Mortality comparison between the first and second/third waves among 3,795 critical COVID-19 patients with pneumonia admitted to the ICU: a multicentre retrospective cohort study

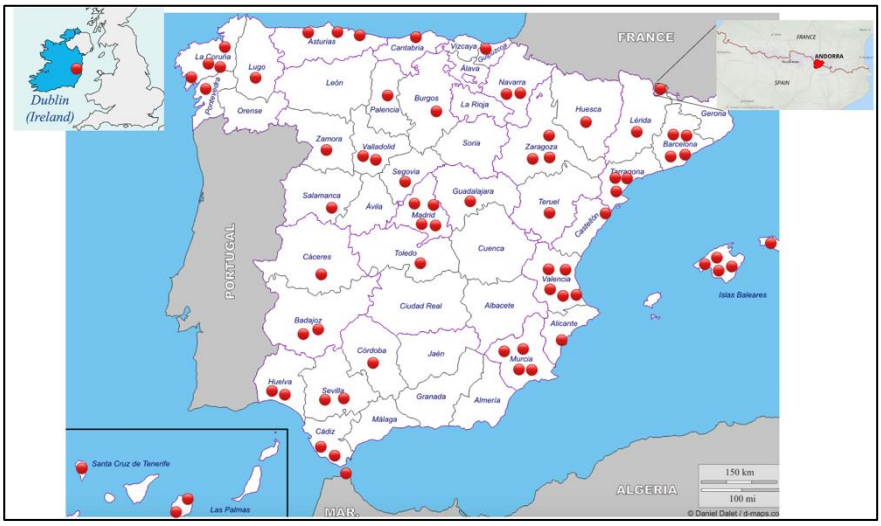
Supplemental material

MATERIAL AND METHODS

This observational, retrospective cohort study was conducted in 73 Intensive Care Units (71 across Spain, one from Andorra and one from Ireland). Geographical areas corresponding to the participating centres are depicted below.

Participants included per each centre

Joan XXIII Hospital, Tarragona - 182	Arnau de Vilanova Hospital, Lleida - 73	Virgen Macarena, Sevilla - 31
Quiron Hospital, Huelva - 4	Infanta Elena Hospital, Huelva - 6	Virgen de la Arrixaca, Murcia - 25
Montecelo Hospital, Pontevedra - 26	Santa Lucia Hospital, Cartagena - 236	CHUIMI, Gran Canaria - 26
Comarcal Inca Hospital, Mallorca - 18	Mateu Orfila, Menorca, 34	Quiron PP Mallorca - 40
Moreales Meseguer, Murcia - 33	San Agustin Hospital, Asturias - 17	Reina Sofía Hospital, Cordoba - 37
Clinic Hospital, Valencia - 48	San Pedro Alcantara Hospital, Caceres - 25	Guadalajara University Hospital - 185
La Palma General Hospital, Las Palmas - 7	Virgen Concha Hospital, Zamora - 36	Virgen Valme Hospital, Sevilla - 93
Ifema Hospital, Madrid - 22	Son Llatzer Hospital, Mallorca - 152	Nuestra Señora Gracias H, Zaragoza - 35
CHU Hospital, S. Compostela - 69	CHUAC Hospital A Coruña - 40	La Ribera Hospital, Alzira - 46
Lucus Augusti Hospital, Lugo - 14	Garcia Orcoyen Hospital, Navarra - 25	Verge Cinta, Tortosa - 37
Arnau Vilanova, Valencia - 22	Clinic Hospital, Salamanca - 97	N. Señora Meritxell Hospital, Andorra - 78
Dr Peset Hospital, Valencia - 27	Vall d 'Hebron Hospital, Barcelona - 193	Vinaros Hospital - 10
Central Hospital, Asturias - 136	Cabueñes Hospital, Gijón - 18	Reina Sofía Hospital, Murcial - 15
Miquel Servet Hospital, Zaragoza - 23	Reina Sofía Hospital, Tudela - 26	Sant Joan Hospital, Reus - 33
General Hospital, Segovia - 64	La Fe Hospital, Valencia - 163	Del Mar Hospital, Barcelona - 25
Mutua de Terrassa - 51	Del Mar Menor Hospital, Murcia - 8	Dr Negrin Hospital, Palmas Gran Canaria - 17
REA A Coruña - 17	Virgen lirios Hospital, Alcoy - 5	San Carlos Hospital, Madrid - 147
Puerto Real Hospital, Cadiz - 11	Princ. Asturias Hospital, Madrid - 71	Parc Tauli Hospital, Sabadell - 20
Lozano Blesa Hospital, Zaragoza - 85	Marqués Valdecillas Hospital, Cantabria - 9	Ceuta Hospital - 1
Rafael Mendez Hospital, Lorca - 112	San Jorge Hospital, Huesca - 22	Obispo Polanco Hospital, Teruel – 21
Son Espases Hospital, Mallorca - 19	La Moncloa Hospital, Madrid - 30	N. Señora Prado, Toledo – 45
University Hospital, Jerez - 88	Assistencial Complex, Palencia - 33	Donostia Hospital, San Sebastian – 58
Mérida Hospital, Badajoz - 20	University Hospital, Burgos - 98	University Hospital, Ferrol – 26
St. James Hospital, Dublin - 52	Rio Hortega Hospital, Valladolid - 82	Can Ruti Hospital, Badalona – 79
University Hospital, Badajoz - 16		



Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity	No subgroups

SROBE Statement checklist

	Item No.	Recommendation	Section or Page in the manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, last paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods data collection and supplement
Bias	9	Describe any efforts to address potential sources of bias	Methods (statistical analysis) and limitation section in the discussion
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Not addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Methods
		(*e*) Describe any sensitivity analyses	No sensitivity analysis
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results and flowchart
		(b) Give reasons for non-participation at each stage	Results and exclusion criteria
		(c) Consider use of a flow diagram	Supplement
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate number of participants with missing data for each variable of interest	Supplement
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Methods
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

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

Study definitions

The confirmation of a case of SARS-CoV-2 infection was accomplished by positive reverse transcription-polymerase chain reaction, either at hospital or ICU admission, from specimens collected with nasopharyngeal and oropharyngeal swabs according to the WHO recommendations.[1] Lower respiratory tract specimens were collected when patients were under MV and high clinical suspicion was present, if previous tests were negatives.

Shock at ICU admission was defined as the requirement of vasopressor therapy to maintain appropriate main blood pressure, despite adequate fluid resuscitation targeted by dynamic haemodynamic parameters and/or echocardiography, according to Surviving Sepsis Campaign guidelines.[2]

Myocardial dysfunction was diagnosed in patients with shock and evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, needing the initiation of dobutamine.[3]

Acute kidney injury was defined according International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.[4]

Community-acquired respiratory co-infection (CARC) or bacterial co-infection was considered in patients with confirmation of SARS-CoV-2 infection showing recurrence of fever, increase in cough and production of purulent sputum plus positive bacterial/fungal respiratory or blood cultures within the first two days of ICU admission.[5]

Hematological diseases included acute leukemia, myelodysplastic syndrome and lymphomas.

Chronic Heart Diseases was defined according to the New York Heart Association (NYHA) Functional Classification III and IV.

References

1 World Health Organization. Clinical management of COVID-19. Interim guidance 27 May 2020. 2020.

2 Rhodes A, Evans LE, Alhazzani W, *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; **45**: 486–552.

3 Alhazzani W, Møller MH, Arabi YM, *et al.* Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med Care Med* 2020; **46**: 854–87.

4 Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204–12.

5 Martín-Loeches I, Sanchez-Corral A, Diaz E, *et al.* Community-acquired respiratory coinfection in critically III patients with pandemic 2009 influenza A(H1N1) virus. *Chest* 2011; **139**: 555–62.

TABLES

Table 1. Full list of the variables collected during the study

General characteristics
Hospital type (According to beds number: <200, 200-500 and > 500)
Gender (male/female)
Age
Body mass index
Date of symptom onset
Date of Hospital admission
Date of ICU admission
Date of ICU discharge
Data of Hospital discharge
GAP ICU (time between hospital to ICU admission, days)
GAP diagnosis (time to symptom onset to diagnosis confirmation, days)
GAP antiviral treatment (time from onset of symptoms to first dose of antiviral, days)
Illness severity
APACHE (Acute Physiology and Chronic Health Evaluation) II score
Sequential Organ Failure Assessment (SOFA) score
ARDS (acute respiratory distress syndrome) Mild, moderate or severe.
Number of pulmonary infiltrates on chest X-ray
Comorbidities
Asthma
Chronic Pulmonary Obstructive Disease
Arterial Hypertension
Dyslipidaemia
Obesity (BMI > 30 Kg/m^2)
Diabetes mellitus
Ischemic heart disease
Chronic Heart disease (New York Heart Association (NYHA) Functional Classification III and IV)
Chronic kidney disease (Estimated Glomerular Filtration Rate (eGFR) < 60 $ml/min/1{\cdot}73m^2$)
Haematological disease (acute leukaemia, myelodysplastic syndrome and lymphomas)
Pregnancy
HIV/AIDS (Human immunodeficiency virus infection and acquired immunodeficiency syndrome)
Neuromuscular disease
Immunological disease
Hypothyroidism
Other underlying conditions
Laboratory findings
D-Lactate dehydrogenase (LDH)
White blood cell (WBC) count
Creatinine
C-Reactive Protein (CRP)
Procalcitonin (PCT)
Lactate
D-dimer

Ferritin
Arterial blood gas test
Treatment at ICU admission
Corticosteroids (type of corticosteroid, indication and duration)
Antibiotics
Lopinavir/ritonavir
Hydroxychloroquine
Tocilizumab
Interferon β
Remdesivir
Prior anti-hypertensive treatment (ACE: Angiotensin Converting Enzyme Inhibitors. ARB: Angiotensin receptor blockers)
Oxygenation and respiratory support within the first 24 hours of ICU admission
Oxygen mask
High Flow nasal cannula
Non-invasive ventilation
Invasive mechanical ventilation
Ventilatory parameters: Fraction of inspired oxygen (FiO2) Partial pressure of oxygen (PaO2) PaO2/FiO2 ratio Positive end-expiratory pressure (PEEP) Tidal volume (Vt) Plateau pressure
Complications at ICU admission
Shock
Acute kidney injury (According to RIFLE criteria)
Myocardial dysfunction
Community-acquired co-infection (CARC)
Outcomes
ICU mortality
Length of ICU stay
Duration of mechanical ventilation
Ventilator-associated pneumonia (VAP)

Table 2. Comparison of medical and respiratory management of the COVID-19 patients with pneumonia according to the country of inclusion.
Ireland contributed with the inclusion of patients only in the first wave. Consequently, the comparisons have been made with those patients from Spain and Andorra corresponding to the first wave.

	Spain n=2389	**Andorra n= 38**	**Ireland n=52**	**P value**
Demographics				
Age (years)	64 (55-71)	63 (57-73)	63 (55-68)	0·23
Gender (male)	1686 (70·6%)	22 (57·9%)	36 (69·2%)	0·39
Treatments at ICU admission				
Corticosteroids	1405 (58·8%)	23 (60.5%)	16 (30·8%)	<0·001
Tocilizumab	708 (29·6%)	6 (15·8%)	2 (3·8%)	<0·001
Antibiotics	2221 (93%)	35 (92·1%)	52 (100%)	0·14
Lopinavir/ritonavir	1986 (83·1%)	27 (71·1%)	52 (100%)	<0·001
Remdesivir	42 (1·8%)	0 (0%)	0 (0%)	0·44
Hydroxychloroquine	2237 (93·6%)	35 (92·1%)	40 (76·9%)	<0·001
Respiratory management				
Conventional oxygen therapy	375 (15·7%)	18 (47·8%)	25 (48·1%)	<0·001
High flow nasal cannula	443 (18·5%)	5 (13·2%)	2 (3·8%)	0·01
Non-invasive mechanical ventilation	128 (5·4%)	1 (2·6%)	1 (1·9%)	0·38
Invasive mechanical ventilation at 24 hours of admission	1645 (68·9%)	29 (76·3%)	27 (51·9%)	0·007
Need of invasive mechanical ventilation	1893 (79·2%)	30 (78·9%)	37 (71·2%)	0·36
Duration of invasive mechanical ventilation	15 (8-26)	15 (9-20)	14 (7-27)	0·95
Prone position	1478 (61·9%)	29 (76·3%)	41 (78·8%)	0·01
Nitric oxide	88 (3·7%)	1 (2·6%)	3 (5·8%)	0·69
Extracorporeal membrane oxygenation therapy	50 (2·1%)	0 (0%)	1 (1·9%)	0·66

Table 3. Comparison of medical and respiratory management of the COVID-19 patients with pneumonia according to the country of inclusion during the first and second/third waves.
No patients from Ireland were included during the second/third waves.

	Spain n=3665	**Andorra n= 78**	**P value**
Demographics			
Age (years)	64 (54-71)	64 (56-71)	0·35
Gender (male)	2596 (70·8%)	54 (69·2%)	0·76
Treatments at ICU admission			
Corticosteroids	2628 (71·7%)	62 (79·5%)	0·13
Tocilizumab	790 (21·6%)	6 (7·7%)	0·003
Antibiotics	3003 (81·9%)	59 (75·6%)	0·15
Lopinavir/ritonavir	2017 (55%)	27 (34·6%)	<0·001
Remdesivir	250 (6·8%)	4 (5·1%)	0·55
Hydroxychloroquine	2242 (61·2%)	35 (44·9%)	0·004
Respiratory management			
Conventional oxygen therapy	526 (14·4%)	25 (32·1%)	<0·001
High flow nasal cannula	1062 (29%)	27 (34·6%)	0·34
Non-invasive mechanical ventilation	215 (5·9%)	3 (3·8%)	0·42
Invasive mechanical ventilation at 24 hours of admission	2407 (63·7%)	52 (66·7%)	0·91
Need of invasive mechanical ventilation	2798 (76·3%)	55 (70·5%)	0·22
Duration of invasive mechanical ventilation	15 (9-27)	15 (8-24)	0·79
Prone position	2178 (59·4%)	50 (64·1%)	0·42
Nitric oxide	123 (3·4%)	1 (1·3%)	0·30
Extracorporeal membrane oxygenation therapy	80 (2·2%)	0 (0%)	0·18

Table 4. Comparison between survivors and non-survivors among critically ill COVID-19 patients admitted to the ICU during the whole study period.

Data are expressed as number (%) or medians (IQR). Obesity is defined as body mass index >30 kg/m^2. Diagnosis gap is the time between the symptom onset and confirmed diagnosis. Hospital gap is the time between the symptom onset and hospital admission. ICU gap is the time between hospital admission and ICU admission. * At ICU admission. BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; CARC, Community-Acquired Respiratory Coinfection; HFNC, High-flow nasal cannula.

	Whole cohort (n = 3795)		
	Survivors (n = 2629)	**Non-survivors (n = 1166)**	**P value**
Demographic characteristics			
Age (years)	61 (52–69)	69 (62–75)	<0·001
Gender			0·004

Male Female	1824 (69·4%) 805 (30·6%)	862 (73·9%) 304 (26·1%)	
BMI (kg/m^2)	28 (25–32)	28 (26–31)	0·18
Comorbidities			
Hypertension	1075 (40·9%)	676 (58%)	<0·001
Obesity	935 (35·6%)	421 (36·1%)	0·73
Diabetes mellitus	531 (20·2%)	337 (28·9%)	<0·001
Dyslipidaemia	212 (8·1%)	93 (8%)	0·93
COPD	137 (5·2%)	132 (11·3%)	<0·001
Asthma	170 (6·5%)	75 (6·4%)	0·95
Ischemic heart disease	116 (4·4%)	132 (11·3%)	<0·001
Immunosuppression	122 (4·6%)	91 (7·8%)	<0·001
Chronic kidney disease	105 (4%)	98 (8·4%)	<0·001
Course of illness (days)			
Diagnosis gap	6 (3–8)	5 (3–8)	0·04
Hospital gap	7 (3–8)	6 (4–8)	<0·001
ICU gap	2 (0–2)	2 (0–4)	0·70
Severity of illness			
APACHE II score	12 (9–16)	16 (13–20)	<0·001
SOFA score	4 (3–6)	6 (4–8)	<0·001
Pulmonary infiltrates (quadrants)*	3 (2–4)	3 (2–4)	<0·001
ARDS* Mild Moderate Severe	 353/2063 (17·1%) 1083/2063 (52·5%) 627/2063 (30·4%)	 123/924 (13·3%) 387/924 (41·9%) 414/924 (44·8%)	 0·01 <0·001 <0·001
Laboratory data*			
D-dimer (ng/ml)	890 (526–1988)	1471 (774–3995)	<0·001
C-reactive Protein (mg/dl)	13 (7–22)	15 (8–25)	<0·001
Organ failure and complications			
Invasive mechanical ventilation	1078 (41%)	710 (60·9%)	<0·001
Shock*	803 (30·5%)	552 (47·3%)	<0·001
Acute kidney injury*	450 (17·1%)	571 (49%)	<0·001
Myocardial dysfunction*	139 (5·3%)	219 (18·8%)	<0·001
CARC*	208 (7·9%)	131 (11·2%)	<0·001
Ventilator-associated pneumonia	451 (17·2%)	324 (27·8%)	<0·001
HFNC failure	462 (17·6%)	213 (18·3%)	<0·001
Treatments*			
Corticosteroids	1862 (70·8%)	844 (72·4%)	0·31
Tocilizumab	571 (21·7%)	227 (19·5%)	0·16
Remdesivir	193 (7·3%)	61 (5·2%)	0·02
COVID-19 Wave First Second/third	 1692 (64·4%) 937 (35·6%)	 787 (67·5%) 379 (32·5%)	0·06

Table 5. Causative microorganisms of the ventilator-associated pneumonia (VAP) according COVID-19 waves among critically ill patients.

All episodes of infection needed microbiological confirmation, with the isolation in the tracheal aspirate of at least 10^5 colony-forming units (CFU) per mL, or in bronchoalveolar lavage of at least 10^4 CFU per mL.

	VAP First wave N=447	**VAP Second/third waves N=328**	**P value**
Pseudomonas aeruginosa	136 (30·4%)	84 (25·6%)	0·14
Methicillin-susceptible *Staphylococcus aureus*	51 (11·4%)	51 (15·6%)	0·09
Klebsiella pneumoniae	37 (8·3%)	43 (13·1%)	0·03
Serratia marcescens	31 (6·9%)	13 (4%)	0·07
Methicillin-resistant *Staphylococcus aureus*	29 (6·5%)	9 (2·7%)	0·02

Escherichia coli	23 (5·1%)	15 (4·6%)	0·71
Stenotrophomonas maltophilia	19 (4·3%)	16 (4·9%)	0·68
Aspergillus spp.	17 (3·8%)	33 (10%)	<0·001
Enterobacter cloacae	16 (3·6%)	14 (4·3%)	0·62
Other microorganisms	88 (19·7%)	50 (15·2%)	0·11

Table 6. Univariable analysis for in-hospital mortality among critically ill COVID-19 patients admitted to the ICU during the whole study period.
Data are expressed as number (%) or medians (IQR). Obesity is defined as body mass index >30 kg/m^2. Diagnosis gap is the time between the symptom onset and confirmed diagnosis. Hospital gap is the time between the symptom onset and hospital admission. ICU gap is the time between hospital admission and ICU admission. *At ICU admission. BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; CARC, Community-Acquired Respiratory Coinfection; HFNC, High-flow nasal cannula.

Table 7. Binary logistic regression analysis for risk factors of in-hospital mortality.

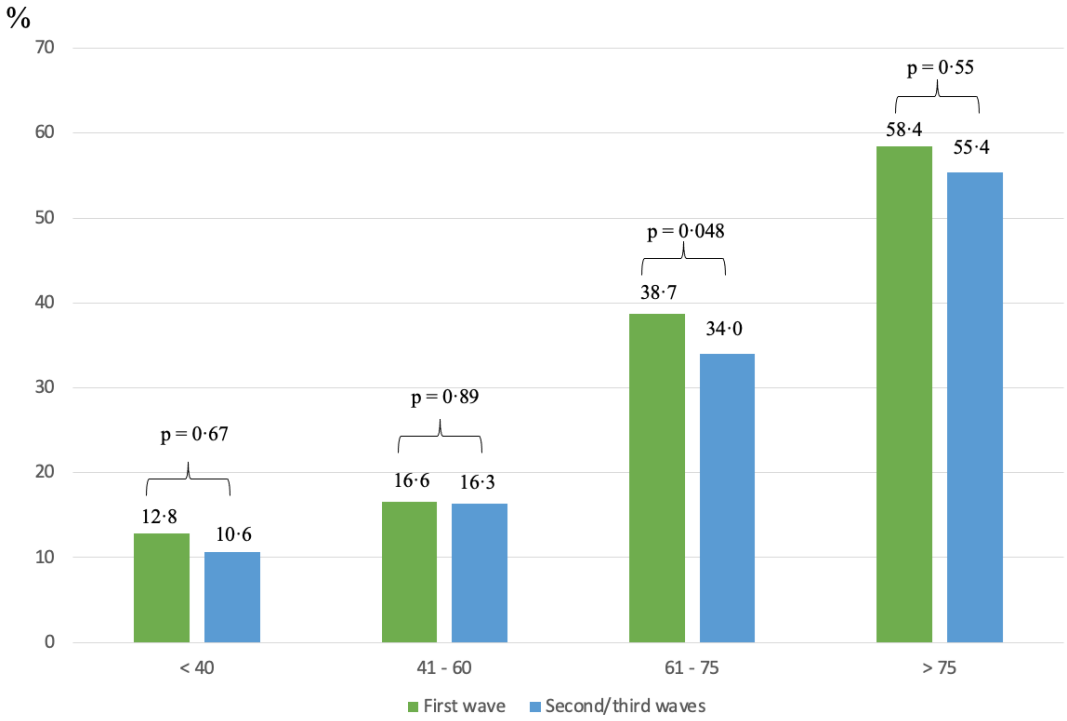
	Whole cohort (n = 3795)		
	Survivors (n = 2561)	**Non-survivors (n = 1234)**	**P value**
Demographic characteristics			
Age (years)	61 (52–69)	69 (62–75)	<0·001
Gender (male)	1776 (69·3%)	910 (73·7%)	0·005
BMI (kg/m^2)	28 (26–32)	28 (26–32)	0·47
Comorbidities			
Hypertension	1039 (40·6%)	712 (57·7%)	<0·001
Obesity	916 (35·8%)	440 (35·7%)	0·78
Diabetes mellitus	508 (19·8%)	360 (29·2%)	<0·001
Dyslipidaemia	205 (8%)	100 (8·1%)	0·91
COPD	132 (5·2%)	137 (11·1%)	<0·001
Asthma	164 (6·4%)	81 (6·6%)	0·80
Ischemic heart disease	108 (4·2%)	140 (11·3%)	<0·001
Immunosuppression	116 (4·5%)	97 (7·9%)	<0·001
Chronic kidney disease	97 (3·8%)	106 (8·6%)	<0·001
Course of illness (days)			
Diagnosis gap	6 (3–8)	5 (3–8)	0·06
Hospital gap	7 (5–9)	6 (4–8)	<0·001
ICU gap	2 (0–4)	2 (0–4)	0·82
Severity of illness			
APACHE II score	12 (9–16)	16 (13–20)	<0·001
SOFA score	4 (3–6)	6 (4–8)	<0·001
Pulmonary infiltrates (quadrants)*	3 (2–4)	3 (2–4)	<0·001
ARDS*			
Mild	348 (13·6%)	128 (10·4%)	0·005
Moderate	1059 (41·4%)	411 (33·3%)	<0·001
Severe	609 (23·8%)	432 (35%)	<0·001
Laboratory data*			
D-dimer (ng/ml)	881 (520–1903)	1476 (770–4014)	<0·001
C-reactive Protein (mg/dl)	13 (7–22)	16 (8–25)	<0·001
Organ failure and complications			
Invasive mechanical ventilation	1047 (40·9%)	741 (60%)	<0·001
Shock*	772 (30·1%)	583 (47·2%)	<0·001
Acute kidney injury*	433 (16·9%)	588 (47·6%)	<0·001
Myocardial dysfunction*	128 (5%)	230 (18·6%)	<0·001
CARC*	201 (7·8%)	138 (11·2%)	<0·001
Ventilator-associated pneumonia	435 (17%)	340 (27·6%)	<0·001
HFNC failure	452 (17·6%)	223 (18·1%)	0·75
Treatments*			
Corticosteroids	1818 (71%)	888 (72%)	0·51
Tocilizumab	558 (21·8%)	240 ()19·4%	0·11
Remdesivir	190 (7·4%)	64 (5·2%)	0·01
COVID-19 Wave			0·04
First	1645 (64·2%)	834 (67·6%)	
Second/third	916 (35·8%)	400 (32·4%)	

	Odds ratio	95% confidence interval	P value
Age	1·06	1·05–1·07	<0·001
Male gender	1·13	0·91–1·42	0·25
Hypertension	1·10	0·89–1·36	0·33
Diabetes mellitus	1·01	0·80–1·26	0·93
Chronic Obstructive Pulmonary Disease	1·25	0·88–1·77	0·20
Chronic ischemic heart disease	1·61	1·11–2·32	0·01
Immunosuppression	1·93	1·31–2·83	0·001
Chronic kidney disease	1·28	0·86–1·93	0·22
Hospital gap	0·96	0·94–0·98	0·004
APACHE II score	1·01	0·99–1·03	0·17
SOFA score	1·06	1·02–1·11	0·007
Number of Quadrants with pulmonary infiltrates	1·11	1·00–1·23	0·05
Mild ARDS	0·60	0·40–0·88	0·009
Moderate ARDS	0·71	0·51–0·97	0·03
Severe ARDS	1·24	0·98–1·71	0·19
D-dimer	1·00	1·00–1·00	0·05
C-reactive protein	1·01	1·01–1·01	0·01
Invasive mechanical ventilation	1·72	1·38–2·14	<0·001
Shock at ICU admission	1·06	0·84–1·33	0·63
Acute kidney injury	2·80	2·25–3·45	<0·001
Myocardial dysfunction	2·83	2·10–3·82	<0·001
Community-acquired respiratory co-infection	1·40	1·03–1·91	0·03
Ventilator-associated pneumonia	1·49	1·19–1·85	<0·001
Remdesivir	1·17	0·78–1·77	0·43
COVID-19 Wave	0·83	0·67–1·04	0·10

FIGURES

Figure 1. Proportions of missing data of the baseline explanatory variables included in the study.

Figure 2. Stratified age-related crude ICU mortality comparing the first with the second/third waves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> 75
First wave
Second/third waves