatible signs or symptoms together with any other diagnostic finding (e.g., radiological evidence of pulmonary involvement) or with inconclusive PCR assay were deemed as highly suspected of SARS-CoV-2 infection. Leukopenia was defined as white blood cells count < 4000/L, whereas

lymphocytopenia as lymphocytes count < 1500/L [2]. For blood tests whose normality thresholds were not predefined (e.g., troponin I, d-dimers, procalcitonin), abnormal levels were according to local laboratory cutoffs. Severe chronic kidney disease (CKD) was defined as an estimated Glomerular Filtration Rate (eGFR) ≤ 30 ml/min calculated by means of the Cockcroft-Gault formula. Body mass index was calculated through the formula weight (in kilograms) divided by the square of the height (in meters). Details of all the remaining variables assessed in the analysis are available online (https://hopeprojectmd.com). We referred to the Charlson Comorbidity Index to identify the chronic comorbid conditions which might impact the long-term survival: hypertension, diabetes mellitus, coronary artery disease, heart failure, COPD, cerebrovascular events, severe renal failure, connective disease, liver disease, history of cancer, HIV infection [4].

Furthermore, four different age groups(< 35; 35–44; 45–54; 55–64) were generated in the younger cohort and three for the elderly patients (65–74; 75–84; ≥ 85 years). Trends through increasing age categories of the following parameters were evaluated: mortality, multiple comorbidities (defined as ≥ 3 comorbid diseases), combined pharmacological therapies (defined as the association of Chloroquine and an antiviral drug), access to ICU, and treatment with IMV. In order to evaluate the differential case fatality rate according to age among patients undergoing IMV or admitted in ICU, in view of the reduced numerosity, a division in four age groups was used (< 55; 55–64; 65–74; ≥ 75).

Statistical analysis

The study population was primarily divided into two groups: patients younger than 65 years and patients ≥ 65 years; moreover all the assessed variables were also presented according to age categories within the younger cohort. Continuous variables were summarized as means with standard deviations and categorical variables as frequencies or percentages. Baseline characteristics, hospital admission parameters, inpatients medications, ICU admission, in-hospital instrumental treatments, in-hospital complications, and mortality rates were compared between age groups using the Pearson's Chi-squared test or Fisher exact test, when appropriated, for categorical variables and the unpaired Student's t test or analysis of variance for continuous variables. For the primary endpoint of the study, the association with all the baseline characteristics and hospital admission findings was tested in the whole population and in the group < 65 years; a stepwise logistic regression with the forward selection method (P for entry < 0.05) was used to choose the final multivariable model to predict in-hospital death, reporting results as point estimates and 95% confidence intervals (CI) of the odds ratio. Additional sensitivity analyses were based on penalized logistic regression, missing data imputation, and classification and regression tree (CART) analyses. Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustment.

A receiver-operating characteristic (ROC) curve analysis with Youden index measure was performed to determine the best cutoff value of age for predicting the in-hospital mortality. Computations were performed with SPSS 22.0 (SPSS; Chicago, IL, USA) and Stata 13.0 (Stata Corp, College Station, TX, USA).

Results

Overall population

A total of 5868 hospitalized patients with confirmed or highly suspected SARS-CoV-2 infection from 39 centers in 31 cities and seven countries who completed their hospital course were finally included in the HOPE registry by May 05, 2020. Our study population included 5746 patients, owing to the exclusion of 122 patients from the analysis for incompleteness of demographic data or because aged < 18 years (Appendix Fig. 3). Enrollment rates by country of citizenship are shown in Appendix Fig. 4.

Analysis of the young cohort

Table 1 depicts the distribution of demographic characteristics, coexisting conditions, and home medications among young (< 65 years) patients overall and by the four predefined age classes, along with the between-groups differences. In brief, overall patients younger than 65 years were 2676 (mean age 49.63 ± 10.44 years, male 59.4%). All risk factors showed to significantly augment through increasing age classes, as well as several comorbidities such as severe CKD, any lung disease, COPD, previous cardiac, cerebrovascular, liver, and cancer disease. The same trend was found in the analysis of the rates of comorbidities per age classes and was maintained when the investigation was extended over the age of 65 (Appendix Table 4). Symptoms, signs, and laboratory results recorded at admission are displayed in Table 2. Several parameters suggestive of worse clinical presentation showed to be associated with age. Indeed, between the four age groups of the young cohort, a stepwise increasing prevalence of severe dyspnea, fatigue, tachypnea, peripheral oxygen saturation < 92%, instrumental evidence of bilateral pulmonary infiltrates, and more pronounced signs of systemic inflammation and multi-organ involvement (proven by the levels of procalcitonin, C-Reactive protein, D-dimer, troponin I, transaminases, LDH) were detected. In-hospital clinical course and treatments are described in Table 3.

Table 1 Baseline characteristics of HOPE PROJECT young population divided according to age categories

		Age (years old)				
	Overall < 65 (n = 2676)	< 35 (n = 269)	35–44 (n = 506)	45–54 (n = 837)	55–64 (n = 1064)	P
Baseline characteristics						
Male	1589/2676 (59.4%)	129/269 (48.0%)	292/506 (57.7%)	527/837 (63.0%)	641/1064 (60.2%)	< 0.001
Body mass index (kg/m^2)	27.84 ± 6.88	27.65 ± 13.10	26.76 ± 5.76	28.06 ± 5.74	28.23 ± 5.89	0.061
Comorbidities						
Hypertension	698/2667 (26.2%)	14/268 (5.2%)	53/504 (10.5%)	204/835 (24.4%)	427/1060 (40.3%)	< 0.001
Dyslipidemia	470/2659 (17.7%)	4/265 (1.5%)	37/503 (7.4%)	129/832 (15.5%)	300/1059 (28.3%)	< 0.001
Diabetes Mellitus	243/2676 (9.1%)	5/269 (1.9%)	26/506 (5.1%)	53/837 (6.3%)	159/1064 (14.9%)	< 0.001
Obesity	440/2214 (19.2%)	26/229 (11.4%)	61/416 (14.7%)	149/696 (21.4%)	204/873 (23.4%)	< 0.001
Former smokers	276/2676 (10.3%)	1/269 (0.4%)	31/506 (6.1%)	77/837 (9.2%)	167/1064 (15.7%)	< 0.001
Current smoking	190/2428 (7.8%)	16/243 (6.6%)	22/456 (4.8%)	58/757 (7.7%)	94/972 (9.7%)	0.013
Severe chronic kidney disease	58/2676 (2.2%)	2/269 (0.7%)	6/506 (1.2%)	18/837 (2.2%)	32/1064 (3.0%)	0.038
Any lung disease	330/2676 (12.3%)	24/269 (8.9%)	50/506 (9.9%)	96/837 (11.5%)	160/1064 (15.0%)	0.004
Asthma	167/2676 (6.2%)	18/269 (6.7%)	37/506 (7.3%)	58/837 (6.9%)	54/1064 (5.1%)	0.237
Chronic obstructive pulmonary disease	67/2676 (2.5%)	0/269 (0.0%)	2/506 (0.4%)	11/837 (1.3%)	54/1064 (5.1%)	< 0.001
Interstitial	9/2676 (0.3%)	0/269 (0.0%)	0/506 (0.0%)	4/837 (0.5%)	5/1064 (0.5%)	0.298
Restrictive	9/2676 (0.3%)	0/269 (0.0%)	0/576 (0.0%)	4/837 (0.5%)	5/1064 (0.5%)	0.298
Other	78/2676 (2.9%)	6/269 (2.2%)	11/506 (2.2%)	19/837 (2.3%)	42/1064 (3.9%)	0.083
Cardiac disease	209/2654 (7.9%)	7/268 (2.6%)	16/505 (3.2%)	57/828 (6.9%)	129/1053 (12.3%)	< 0.001
Coronary artery disease	76/2676 (2.8%)	1/269 (0.4%)	5/506 (1.0%)	18/837 (2.2%)	52/1064 (4.9%)	< 0.001
Cardiomyopathy/heart failure	23/2676 (0.9%)	1/269 (0.4%)	4/506 (0.8%)	6/837 (0.7%)	12/1064 (1.1%)	0.598
Valvular heart disease	20/2676 (0.7%)	1/269 (0.4%)	2/506 (0.4%)	8/837 (1.0%)	9/1064 (0.8%)	0.575
Arrhythmia	55/2676 (2.1%)	3/269 (1.1%)	4/506 (0.8%)	14/837 (1.7%)	34/1064 (3.2%)	0.598
Combined	24/2676 (0.9%)	0/269 (0.0%)	1/506 (0.2%)	8/837 (1.0%)	15/1064 (1.4%)	0.038
Atrial Fibrillation	22/2676 (0.8%)	0/269 (0.0%)	3/506 (0.6%)	7/837 (0.8%)	12/1064 (1.1%)	0.038
Cerebrovascular disease	60/2624 (2.3%)	2/265 (0.8%)	10/499 (2.0%)	13/822 (1.6%)	35/1038 (3.4%)	0.016
Connective disease	62/2630 (2.4%)	4/264 (1.5%)	12/498 (2.4%)	14/825 (1.7%)	32/1043 (3.1%)	0.198
Liver disease	75/2627 (2.9%)	5/265 (1.9%)	10/496 (2.0%)	17/823 (2.1%)	43/1043 (4.1%)	0.018
Cancer disease	149/2634 (5.7%)	2/267 (0.7%)	13/500 (2.6%)	47/819 (5.7%)	87/1048 (8.3%)	< 0.001
Immunosuppression	161/2523 (6.4%)	14/255 (5.5%)	22/479 (4.6%)	47/786 (6.0%)	78/1003 (7.8%)	0.094
Prior tuberculosis	4/2676 (0.1%)	0/269 (0.0%)	1/506 (0.2%)	1/837 (0.1%)	2/1064 (0.2%)	0.888
HIV infection	15/2676 (0.6%)	3/269 (1.1%)	3/506 (0.6%)	5/837 (0.6%)	4/1064 (0.4%)	0.539
Partially dependent	58/2676 (2.2%)	3/269 (1.1%)	5/506 (1.0%)	17/837 (2.0%)	33/1064 (3.1%)	0.027
Totally dependent	37/2676 (1.4%)	3/269 (1.1%)	6/506 (1.2%)	14/837 (1.7%)	14/1064 (1.3%)	0.841
Home therapy						
Home oxygen therapy	35/2651 (1.3%)	0/267 0.0%)	2/502 (0.4%)	11/830 (1.3%)	22/1052 (2.1%)	0.009
Aspirin	165/2643 (6.2%)	1/266 (0.4%)	10/499 (2.0%)	42/829 (5.1%)	112/1049 (10.7%)	< 0.001
Other antiplatelet drug	29/2627 (1.1%)	1/265 (0.4%)	2/496 (0.4%)	9/824 (1.1%)	17/1042 (1.6%)	0.104
Oral anticoagulation	58/2631 (2.2%)	3/265 (1.1%)	4/498 (0.8%)	13/827 (1.6%)	38/1041 (3.7%)	0.001
ACE/ARBs	524/2649 (19.8%)	7/267 (2.6%)	35/500 (7.0%)	141/829 (17.0%)	34,171,053 (32.4%)	< 0.001
Beta blockers	199/2639 (7.5%)	1/266 (0.4%)	14/499 (2.8%)	67/824 (8.1%)	117/1050 (11.1%)	< 0.001
Beta agonist inhalation therapy	158/2643 (6.0%)	13/268 (4.9%)	25/502 (5.0%)	49/828 (5.9%)	71/1045 (6.8%)	0.434
Glucocorticoids inhalation therapy	136/2650 (5.1%)	6/269 (2.2%)	13/501 (2.6%)	39/830 (4.7%)	78/1050 (7.4%)	< 0.001
D vitamin supplement	114/2641 (4.3%)	5/268 (1.9%)	14/498 (2.8%)	35/829 (4.2%)	60/1046 (5.7%)	0.008
Benzodiazepines	226/2644 (8.5%)	6%266 (2.3%)	18/501 (3.6%)	79/832 (9.5%)	123/1045 (11.8%)	< 0.001
Antidepressant drugs	187/2640 (7.1%)	9/268 (3.4%)	15/501 (3.0%)	67/827 (8.1%)	96/1044 (9.2%)	< 0.001

Values are expressed as mean ± standard deviation or n (%)

Table 2 Admission parameters of HOPE PROJECT young population divided according to age categories

		Age (years old)				
	Overall < 65 (*n* = 1612)	< 35 (*n* = 269)	35–44 (*n* = 506)	45–54 (*n* = 837)	55–64 (*n* = 1064)	***P***
Symptoms and clinical parameters						
Asymptomatic	153/2641 (5.8%)	21/264 (8.0%)	42/501 (8.4%)	61/828 (7.4%)	29/1048 (2.8%)	< 0.001
Dyspnea						
Mild	815/2676 (30.5%)	85/269 (31.6%)	166/506 (32.8%)	273/837 (32.6%)	291/1064 (27.3%)	0.042
Moderate	477/2676 (17.8%)	41/269 (15.2%)	80/506 (15.8%)	136/837 (16.2%)	220/1064 (20.7%)	0.019
Severe	182/2676 (6.8%)	5/269 (1.9%)	217/506 (4,2%)	67/837 (8.0%)	89/1064 (8.4%)	< 0.001
Tachypnea (> 22 breaths per minute)	555/2590 (21.4%)	37/260 (14.2%)	86/487 (17.7%)	180/814 (22.1%)	252/1029 (24.5%)	< 0.001
Peripheral oxygen saturation < 92%	604/2585 (23.4%)	31/255 (12.2%)	79/493 (16.0%)	190/819 (23.2%)	304/1018 (29.9%)	< 0.001
Fatigue	1148/2586 (44.4%)	91/259 (35.1%)	203/485 (41.9%)	368/818 (45.0%)	486/1024 (47.5%)	0.003
Hypo/anosmia	276/2480 (11.1%)	27/250 (10.8%)	60/465 (12.9%)	85/787 (10.8%)	104/978 (10.6%)	0.607
Dysgeusia	269/2475 (10.9%)	27/251 (10.8%)	60/461 (13.0%)	80/786 (10.2%)	102/977 (10.4%)	0.429
Sorethroat	419/2516 (16.7%)	64/254 (25.2%)	82/473 (17.2%)	141/797 (17.7%)	132/992 (13.3%)	< 0.001
Fever	2231/2649 (84.2%)	213/267 (79.8%)	422/503 (83.9%)	699/831 (84.1%)	897/1048 (85.6%)	0.139
Max temper (°C)	37.75 ± 1.03	37.72 ± 1.03	37.79 ± 1.05	37.81 ± 1.01	37.71 ± 1.02	0.210
Cough	1945/2640 (73.7%)	186/268 (69.4%)	364/503 (72.4%)	621/839 (74.8%)	774/1039 (74.5%)	0.274
Vomiting	197/2561 (7.7%)	23/256 (9.0%)	40/483 (8.3%)	59/809 (7.3%)	75/1013 (7.4%)	0.768
Diarrhea	545/2558 (21.2%)	54/256 (21.1%)	108/484 (22.3%)	166/812 (29.4%)	217/106 (21.4%)	0.884
Arthromyalgia	1002/2572 (39.0%)	114/258 (44.2%)	201/485 (41.4%)	308/815 (37.8%)	379/1014 (37.4%)	0.124
Chest X-Ray abnormalities	2104/2676 (78.6%)	181/269 (67.3%)	388/506 (76.7%)	660/837 (78.9%)	875/1064 (82.2%)	< 0.001
Unilateral infiltrates	475/2676 (17.8%)	55/269 (20.4%)	96/506 (19.0%)	155/837 (18.5%)	169/1064 (15.9%)	0.192
Bilateral infiltrates	1629/2676 (60.9%)	126/269 (46.8%)	292/506 (57.7%)	505/837 (60.3%)	706/1064 (66.4%)	< 0.001
Abnormal blood pressure (< 90 mmHg)	128/2449 (5.2%)	13/236 (5.5%)	25/460 (5.4%)	41/775 (5.3%)	49/978 (5.0%)	0.981
Glasgow Coma Scale	14.93 ± 0.69	14.92 ± 0.83	14.94 ± 0.69	14.95 ± 0.58	14.92 ± 0.68	0.801
Laboratory parameters						
Elevated D-dimer	1246/2329 (53.5%)	93/224 (41.5%)	191/435 (43.9%)	397/740 (53.6%)	565/930 (60.8%)	< 0.001
Elevated procalcitonin	324/1945 (16.7%)	20/209 (9.6%)	38/356 (10.7%)	119/615 (19.3%)	147/765 (19.2%)	< 0.001
Elevated C-Reactive Protein	2167/2583 (83.9%)	177/256 (69.1%)	390/491 (79.4%)	692/812 (85.2%)	908/1024 (88.7%)	< 0.001
Elevated troponin I	120/1412 (8.5%)	3/155 (1.9%)	15/255 (5.9%)	42/452 (9.3%)	60/550 (10.9%)	0.002
Elevated transaminases	1033/2444 (42.3%)	67/242 (27.7%)	192/461 (41.6%)	328/772 (42.5%)	446/969 (46.0%)	< 0.001
Elevated ferritin	844/1474 (57.3%)	50/136 (36.8%)	145/279 (52.0%)	271/478 (56.7%)	378/581 (65.1%)	< 0.001
Elevated triglycerides	270/1263 (21.4%)	25/138 (18.1%)	50/255 (19.6%)	85/397 (21.4%)	110/473 (23.3%)	0.505
Elevated LDH	1541/2389 (64.5%)	113/231 (48.9%)	269/457 (58.9%)	473/756 (62.6%)	686/945 (72.6%)	< 0.001
Creatinine (mg/dL)	0.99 ± 0.83	0.86 ± 0.70	0.93 ± 0.49	1.02 ± 0.91	1.03 ± 0.91	0.007
Creatinine > 1.5 mg/dL	227/2574 (8.8%)	10/256 (3.9%)	41/491 (8.4%)	81/809 (10.0%)	95/1018 (9.3%)	0.022
Natrium (mmol/L)	137.80 ± 4.04	138.31 ± 3.56	138.21 ± 3.68	137.67 ± 4.23	138.31 ± 3.56	0.005
Leukocytes (/mL)	6841.66 ± 3511.94	6516.18 ± 3182.60	6616.38 ± 3316.28	6995.51 ± 3797.85	6909.32 ± 3438.82	0.103
Leukocytes < 4000 m/L	408/2588 (15.8%)	49/256 (19.1%)	68/494 (13.8%)	130/815 (16.0%)	161/1023 (15.7%)	0.295
Lymphocytes (/mL)	1476.55 ± 1866.44	1744.19 ± 2523.73	1597.72 ± 2122.98	1494.35 ± 1583.58	1336.46 ± 1733.96	0.005
Lymphocytes < 1500/mL	1783/2549 (69.9%)	153/252 (60.7%)	331/490 (67.6%)	536/800 (67.0%)	763/1007 (75.8%)	< 0.001
Hemoglobin (g/dL)	13.92 ± 1.69	14.02 ± 1.73	13.89 ± 1.68	13.96 ± 1.74	13.87 ± 1,65	0.430
Anemia (HB < 12 g/dL)	463/2577 (18.0%)	42/253 (16.6%)	100/490 (20.4%)	145/814 (17.8%)	176/1020 (17.3%)	0.446
Platelet (/mL)	225,743.76 ± 99,017.14	223,541.18 ± 82,546.94	225,343.70 ± 99,649.30	233,343.37 ± 105,057.20	223,541.176 ± 82,546.94	0.049
Platelet < 150,000/mL	52/2585 (20.2%)	33/255 (12.9%)	91/492 (18.5%)	154/814 (18.9%)	244/1024 (23.8%)	< 0.001
Arterial blood gas analysis						
PH value	7.42 ± 0.08	7.41 ± 0.66	7.40 ± 0.09	7.42 ± 0.08	7.43 ± 0.07	0.002
PaO2 (mmHg)	76.08 ± 25.23	83.01 ± 23.47	82.73 ± 24.05	76.96 ± 24.87	71.22 ± 25.40	< 0.001
PaCO2 (mmHg)	34.47 ± 8.66	33.86 ± 8.44	33.74 ± 9.63	34.87 ± 9.01	34.57 ± 7.96	0.465
Saturation O2 (%)	93.11 ± 9.85	95.91 ± 3.89	94.98 ± 6.68	92.82 ± 11.66	91.83 ± 10.15	< 0.001

Values are expressed as mean ± standard deviation or n (%)

Progressively worse clinical conditions are demonstrated through incremental age classes, as expected, and are paralleled with more aggressive therapies, either pharmacological and/or supportive of the respiratory function.

Analysis of young patients as compared with elderly patients

Appendix Table5 depicts the distribution of demographic characteristics, coexisting conditions, home medications, and clinical information at admission among young (< 65 years) and elderly patients (≥ 65 years), along with the between-groups differences. Older patients had a greater prevalence of risk factors and comorbidities, as predictable. The 83.9% of patients ≥ 65 years had at least 1 comorbidity, while the 24.8% had ≥ 3 comorbid diseases, compared to the 4.0% of the younger counterpart. At admission symptoms, signs, and laboratory results are in line with the "age related" trend already seen among the age groups generated within the younger cohort: Patients ≥ 65 years more frequently presented with severe pulmonary and multi-organ involvement (Appendix Table 6). According to pharmacological

Table 3 In-hospital clinical course and medical management of the HOPE PROJECT young population divided according to age categories

		Age (years old)				
	Overall < 65 (n = 2676)	< 35 (n = 269)	35–44 (n = 506)	45–54 (n = 837)	55–64 (n = 1064)	P
ICU admission	255/2676 (9.5%)	9/269 (3.3%)	22/506 (4.3%)	81/837 (9.7%)	143/1064 (13.4%)	< 0.001
Death	182/2676 (6.8%)	6/269 (2.2%)	14/506 (2.8%)	55/837 (6.6%)	107/1064 (10.1%)	< 0.001
Complications during hospital/ICU stay						
Respiratory insufficiency	971/2635 (36.9%)	46/266 (17.3%)	126/497 (25.4%)	302/826 (36.6%)	497/1046 (47.5%)	< 0.001
Heart failure	60/2632 (2.3%)	4/266 (1.5%)	5/493 (1.0%)	13/823 (1.6%)	38/1041 (3.7%)	0.002
Acute kidney injury	180/2620 (6.9%)	7/265 (2.6%)	14/492 (2.8%)	52/822 (6.3%)	107/1041 (10.3%)	< 0.001
Upper respiratory tract infection	333/2593 (12.8%)	37/260 (14.2%)	66/490 (13.5%)	99/816 (12.1%)	131/1027 (12.8%)	0.803
Unilateral pneumonia	445/2626 (16.9%)	59/263 (22.4%)	83/496 (16.7%)	152/821 (18.5%)	151/1946 (14.4%)	0.008
Bilateral pneumonia	180/2626 (68.6%)	137/263 (52.1%)	322/496 (64.9%)	553/821 (67.4%)	789/1046 (75.4%)	< 0.001
Sepsis	210/2612 (8.0%)	10/263 (3.8%)	29/498 (5.8%)	63/820 (7.7%)	108/1031 (10.5%)	< 0.001
Systemic inflammatory response syndrome	384/2605 (14.7%)	22/264 (8.3%)	52/494 (10.5%)	112/814 (13.8%)	198/1033 (19.2%)	< 0.001
Any relevant bleeding	38/2586 (1.5%)	2/262 (0.8%)	8/491 (1.6%)	12/813 (1.5%)	16/1020 (1.6%)	0.787
Hemoptysis	42/2591 (1.6%)	1/263 (0.4%)	11/491 (2.2%)	14/814 (1.7%)	16/1023 (1.6%)	0.285
Embolic event	39/2596 (1.5%)	3/265 (1.1%)	2/486 (0.4%)	10/817 (1.2%)	24/1028 (2.3%)	0.024
Rash cutaneous	64/2006 (3.2%)	4/202 (2.0%)	14/381 (3.7%)	20/646 (3.1%)	26/777 (3.3%)	0.723
Oxygen therapy during hospital stay						
Oxygen therapy	1575/2615 (60.2%)	114/265 (43.0%)	246/493 (49.9%)	488/820 (59.5%)	727/1037 (70.1%)	< 0.001
High flow nasal cannula	445/2593 (17.2%)	32/260 (12.3%)	64/487 (13.1%)	148/818 (18.1%)	201/1028 (19.6%)	0.002
Non-invasive mechanical ventilation	306/2615 (11.7%)	20/265 (7.5%)	36/494 (7.3%)	103/821 (12.5%)	147/1035 (14.2v	< 0.001
Invasive mechanical ventilation	218/2599 (8.4%)	9/263 (3.4%)	19/491 (3.9%)	67/816 (8.2%)	123/1029 (12.0%)	< 0.001
Prone position	249/2586 (9.6%)	13/261 (5.0%)	29/490 (5.9%)	80/812 (9.9%)	127/1023 (12.4%)	< 0.001
Circulatory support or ECMO	122/2594 (4.7%)	6/263 (2.3%)	8/489 (1.6%)	34/815 (4.2%)	74/1027 (7.2%)	< 0.001
Medical therapy during hospital stay						
Glucocorticoids	564/2595 (21.7%)	34/258 (13.2%)	79/493 (16.0%)	178/812 (21.9%)	273/1032 (26.5%)	< 0.001
Antiviral drugs	1753/2627 (66.7%)	153/265 (57.7%)	338/49 (67.7%)	553/824 (67.1%)	709/1039 (68.2%)	0.012
Chloroquine	2259/2628 (86.0%)	182/263 (69.2%)	412/496 (83.1%)	729/826 (88.3%)	936/1043 (89.7%)	< 0.001
Antibiotics	1758/2488 (70.7%)	141/244 (57.8%)	306/484 (63.2%)	553/770 (71.8%)	758/990 (76.6%)	< 0.001
Chloroquine + antiviral drugs	1588/2612 (60.8%)	120/263 (45.6%)	301/495 (60.8%)	513/821 (62.5%)	654/1033 (63.3%)	< 0.001
Interferon or similar	382/2597 (14.7%)	30/263 (11.4%)	77/491 (15.7%)	113/817 (13.8%)	162/1026 (15.8%)	0.249
Tolicizumab or similar	229/2602 (8.8%)	11/265 (4.2%)	28/491 (5.7%)	62/819 (7.6%)	128/1027 (12.5%)	< 0.001
ACE/ARBs	331/2570 (12.9%)	5/263 (1.9%)	32/486 (6.6%)	101/806 (12.5%)	193/1015 (19.0%)	< 0.001
Anticoagulation	1118/1673 (66.8%)	73/168 (43.5%)	163/291 (56.0%)	372/550 (67.6%)	510/664 (76.8%)	< 0.001

Values are expressed as n (%)

ECMO = ExtraCorporeal Membrane Oxygenation; ICU = Intensity Care Unit

regimens and intensive treatments, it seems noteworthy to describe some discrepancies between younger and older patients (Appendix Table 7). Although the rates of ICU admission were comparable between the two age groups, IMV was applied to the 8.4% and the 6.4% of the younger and older population, respectively ($p = 0.005$), being the opposite for the non-invasive respiratory support use (15.3% in the elderly vs. 11.7% in the young counterpart, $p < 0.001$). Additionally, if glucocorticoids and antibiotics were the most common inpatients' medications in the elderly group, chloroquine and antiviral drugs (the drugs probably trusted as the most effective) were more frequently used in patients < 65 years.

Analysis of endpoints

The in-hospital case fatality rate in the overall population was 20.3%: death occurred in 182 (6.8%) of patients < 65 years and in 985 (32.1%) of patients in the older cohort ($p < 0.001$). Between the four age groups of the young population a stepwise increasing mortality rate was depicted through age categories and was paralleled by a concomitant increasing rates of ICU access, IMV, and use of combined pharmacological therapies (Appendix Table 8 and Fig. 1a).As the optimal threshold value (cutoff point) for mortality was detected by the mean of the Youden index

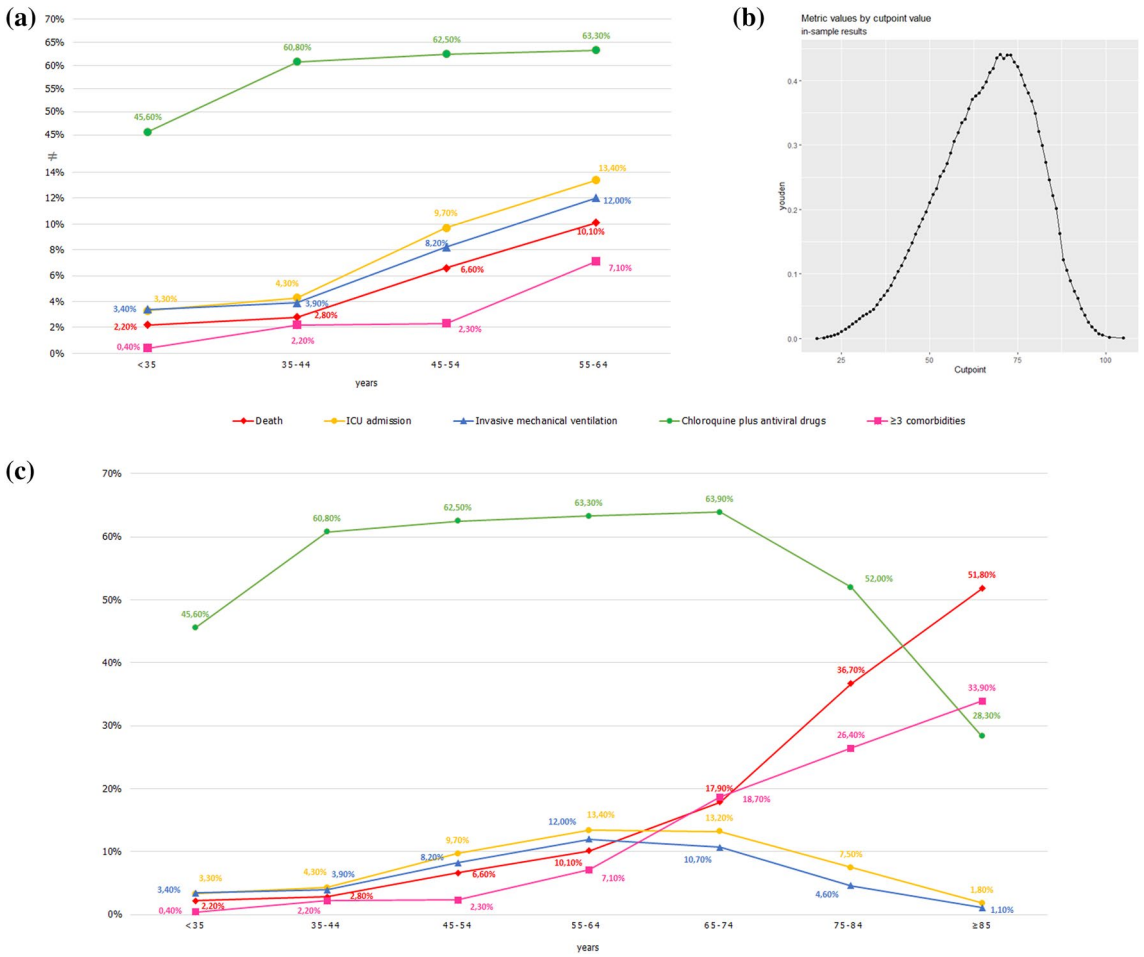

Fig. 1 **a** Trends of in-hospital death, multiple comorbidities (defined as ≥ 3 comorbid diseases), combined pharmacological therapies (defined as the association of chloroquine and an antiviral drug), access to Intensity Care Unit (ICU), and treatment with invasive mechanical ventilation through increasing age categories among the young population; **b** Youden index measure performed to determine the best cutoff value of age for predicting in-hospital mortality; **c** Trends of in-hospital death, multiple comorbidities (defined as ≥ 3 comorbid diseases), combined pharmacological therapies (defined as the association of chloroquine and an antiviral drug), access to Intensity Care Unit (ICU), and treatment with invasive mechanical ventilation through increasing age categories among the whole population

around 65–70 years (Fig. 1b), case fatality rate was also evaluated in the entire study population separated into seven age-groups as described in the methods and displayed in Fig. 1c. The bend of the mortality curve was confirmed after 65 years of age. What is noteworthy is the change of the trend of in-hospital treatments when the entire study sample is considered: The rates of access to ICU, combined pharmacological therapies, and IMV did not follow the trend of mortality any longer, but described a dome-like trend peaking between the age of 55 and 75, and declining afterward (Appendix Table 9 and Fig. 1).

Mortality rates were also evaluated in both the subpopulations of patients admitted to ICU and assisted with IMV: also in this subanalysis, after the division in four age groups (< 55; 55–64; 65–74; ≥ 75),the case fatality rate showed to increase with age (Appendix Table 5 and Fig. 2).

Multivariable Logistic-Regression Analysis

A multivariable logistic-regression model was developed. Independent predictors of in-hospital death, their corresponding odds ratios, and 95% confidence intervals are shown in Appendix Table 10. In the overall population, among baseline characteristics, age, severe CKD, partially dependence status, and oral anticoagulation treatment were associated with a higher risk of in-hospital death together with some clinical vitals and instrumental/laboratory parameters at admission: tachypnea, bilateral abnormalities at chest X-ray, elevated procalcitonin, and WBC count.

Considering the younger population (< 65 years) only, body mass index and cancer were the only independent predictors of in-hospital mortality among demographic and coexisting conditions, while at triage severe dyspnea, tachypnea, bilateral abnormalities at chest X-ray, creatinine > 1.5 mg/dL, and lymphocytopenia were associated with higher rate of case fatality.

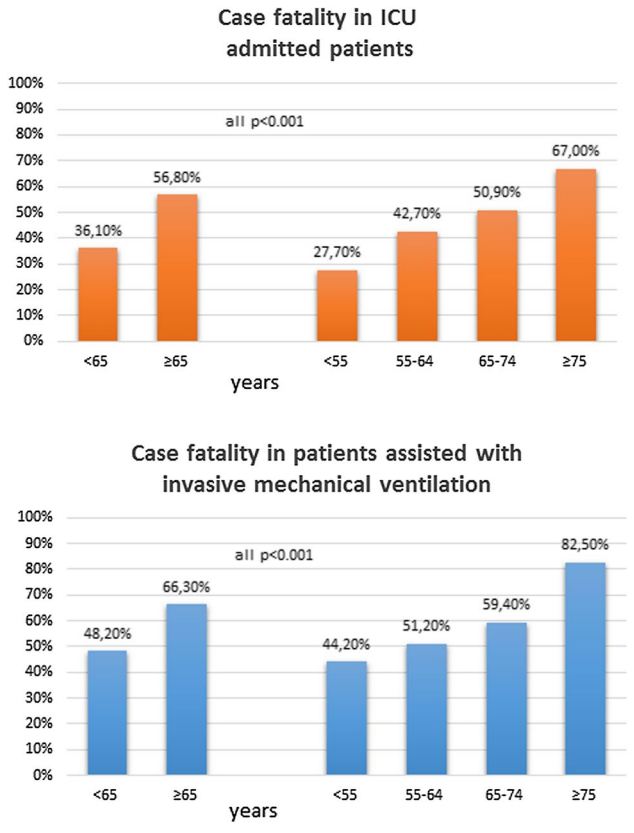

Fig. 2 Case fatality rate in patients admitted to Intensity Care Unit (ICU) and patients assisted with invasive mechanical ventilation divided according to age categories

Clinical endpoints according to gender

The primary and secondary endpoints were investigated in male vs. female patients younger than 65 years. As displayed in Appendix Table 11, female patients showed better prognosis in terms of mortality, access to ICU, and need for IMV. Baseline characteristics were also analyzed and compared between gender(Appendix Table 12), showing higher prevalence of risk factors and cardiac disease among male patients. In the subpopulation of the youngest patients (aged < 45), in female individuals significantly lower rates of in-hospital death and IMV were confirmed, in this case despite the lack of significant differences in terms of cardiovascular risk factors or coexisting conditions between the genders (Appendix Table 13).

Discussion

Since the beginning of the COVID-19 outbreak clinical data from multicentre registries have been collected worldwide [5–8]. To the best of authors' knowledge, this is the largest investigation on clinical characteristics, therapy, and in-hospital outcome of patients < 65 years admitted with COVID-19, also in comparison with elderly patients. The main findings of the present study are: (1) among patients < 65 years in-hospital mortality was positively correlated with age and the same association was also proven for the access to ICU and the treatment with IMV, secondary endpoints of the study; (2) over 65 years of age only the association between age and mortality was persistent, while the rates of access to ICU and IMV started to decline; (3) younger patients recognized specific predictors of case fatality.

Overall in-hospital mortality rate in our study was 20.3%, being deaths unequally distributed between patients younger than 65 years and older (6.8% vs. 32.1%). Moreover, when multiple age classes were considered, case fatality rate showed to increase in a stepwise fashion among both the younger and older cohort (Appendix Table 11). Relevance

of age as one of the most powerful mortality predictors is confirmed in our regression analysis (Appendix Table 10). The explanation for the increasing mortality through age categories among patients < 65 years can be easily found in the escalating rate of risk factors and comorbidities, which led to worse clinical presentation at admission and less favorable in-hospital clinical course (Table 1). These differences were enhanced when evaluated between larger age classes, such as in the case of patients younger than 65 years vs older. Patients aged more than 65 years, at the time of hospital access, more frequently presented symptoms and signs of severe pulmonary involvement such as severe dyspnea, tachypnea, low peripheral oxygen saturation (Appendix Table 6). This difference could suggest a different stage of the disease at the moment of admission, which might play a role in patients' prognosis.

Moreover, it seems noteworthy to describe the different trends of the primary and secondary endpoints before and after the age cutoff of 65 years. In the younger cohort mortality, ICU access, and IMV consensually increased through age decades; in the elderly group, despite an even sharper mortality curve (in line with the result of the Youden index measure), admission to ICU and treatment with IMV progressively lessened, as well as the treatment with complex pharmacological regimens (Fig. 1a,b,c) [9, 10]. The more "conservative" treatment in the elderly patients, relative to the patients < 65 years, can recognize several reasons. One reason for this age-related differential approach could be the higher rate of comorbidities (e.g., chronic kidney disease or liver disease), which were often simultaneously coexisting in the same patient and made the more aggressive drugs therapies contraindicated or deemed to be poorly tolerated. In the second place, starting compromised general conditions and short life-expectancy might have advised the treating physicians to avoid therapeutic obstinacy. In the third place, it should be taken into consideration that the enrollment period entirely covered the peak of the pandemic, when high pressure was exerted on the healthcare systems. The hypothesis that at the climax of the pandemic, resources, such as mechanical ventilators, could have not coped with all the needs seems possible. In the context of the COVID 19 epidemic, national societies of Anesthesiology have indicated indeed that, in the presence of serious shortage of healthcare resources, intensive treatments must be guaranteed to the patients with greater chances of therapeutic success, evaluated on the basis of the type and severity of the disease, the presence of comorbidities, the impairment of other organs and systems, and their reversibility [11–14]. Despite all the enrolling nations have been making all the possible efforts to increase health service resources (especially ICU beds) and to optimize their exploitation by patients' transfer toward centers with greater availability, the application of the rationing criterion during the peak of this maxi-emergency cannot be ruled out. Our data, nevertheless, exclude the use of age as the sole criterion for the allocation of possibly limited invasive treatments, as proved by the stepwise increase in the number of coexisting comorbidities through incremental age categories (Appendix Table 4).

The influence of a differential therapeutic approach (both pharmacological and instrumental) through different age classes on patients' outcome is impossible to infer in the absence of randomized controlled data, which are not expected. Appendix Table 9 shows indeed the influence of age on mortality rate among patients undergone IMV: case fatality ranged from 44.2% in patients younger than 55 years to the 82.5% in patients aged 75 or older, proving in this category very poor survival expectance. Moreover, further caution in the interpretation of these data is advised as it is licit to hypothesize a selection bias in the choice of the elderly patients to be treated more invasively, so that the latter mortality rate could be underestimated. On the basis of this evidence, what is conversely noteworthy is the potential unreliability of surrogate endpoints such as access to ICU or IMV as prognosis indicators when the cutoff for elderly definition is passed. Indeed, in ours as in several other recent reports these parameters have been used single handedly or within composite endpoints as indicators of negative clinical course [3, 6].

Besides age, in the younger population (< 65 years) independent predictors of in-hospital mortality among anamnestic factors and coexisting conditions were body mass index and history of cancer. The analysis of the population younger than 65 years, stratified by the presence or absence of obesity, demonstrated that obesity was associated with a significant increase in all the predefined endpoints, both primary and secondary; in detail, as shown in Appendix Table 14, obese young patients faced a mortality rate almost double as compared to the non-obese counterpart (11.6% vs. 6.4%, respectively). This finding seems noteworthy since confirms some initial analogous evidences [15]. Moreover, despite not included among the most powerful predictors of mortality in our young cohort, recent evidences suggested a potential effect of gender on mortality [16, 17]. The study endpoints were thus investigated relative to the patients' gender, with the evidence of a better outcome in terms of mortality, access to ICU, and need for IMV for the female sex (Appendix Table 11). In the whole category of patients younger than 65 years the higher prevalence of risk factors and cardiac disease among male patients could explain this finding. Nevertheless, the same finding in the subpopulation of patients aged less than 45, in which baseline characteristics are very similar between genders, opened to different hypotheses such as possible hormonal protection, in line with other initial reports [18].

Our study has some limitations. First, the study design is observational, and thus, data would result in selection bias.

As a consequence, even though our dataset was large and the study provides a wide overview of the 'real-world' prognosis and management of patients hospitalized for COVID-19, the study should be considered as hypotheses generating. Second, some clinical characteristics and incident events in the participating centers could have not been diagnosed and/or been reported.

In conclusion, our study confirmed that age negatively impacts on both the primary and the secondary endpoints in patients younger than 65 years. In older patients, only case fatality rate keeps augmenting in a stepwise manner through increasing age categories, while therapeutic approaches become more conservative. Besides age, obesity, and gender seem to both play a role in the outcome of patients younger than 65 years.

Appendix

See Tables 4,5,6,7,8,9,10,11,12,13,14 and Figs. 3, 4

Table 4 Comorbidities among HOPE PROJECT population divided according to age categories

	Age (years old)							
	< 35 (*n* = 269)	35–44 (*n* = 506)	45–54 (*n* = 837)	55–64 (*n* = 1064)	65–74 (*n* = 1279)	75–84 (*n* = 1139)	> 85 (*n* = 652)	*P*
*Comorbidities**								
At least 1	31/269 (11.5%)	108/506 (21.3%)	309/837 (36.9%)	597/1064 (56.1%)	981/1139 (87.9%)	593/1139 (87.9%)	593/652 (91.0%)	< 0.001
At least 2	7/269 (2.6%)	24/506 (4.7%)	74/837 (8.8%)	231/1064 (21.7%)	545/1279 (42.6%)	624/1139 (54.8%)	425/652 (65.2%)	< 0.001
At least 3	1/269 (0.4%)	11/506 (2.2%)	19/837 (2.3%)	76/1064 (7.1%)	239/1279 (18.7%)	301/1139 (26.4%)	221/652 (33.9%)	< 0.001
At least 4	0/269 (0.0%)	1/506 (0.2%)	3/837 (0.4%)	27/1064 (2.5%)	93/1279 (7.3%)	94/1139 (8.3%)	75/652 (11.5%)	< 0.001
At least 5	0/269 (0.0%)	0/506 (0.0%)	1/837 (0.4%)	5/1064 (0.5%)	17/1279 (1.3%)	29/1139 (2.5%)	20/652 (3.1%)	< 0.001

*Hypertension, diabetes mellitus, coronary artery disease, heart failure, COPD, cerebrovascular events, severe renal failure, connective disease, liver disease, history of cancer, HIV infection

Values are expressed as n (%)

Table 5 Baseline characteristics of HOPE PROJECT population divided according to age categories

	Age (years-old)		
	< 65 (n = 2676)	≥ 65 (n = 3070)	*P*
Baseline characteristics			
Male	1589/2676 (59.4%)	1784/3070 (58.1%)	0.330
Age (years)	49.63 ± 10.44	77.42 ± 7.85	< 0.001
Body mass index (kg/m^2)	27.84 ± 6.88	28.20 ± 5.23	0.145
Comorbidities			
Hypertension	698/2667 (26.2%)	2121/3052 (69.5%)	< 0.001
Dyslipidemia	470/2659 (17.7%)	1462/3026 (48.3%)	< 0.001
Diabetes Mellitus	243/2676 (9.1%)	829/3070 (27.0%)	< 0.001
Obesity	440/2214 (19.2%)	586/2320 (25.3%)	< 0.001
Current smoking	190/2428 (7.8%)	112/2683 (4.2%)	< 0.001
Severe chronic kidney disease	58/2676 (2.2%)	324/3067 (10.6%)	< 0.001
Any lung disease	330/2676 (12.3%)	746/3070 (24.3%)	< 0.001
Asthma	167/2676 (6.2%)	135/30,370 (4.4%)	0.002
Chronic obstructive pulmonary disease	67/2676 (2.5%)	348/3070 (11.3%)	< 0.001
Interstitial	9/2676 (0.3%)	27/3070 (0.9%)	0.009
Restrictive	9/2676 (0.3%)	38/3070 (1.2%)	< 0.001
Other	78/2676 (2.9%)	197/3070 (6.4%)	< 0.001
Cardiac disease	209/2654 (7.9%)	1104/3039 (36.3%)	< 0.001
Coronary artery disease	76/2676 (2.8%)	323/3070 (10.5%)	< 0.001
Cardiomyopathy/heart failure	23/2676 (0.9%)	96/3070 (3.1%)	< 0.001
Valvular heart disease	20/2676 (0.7%)	110/3070 (11.0%)	< 0.001
Arrhythmia	55/2676 (2.1%)	343/3070 (11.2%)	< 0.001
Combined	24/2676 (0.9%)	214/3070 (7.0%)	< 0.001
Atrial Fibrillation	22/2676 (0.8%)	177/3070 (5.8%)	< 0.001
Cerebrovascular disease	60/2624 (2.3%)	386/2986 (12.9%)	< 0.001
Connective disease	62/2630 (2.4%)	98/2983 (3.3%)	0.037
Liver disease	75/2627 (2.9%)	134/2970 (4.5%)	< 0.001
Cancer disease	149/2634 (5.7%)	608/2998 (20.3%)	< 0.001
Immunosuppression	161/2523 (6.4%)	247/2782 (8.9%)	0.001
Prior tuberculosis	4/2676 (0.1%)	11/3070 (0.4%)	0.194
HIV infection	15/2676 (0.6%)	6/3070 (0.2%)	0.22
Partially dependent	58/2676 (2.2%)	470/3070 (15.3%)	< 0.001
Totally dependent	37/2676 (1.4%)	189/3070 (6.3%)	< 0.001
At least 1 comorbidity*	1045/2676 (39.1%)	2575/3070 (83.9%)	< 0.001
At least 2 comorbidities*	336/2676 (12.6%)	1594/3070 (51.9%)	< 0.001
At least 3 comorbidities*	107/2676 (4.0%)	761/3070 (24.8%)	< 0.001
Home therapy			
Home oxygen therapy	35/2651 (1.3%)	140/3030 (4.6%)	< 0.001
Aspirin	165/2643 (6.2%)	690/2996 (23.0%)	< 0.001
Other antiplatelet drug	29/2627 (1.1%)	177/2938 (6.0%)	< 0.001
Oral anticoagulation	58(2631 (2.2%)	528/2991 (17.7%)	< 0.001
ACE/ARBs	524/2649 (19.8%)	1518/3020 (50.3%)	< 0.001
Beta blockers	199/2639 (7.5%)	721/3002 (24.0%)	< 0.001
Beta agonist inhalation therapy	158/2643 (6.0%)	407/2983 (13.6%)	< 0.001
Glucocorticoids inhalation therapy	136/2650 (5.1%)	369/2994 (12.3%)	< 0.001
D vitamin supplement	114/2641 (4.3%)	478/2973 (16.1%)	< 0.001
Benzodiazepines	226/2644 (8.5%)	633/3006 (21.1%)	< 0.001
Antidepressant	187/2640 (7.1%)	547/2997 (18.3%)	< 0.001

Values are expressed as mean ± standard deviation or n (%)

*Hypertension, diabetes mellitus, coronary artery disease, heart failure, COPD, cerebrovascular events, severe renal failure, connective disease, liver disease, history of cancer, HIV infection

Table 6 Admission parameters of HOPE PROJECT population divided according to age categories

	Age (years-old)		
	< 65 ($n = 2676$)	≥ 65 ($n = 3070$)	*P*
Symptoms and clinical parameters			
Asymptomatic	153/2641 (5.8%)	131/3015 (4.3%)	0.013
Dyspnea			
Mild	815/2676 (30.5%)	776/3070 (25.3%)	< 0.001
Moderate	477/2676 (17.8%)	655/3070 (21.3%)	0.001
Severe	182/2676 (6.8%)	340/3070 (11.1%)	< 0.001
Tachypnea (> 22 breaths per minute)	555/2590 (21.4%)	939/2910 (32.3%)	< 0.001
Peripheral oxygen saturation < 92%	604/2585 (23.4%)	1358/2972 (45.7%)	< 0.001
Fatigue	1148/2586 (44.4%)	1209/2927 (48.1%)	0.005
Hypo/anosmia	276/2480 (11.1%)	98/2812 (3.5%)	0.001
Dysgeusia	269/2475 (10.9%)	133/2811 (4.7%)	< 0.001
Sorethroat	419/2516 (16.7%)	243/2849 (8.5%)	< 0.001
Fever	2231/2649 (84.2%)	2279/3016 (75.6%)	< 0.001
Max temper (°C)	37.75 ± 1.03	37.53 ± 0.99	< 0.001
Cough	1945/2640 (73.7%)	1910/2997 (63.7%)	< 0.001
Vomiting	197/2561 (7.7%)	218/2923 (7.5%)	0.744
Diarrhea	545/2558 (21.2%)	532/2927 (18.2%)	0.005
Arthromyalgia	1002/2572 (39.0%)	776/2910 (26.7%)	< 0.001
Chest X-Ray abnormalities	2104/2676 (78.6%)	2449/3070 (79.8%)	0.285
Unilateral infiltrates	475/2676 (17.8%)	543/3070 (17.7%)	0.950
Bilateral infiltrates	1629/2676 (60.9%)	1906/3070 (62.1%)	0.347
Abnormal blood pressure (< 90 mmHg)	128/2449 (5.2%)	271/2729 (9.9%)	< 0.001
Glasgow Coma Scale	14.93 ± 0.69	14.60 ± 1.44	< 0.001
Laboratory parameters			
Elevated D-dimer	1246/2329 (53.5%)	1895/2542 (74.5%)	< 0.001
Elevated procalcitonin	324/1945 (16.7%)	558/2121 (26.3%)	< 0.001
Elevated C-Reactive Protein	2167/2583 (83.9%)	2774/2956 (93.8%)	< 0.001
Elevated troponin I	120/1412 (8.5%)	282/1371 (20.6%)	< 0.001
Elevated transaminases	1033/2444 (42.3%)	1077/2771 (38.9%)	0.013
Elevated ferritin	844/1474 (57.3%)	914/1488 (61.4%)	< 0.021
Elevated triglycerides	270/1263 (21.4%)	243/1265 (19.2%)	0.175
Elevated LDH	1541/2389 (64.5%)	2129/2696 (79.0%)	< 0.001
Creatinine (mg/dL)	0.99 ± 0.83	1.21 ± 0.91	< 0.001
Natrium (mmol/L)	137.80 ± 4.04	137.55 ± 5.47	0.057
Leukocytes (/mL)	6841.66 ± 3511.94	7398.29 ± 4176.24	< 0.001
Leukocytes < 4000/mL	408/2588 (15.8%)	415/2992 (13.9%)	< 0.001
Lymphocytes (/mL)	1476.55 ± 1866.44	1188.22 ± 1766.87	< 0.001
Lymphocytes < 1500/mL	1783/2549 (69.9%)	2451/2923 (83.9%)	< 0.001
Hemoglobin (g/dL)	13.92 ± 1.69	13.20 ± 1.95	< 0.001
Anemia (HB < 12 g/dL)	463/2577 (18.0%)	970/2969 (32.7%)	< 0.001
Platelet (/mL)	225,743.76 ± 99,017.14	202,750.30 ± 92,412.18	< 0.001
Platelet < 150,000/mL	52/2585 (20.2%)	892/2972 (30.0%)	< 0.001
Arterial blood gas analysis			
PH value	7.42 ± 0.08	7.44 ± 0.08	< 0.001
PaO2 (mmHg)	76.08 ± 25.23	64.13 ± 24.32	< 0.001
PaCO2 (mmHg)	34.47 ± 8.66	35.38 ± 9.29	0.016
Saturation O2 (%)	93.11 ± 9.85	89.06 ± 12.36	< 0.001

Values are expressed as mean ± standard deviation or n (%)

Table 7 In-hospital clinical course and medical management of the HOPE PROJECT young population divided according to age categories

	Age (years-old)		
	<65 (*n* = 2676)	≥ 65 (*n* = 3070)	*P*
ICU admission	255/2676 (9.5%)	266/3070 (8.7%)	0.255
Death	182/2676 (6.8%)	985/3070 (32.1%)	< 0.001
Complications during hospital/ICU stay			
Respiratory insufficiency	971/2635 (36.9%)	1856/3016 (61.5%)	< 0.001
Heart failure	60/2632 (2.3%)	300/2981 (10.1%)	< 0.001
Acute kidney injury	180/2620 (6.9%)	729/3000 (24.3%)	< 0.001
Upper respiratory tract infection	333/2593 (12.8%)	277/2908 (13.0%)	0.893
Unilateral pneumonia	445/262 (16.9%)	481/2997 (16.0%)	0.366
Bilateral pneumonia	1801/262 (68.6%)	2245/2997 (74.9%)	< 0.0001
Sepsis	210/2612 (8.0%)	405/2962 (13.7%)	< 0.001
Systemic inflammatory response syndrome	384/2605 (14.7%)	693/2941 (23.6%)	< 0.001
Any relevant bleeding	38/2586 (1.5%)	106/2926 (3.6%)	< 0.001
Hemoptysis	42/2591 (1.6%)	52/2958 (1.8%)	0.693
Embolic event	39/2596 (1.5%)	75/2946 (2.5%)	0.006
Oxygen therapy during hospital stay			
Oxygen therapy	1575/2615 (60.2%)	2417/2995(80.7%)	< 0.001
High flow nasal cannula	445/2593 (17.2%)	659/2970 (22.2%)	< 0.001
Non-invasive mechanical ventilation	306/2615 (11.7%)	457/2986 (15.3%)	< 0.001
Invasive mechanical ventilation	218/2599 (8.4%)	190/2957 (6.4%)	0.005
Prone position	249/2586 (9.6%)	314/2950 (10.6%)	0.212
Circulatory support or ECMO	122/2594 (4.7%)	127/2949 (4.3%)	0.477
Medical therapy during hospital stay			
Glucocorticoids	564/2595 (21.7%)	952/2969 (32.1%)	< 0.001
Chloroquine	2259/2628 (86.0%)	2522/3012 (83.7%)	0.020
Antiviral drugs	1753/2627 (66.7%)	1647/2999 (54.9%)	< 0.001
Antibiotics	1758/2488 (70.7%)	2312/2877 (80.4%)	< 0.001
Chloroquine + antiviral drugs	1588/2612 (60.8%)	1549/2983 (51.9%)	< 0.001
Interferon or similar	382/2597 (14.7%)	353/2942 (12.0%)	0.003
Tolicizumab or similar	229/2602 (8.8%)	238/2953 (8.1%)	0.320
ACE/ARBs	331/2570 (12.9%)	754/2858 (26.4%)	< 0.001
Anticoagulation	1118/1673 (66.8%)	1452/1721 (84.4%)	< 0.001
Discharge data			
Discharge ACE/ARBs	354/2675 (12.9%)	650/3070 (21.2%)	< 0.001
Discharge antiplatelet therapy	110/2394 (4.6%)	293/2290 (12.8%)	< 0.001
Discharge anticoagulation	416/2624 (15.9%)	675/2986 (22.6%)	< 0.001

ECMO ExtraCorporeal Membrane Oxygenation, *ICU* Intensity Care Unit

Values are expressed as n (%)

Table 8 In-hospital clinical course and medical management of the HOPE PROJECT population divided according to age categories

	Age (years old)							
	< 35 (*n* = 269)	35–44 (*n* = 506)	45–54 (*n* = 837)	55–64 (*n* = 1064)	65–74 (*n* = 1279)	75–84 (*n* = 1139)	> 85 (*n* = 652)	P
Death	6/269 (2.2%)	14/506 (2.8%)	55/837 (6.6%)	107/1064 (10.1%)	229/1279 (17.9%)	418/1139 (36.7%)	338/652 (51.8%)	< 0.001
ICU admission	9/269 (3.3%)	22/506 (4.3%)	81/837 (9.7%)	143/1064 (13.4%)	169/1279 (13.2%)	85/1139 (7.5%)	12/652 (1.8%)	< 0.001
Invasive mechanical ventilation	9/263 (3.4%)	19/491 (3.9%)	67/816 (8.2%)	123/1029 (12.0%)	133/1245 (10.7%)	50/1094 (4.6%)	7/618 (1.1%)	< 0.001
Chloroquine and antiviral drugs	120/263 (45.6%)	301/495 (60.8%)	513/821 (62.5%)	654/1033 (63.3%)	793/1241 (63.9%)	577/1109 (52.0%)	179/633 (28.3%)	< 0.001

ICU Intensity Care Unit

Values are expressed as n (%)

Table 9 Case fatality in patients assisted with invasive mechanical ventilation and ICU admitted patients divided according to age categories

		AGE (years old)				
Invasive mechanical ventilation	OVERALL (*n* = 408)	< 55 (*n* = 95)	55–64 (*n* = 123)	65–74 (*n* = 133)	≥ 75 (*n* = 57)	*P*
In-hospital death	231/408 (56.6%)	42/95 (44.2%)	63/123 (51.2%)	79/133 (59.4%)	47/57 (82.5%)	< 0.001
ICU admission	OVERALL (*n* = 521)	< 55 (*n* = 112)	55–64 (*n* = 143)	65–74 (*n* = 169)	≥ 75 (*n* = 97)	*P*
In-hospital death	243/521 (46.6%)	31/112 (27.7%)	61/143 (42.7%)	86/169 (50.9%)	65/97 (67.0%)	< 0.001

ICU Intensity Care Unit

Values are expressed as n (%)

Table 10 Risk predictors of death in logistic regression analysis in HOPE PROJECT whole, young and old populations

	Overall population		
	Odds Ratio	95% CI	*P* value
Age (10 years increase)	1.07 (1.97)	1.06–1.08	< 0.001
Severe chronic kidney disease	2.47	1.78–3.42	< 0.001
Partially dependent	1.84	1.37–2.44	< 0.001
Oral anticoagulation therapy	1.66	1.26–2.18	< 0.001
Dysgeusia	0.18	0.09–0.33	< 0.001
Tachypnea	4.14	3.37–5.09	< 0.001
Chest X-ray bilateral abnormalities	1.79	1.44–2.24	< 0.001
Procalcitonin elevated	2.66	2.14–3.30	< 0.001
White blood cell	1.00	1.00–1.00	< 0.001
	< 65 years old		
	Odds Ratio	(95%CI)	*P* value
Age (10 years increase)	1.06 (1.79)	1.03–1.09	< 0.001
Body mass index (10 units increase)	1.03 (1.34)	1.00–1.06	0.027
Cancer	2.99	1.35–6.64	0.007
Severe dyspnea	2.74	1.48–5.08	0.001
Tachypnea	6.08	3.51–10.53	< 0.001
Chest X-ray bilateral abnormalities	2.91	1.48–5.74	0.002
Creatinine > 1.5 mg/dL	4.49	2.33–8.65	< 0.001
Lymphocyte < 1500/mL	2.94	1.45–5.95	0.003
	≥ 65 years old		
	Odds Ratio	(95%CI)	*P* value
Age (10 years increase)	1.07 (1.97)	1.05–1.09	< 0.001
Severe chronic kidney disease	2.68	1.74–4.11	< 0.001
Liver disease	2.21	1.15–4.24	0.017
Oral anticoagulant	1.74	1.22–2.47	0.002
Dysgeusia	0.19	0.08–0.45	< 0.001
Severe dyspnea	3.28	2.13–5.04	< 0.001
Maximum temperature at admission	1.22	1.06–1.42	0.006
Oxygen saturation < 92%	3.12	2.35–4.14	< 0.001
Procalcitonin elevated	2.37	1.71–3.28	< 0.001
Platelet count	1.0	1.0	< 0.001
Glasgow Coma Scale	0.75	0.66–0.85	< 0.001

Table 11 Baseline characteristics of HOPE PROJECT population divided according to age categories and gender

	< 65 years (n = 2676)		
	Female (n = 1087)	Male (n = 1589)	P
In-hospital death	44/1087 (4.0%)	138/1589 (8.7%)	< 0.001
ICU admission	71/1087 (6.5%)	184/1589 (11.6%)	< 0.001
Invasive mechanical ventilation	54/1057 (5.1%)	164/1542 (10.6%)	< 0.001
	< 45 years (n = 775)		
	Female (n = 354)	Male (n = 421)	P
In-hospital death	3/354 (0.8%)	17/421 (4.0%)	0.005
ICU admission	9/354 (2.5%)	22/421 (5.2%)	0.058
Invasive mechanical ventilation	6/346 (1.7%)	22/408 (5.4%)	0.008

ICU = Intensity Care Unit

Values are expressed as n (%)

Table 12 Baseline characteristics of young HOPE PROJECT population divided according to gender

	< 65 years (n = 2676)		
	Female (n = 1087)	Male (n = 1589)	P
Baseline characteristics			
Body mass index (kg/m^2)	27.40 ± 6.34	28.14 ± 7.21	0.071
Comorbidities			
Hypertension	252/1094 (23.2%)	446/1583 (28.2%)	0.004
Dyslipidemia	155/1077 (14.1%)	315/19.9%)	0.000
Diabetes Mellitus	76/1087 (7.0%)	167/1589 (10.5%)	0.002
Obesity	169/895 (18.9%)	271/1319 (20.5%)	0.336
Former smokers	72/1087 (6.6%)	204/1589 (12.8%)	< 0.001
Current smoking	64/996 (6.4%)	126/1432 (8.8%)	0.032
Severe chronic kidney disease	18/1087 (1.7%)	40/1589 (2.5%)	0.133
Any lung disease	124/1087 (11.4%)	206/1589 (13.0%)	0.229
Asthma	76/1087 (7.0%)	91/1589 (5.7%)	0.184
Chronic obstructive pulmonary disease	21/1087 (1.9%)	46/1589 (2.9%)	0.117
Cardiac disease	67/1075 (6.2%)	142/1579 (9.0%)	0.010
Coronary artery disease	21/1087 (1.9%)	55/1589 (3.5%)	0.019
Cardiomyopathy/heart failure	6/1087 (0.6%)	17/1589 (1.1%)	0.154
Cerebrovascular disease	21/1066 (2.0%)	39/1558 (2.5%)	0.369
Connective disease	39/1071 (3.6%)	23/1559 (1.5%)	< 0.001
Liver disease	24/1067 (2.2%)	51/1560 (3.3%)	0.123
Cancer disease	72/1067 (6.7%)	77/1567 (4.9%)	0.045
Immunosuppression	73/1023 (7.1%)	88/1500 (5.9%)	0.200
HIV infection	2/1087 (0.2%)	13/1589 (0.8%)	0.035
Partially dependent	19/1087 (1.7%)	39/1589 (2.5%)	0.218
Totally dependent	15/1087 (1.4%)	22/1589 (1.4%)	0.992
Home therapy			
Aspirin	54/1075 (5.0%)	111/1568 (7.1%)	0.032
Oral anticoagulation	22/1071 (2.1%)	36/1560 (2.3%)	0.663
ACE/ARBs	179/1082 (16.5%)	345/1567 (22.0%)	0.001
Beta blockers	68/1076 (6.3%)	131/1563 (8.4%)	0.049
Beta agonist inhalation therapy	69/1074 (6.4%)	89/1569 (5.7%)	0.423
Glucocorticoids inhalation therapy	59/1080 (5.5%)	77/1570 (4.9%)	0.522

Values are expressed as mean ± standard deviation or n (%)

Table 13 Baseline characteristics of HOPE PROJECT population < 45 years divided according to gender

	< 45 years ($n = 772$)		
	Female ($n = 353$)	Male ($n = 419$)	*P*
Baseline characteristics			
Body mass index (kg/m^2)	26.17 ± 6.97	27.94 ± 10.51	0.070
Comorbidities			
Hypertension	25/353 (7.1%)	42/491 (10.0%)	0.148
Dyslipidemia	11/350 (3.1%)	30/418 (7.2%)	0.013
Diabetes Mellitus	11/31 (3.1%)	20/421 (4.8%)	0.245
Obesity	36/298 (12.1%)	51/347(14.7%)	0.332
Former smokers	10/354 (2.8%)	22/421 (5.2%)	0.094
Current smoking	14/325 (4.3%)	24/374 (6.4%)	0.220
Severe chronic kidney disease	0 (0.0%)	8 (1.9%)	0.009
Any lung disease	32/354 (9.0%)	42/421 (10.0%)	0.658
Asthma	25/354 (7.1%)	30/421 (7.1%)	0.973
Chronic obstructive pulmonary disease	0/354 (0.0%)	2/421 (0.5%)	0.194
Cardiac disease	10/353 (2.80%)	13/420 (3.10%)	0.831
Coronary artery disease	3/354 (0.8%)	3/421 (0.7%)	1.000
Cardiomyopathy/heart failure	2/354 (0.6%)	3/421 (0.7%)	1.000
Cerebrovascular disease	5/351 (1.4%)	7/413 (1.7%)	0.765
Connective disease	10/352 (2.8%)	6/410 (1.5%)	0.186
Liver disease	6/351 (1.7%)	9/410 (2.2%)	0.631
Cancer disease	9/351 (2.6%)	6/416 (1.4%)	0.264
Immunosuppression	19/338 (5.6%)	17&396 (4.3%)	0.406
HIV infection	0/354 (0.0%)	6/421 (1.40%)	0.034
Partially dependent	3/354 (0.8%)	5/421 (1.2%)	0.733
Totally dependent	2/354 (0.6%)	7/421 (1.7%)	0.192
Home therapy			
Aspirin	3/140 (2.1%)	6/129 (4.7%)	0.310
Oral anticoagulation	5/350 (1.40%)	2/413 (0.50%)	0.257
ACE/ARBs	17/352 (4.8%)	25/415 (6.0%)	0.469
Beta blockers	7/350 (2.0%)	8/415 (1.9%)	0.943
Beta agonist inhalation therapy	15/352 (4.3%)	23/418 (5.5%)	0.428
Glucocorticoids inhalation therapy	6/352 (1.7%)	13/418 (3.1%)	0.210

Values are expressed as mean ± standard deviation or n (%)

Table 14 Baseline characteristics of HOPE PROJECT population divided according to age categories and obesity

	< 65 years ($n = 2214$)		
	Non obesity ($n = 1774$)	Obesity ($n = 440$)	*P*
In-hospital death	113/1774 (6.4%)	51/440 (11.6%)	< 0.001
ICU admission	162/1774 (9.1%)	67/440 (15.2%)	< 0.001
Invasive mechanical ventilation	135/1730 (7.8%)	58/431 (13.5%)	< 0.001

ICU Intensity Care Unit

Values are expressed as n (%)

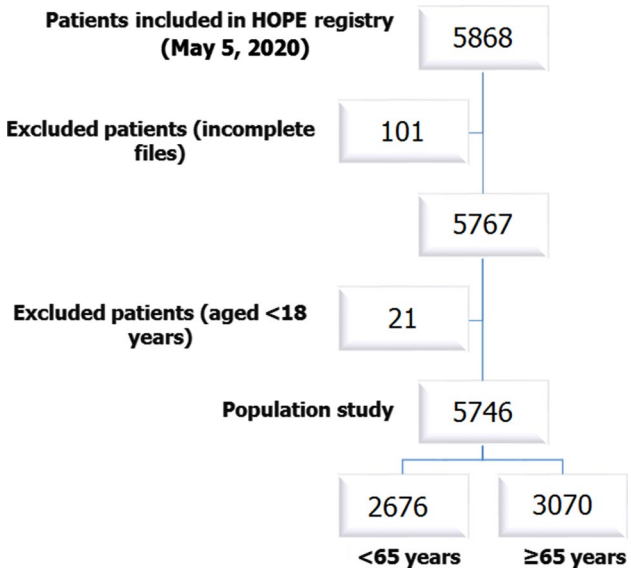

Fig. 3 Flow diagram of patients included in the study

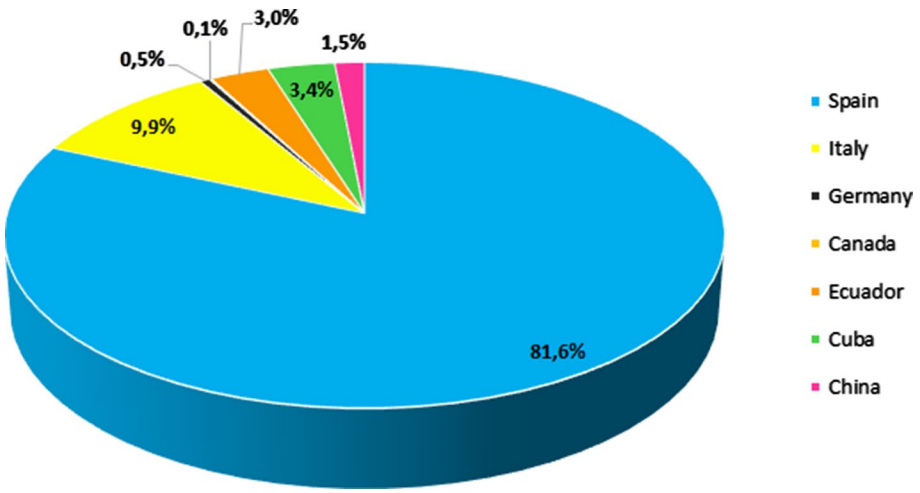

Fig. 4 Enrollment rates by country of citizenship of patients included in the HOPE PROJECT registry

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Author contributions MP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; MP ideated the study, analyzed and interpreted the data, and wrote the manuscript; GBZ contributed substantially to the study design, analyzed and interpreted the data, IJNG contributed to the study design, critically revised the manuscript and approved the final draft of the manuscript; the other authors contributed to the collection of the data, read, reviewed and finally approved the manuscript.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Research Committee from the Hospital Clínico San Carlos (Madrid, Spain) (20/241-E) and the Spanish Agency for Medicines and Health Products classification (EPA-0D).

Consent to participate Written informed consent was waived because of the anonymized nature of the registry and the health alarm situation generated by the pandemia. There were no exclusion criteria, except for patients' explicit refusal to participate.

Consent for publication All authors have participated in the work, have reviewed the manuscript and agree with the content of the article. All authors have approved this submission. No portion of the text has been copied from other material in the literature. The manuscript has not been published and is not being considered for publication elsewhere in whole or in part, in any language.

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