

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

BMJ Open

Impact of ceiling of care on mortality across waves: an inverse probability weighting analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-091249
Article Type:	Original research
Date Submitted by the Author:	16-Jul-2024
Complete List of Authors:	Pallarès, Natàlia; IGTP; Germans Trias i Pujol Research Institute and Hospital (IGTP) Videla, Sebastià; Germans Trias i Pujol University Hospital, Department of Clinical Pharmacology; University of Barcelona, Department of Pathology and Experimental Therapeutics Carratala, Jordi; Hospital Universitari de Bellvitge, Infectious Diseases; Bellvitge Biomedical Research Institute Tebé, Cristian; Germans Trias i Pujol Research Institute and Hospital (IGTP)
Keywords:	COVID-19, INFECTIOUS DISEASES, PALLIATIVE CARE, Epidemiology < INFECTIOUS DISEASES





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

2		
3	1	Impact of ceiling of care on mortality across waves: an inverse probability weighting analysis
4 5	2	Pallarès N ^{1,2} MSc, Videla S ^{3,4} MD PhD, Carratalà J ^{5,6,7,8} MD PhD, Tebé C ¹ MPH PhD, on behalf of
6 7	3	the MetroSud study group and the Divine study group
8	4	1) Biostatistics Support and Research Unit, Germans Trias i Pujol Research Institute and
9	5	Hospital (IGTP), Badalona, Barcelona, Spain
10		
11	6	2) Department of Basic Clinical Practice, School of Medicine and Health Sciences, University of
12 13	7	Barcelona, Spain
14	8	3) Clinical Research Support Area, Department of Clinical Pharmacology, Germans Trias i Pujol
15	9	University Hospital, Badalona, Spain
16		
17	10	4) Department of Pathology and Experimental Therapeutics, School of Medicine and Health
18 19	11	Sciences, University of Barcelona, Spain
20	12	5) Department of Infectious Diseases, Bellvitge University Hospital, Barcelona, Spain
21 22	13	6) Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
23	14	7) Centro de Investigación en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de
24	15	Salud Carlos III, Madrid, Spain.
25 26		
20	16	8) Department of Clinical Sciences, School of Medicine and Health Sciences, University of
28	17	Barcelona, Spain
29	18	
30		
31	19	MetroSud Study group: Gabriela Abelenda-Alonso, Alexander Rombauts, Isabel Oriol,
32	20	Antonella F. Simonetti, Alejandro Rodríguez-Molinero, Elisenda Izquierdo, Vicens Díaz-Brito,
33 34	21	Carlota Gudiol, Judit Aranda-Lobo, Marta Arroyo, Carlos Pérez-López, Montserrat Sanmartí,
35	22	Encarna Moreno, Maria C Alvarez, Ana Faura, Martha González, Paula Cruz, Mireia Colom,
36	23	Andrea Perez, Laura Serrano.
37	24	DIVINE Study mount Minsie Deselé Erik Coho, Jouri Contás Deniel Fornándoz, Leiro
38	25	DIVINE Study group: Mireia Besalú, Erik Cobo, Jordi Cortés, Daniel Fernández, Leire
39	26	Garmendia, Guadalupe Gómez, Pilar Hereu, Klaus Langohr, Gemma Molist, Núria Pérez-
40 41	27 28	Álvarez, Xavier Piulachs.
41	28 29	
43	30	Corresponding author
44	31	Corresponding author
45	32	Natàlia Pallarès, MSc
46	33	Biostatistics Support and Research Unit
47	34	Germans Trias i Pujol Research Institute and Hospital (IGTP)
48 49	35	Campus Can Ruti. Carretera de Can Ruti, Camí de les Escoles s/n. 08916 Badalona, Barcelona,
50	36	Spain
51	37	
52		
53	38	
54		
55 56	39	
56 57	40	
58	40	
59	41	
60		

	1 2		
	2 3 4	42	ABSTRACT
ļ	5	43	Objectives
	7	44	The aim of this study was to compare in-hospital mortality across waves in patients
	8 9	45	without and with a ceiling of care at hospital admission.
	10	46	
	11	46	Study design
	12 13	47	Prospective cohort study.
	14 15	48	Methods
	16 17	49	Adult patients hospitalised for COVID-19 in five centres in Catalonia between March
	18	50	2020 and August 2021 with information available on ceiling of care were included.
	19	51	Three models were constructed to compare in-hospital mortality by wave: a raw
	20 21	52	logistic regression model, a fully clinical adjusted logistic regression model and an
ź	22	53	inverse probability weighting logistic regression model.
	23 24	54	Results
	25		
	26	55	A total of 3982 patients without ceiling of care and 1831 patients with ceiling of care
	27	56	were included. The adjusted odds ratio (OR) of in-hospital mortality in the second
	28 29	57	wave were 0.57 (95%Cl 0.40 to 0.80), in the third 0.56 (95%Cl 0.37 to 0.84) and in the
	30	58	fourth 0.34 (95%CI 0.21 to 0.56) compared with the first wave in subjects without
	31	59	ceiling of care. The adjusted odds ratio were significantly lower in the fourth (0.38
-	32	60	95%CI 0.25 to 0.58) wave compared to the first wave in subjects with ceiling of care.
	33 34	61	Conclusions
	35		
	36	62	In patients without ceiling of care, mortality decreased over time suggesting better
	37	63	disease knowledge and management. In ceiling of care, only fourth-wave patients
	38	64	were less likely to die than first-wave patients. In a future infectious disease pandemic,
	39 40	65	it will be a challenge to improve the management of patients with ceiling of care.
	41	66	
	42	67	
4	43	68	Keywords
	44	69	Keywords
	45 46		
	40 47	70	COVID-19, Infectious diseases, Palliative care, Epidemiology
	48	71	
	49	72	Strengths and limitations of this study
	50	12	Strengths and initiations of this study
	51	73	• This is multicentric study with a large number of subjects included from four
	52 53	74	different waves of the COVID-19 pandemic.
	55 54	75	 Several methods were used to compare in-hospital mortality between waves to
	55		
	56	76	increase the robustness of the estimated effects.
	57	77	 Despite the inverse probability weighting analysis, there may be unobserved
	58	78	characteristics that lead to residual confounding.
	59 60		
6	60		

The national vaccination campaign started for the elderly subjects before the
fourth wave so it could not be used in the adjustment analysis.

to beet terien only

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2	
3 4	81
4 5 6	82
0 7	83
8	84
9	85
10 11	86
12	87
13	88
14	89
15 16	90
17	91
18	92
19 20	93
20 21	94 95
22	96
23	97
24 25	98
25 26	99
27	100
28	101
29 30	102
30 31	103
32	104
33	105
34 35	106
36	107
37	108
38	109
39 40	110
41	111
42	112
43 44	113
44 45	114
46	115
47	116
48 49	117
	118
51	119
52	110
53 54	120
55	121
56	122
57 58	123
58 59	124
59	

60

81 INTRODUCTION

Despite the lack of definition in epidemiology, the term epidemic wave implies a 82 natural pattern of peaks and troughs in the incidence of cases or hospitalisations due 83 to an outbreak [1]. Epidemics often occur in local or global waves, each one with 84 85 variations in severity or in transmission dynamics. For example, the 1918-1920 86 influenza pandemic was a global pandemic caused by the H1N1 virus. It is known to 87 have occurred in three waves. The first wave (spring 1918) was relatively mild and 88 resembled previous flu epidemics, the second wave (autumn 1918) was severe and 89 much more deadly than the first. The third wave (1919) was less severe than the second but more deadly than the first [2]. In 1968, the Hong Kong flu was caused by 90 91 the influenza A subtype H3N2 virus [3]. There were two waves in China (summer 1968 92 and June-December 1970) and, because the virus was highly contagious, it spread rapidly around the world reaching the United States and Europe by the end of 93 94 December 1968. In most places, the second wave caused more deaths than the first 95 [4].

96 Following a similar patron, the COVID-19 pandemic began in Wuhan, China, in 97 December 2019, and spread rapidly across Europe, with the first outbreak in Italy in 98 99 February 2020. During the course of the pandemic, countries and regions experienced 100 several waves with distinct peaks in cases. In Spain, 7 waves of the pandemic have 101 been recorded between March 2020 and September 2023, with almost 14 million 102 confirmed cases and more than 120.000 deaths [5]. Throughout this period, 103 knowledge of the disease has progressively increased with the sequencing of the virus 104 [6], clinical trials to assess treatments efficacy [7,8], the identification of different strains of the virus [9] and the development of vaccines [10]. All these factors, together 105 106 with the natural immunity protection against COVID-19 [11], lead to a reduction in the 107 need for hospitalisation, in-hospital mortality and complications.

109 In general, in a non-pandemic setting, decisions about the ceiling of care are common 110 practice when dealing with patients with a critical prognosis and have implications for 111 the use of life-sustaining measures such as intubation, mechanical ventilation, and 112 cardiopulmonary resuscitation. However, in the peaks of the COVID-19 pandemic, decisions about the maximum level of care that each patient should receive, besides of 113 114 the critical prognosis of the patient, were made in a scenery of emergency with excess 115 demand for critical care and limited availability of clinical resources. Previously 116 published data [12,13] suggest that COVID-19 hospitalised patients who had a ceiling 117 of care were mainly older, had more comorbidities and higher incidence of in-hospital 118 death. However, little is known about the impact of ceiling of care on mortality in 119 hospitalised patients with COVID-19 across pandemic waves.

Our hypothesis is that in-hospital mortality should decrease over time as a result of
increasing knowledge, natural immunity, the effect of new treatments and the
introduction of vaccines. However, the role of the ceiling effect in this process has not
been defined. The aim of this study was to compare in-hospital mortality across

1 2		
3 4 5	125 126	COVID-19 waves between patients with and without a ceiling of care at hospital admission.
6 7	127	
8 9		
10 11		
12 13 14		
15 16		
17 18		
19 20		
21 22 23		
24 25		
26 27		
28 29 30		
31 32		
33 34		
35 36		
37 38 39		
40 41		
42 43		
44 45 46		
47 48		
49 50		
51 52 53		
54 55		
56 57		
58 59		
60		

2		
3 4	128	METHODS
5 6	129	Data source
7	130	The MetroSud study is an observational multicenter study conducted in five centers
8	131	located in the southern metropolitan area of Barcelona (Catalonia, Spain), to
9 10	132	characterise all patients with COVID-19 admitted to these hospitals during four waves
10	133	of the pandemic from March 2020 to August 2021. Analised data of the first wave of
12	134	COVID-19 pandemic embraced from March to April 2020, second wave from October
13	135	to November 2020, third wave from January to February 2021 and fourth wave from
14 15	136	July to August 2021. MetroSud cohort has been previously described [12].
16	137	
17	138	An electronic case report form in REDCap [14] was designed in March 2020 to collect
18	139	study data. Demographic data, comorbidities and other relevant findings on medical
19 20	140	history, previous medications, clinical symptoms, vital signs, laboratory results and
20	141	respiratory exploration were collected at baseline.
22	142	
23	143	The presence or absence of ceiling of care was decided at the emergency room by the
24 25	144	attending physicians according to their criteria, taking into account the patient's
25	145	prognosis and the resources available (mainly intensive care unit (ICU) beds) at each
27	146	participating hospital. Patients without a ceiling of care would have access to an ICU or
28	147	could receive invasive mechanical ventilation (IMV). Otherwise, patients assigned to
29	148	ceiling of care would have limited access to the ICU and, if they required any
30 31	149	respiratory support, it would be non-rebreather mask, high-flow nasal cannula or
32	150	NIMV. In terms of outcomes, the incidence of in-hospital mortality was defined as
33	151	death by any cause during hospitalisation.
34	152	
35 36	153	The study was approved by the Bellvitge Hospital Research Ethics Committee with
37	154	medicines (CREm) in accordance with Spanish legislation and was performed in
38	155	accordance with the Helsinki Declaration of 1964. The need for patient informed
39	156	consent was waived by the ethics committee. Bellvitge's CREm decision was the basis
40 41	157	for the approval of the remaining hospital centers.
42	158	
43	159	Statistical methods
44 45		
43 46	160	To describe cohort characteristics, categorical variables were presented as the number
47	161	of cases and percentage, while continuous variables were expressed as the mean and
48	162	standard deviation (SD) or median and interquartile range (IQR). All analyses were
49 50	163	presented by wave and stratified by ceiling of care.
50 51	164	Once the variables to be used to match patients were identified, multiple imputation
52	165	with chained equations (MICE) [15] was used to create five datasets with complete
53	166	data. Missing data were assumed to be at random. Predictive mean matching was used
54 55	167	to impute continuous variables and binomial logistic regression was used to impute
56	167	binary variables. Information on age, sex and baseline comorbidities was used to
57		
58	169	impute missing values for obesity, body mass index (BMI), race, pneumonia severity
59 60	170	Index (PSI), FiO ₂ , oxygen support, D-dimer, C-reactive protein, leukocytes,

haemoglobin and lymphocytes. Final estimates were adjusted for variability between the five imputed datasets according to the Rubin rules [16] to obtain the final model. With the complete database, three models were constructed to study the association between in-hospital mortality and wave: 1) a crude logistic regression model using wave as a covariate, 2) a fully adjusted logistic regression model and 3) an inverse probability weighting (IPW) logistic regression model. After discussion with clinicians, the variables included in the fully adjusted logistic regression model were baseline variables that define the patient's status at hospital admission: age, sex, race, BMI, obesity, long-term facility, comorbidities (diabetes mellitus, COPD, heart failure, hypertension, renal insufficiency, dyslipidemia, coronary heart disease, haematological neoplasm, solid neoplasm, organ transplantation, immunosuppressive treatment, chronic complex patient (PCC) and patients with advanced chronic disease (MACA), baseline laboratory values (dimer, C-reactive protein, leukocytes, haemoglobin, lymphocytes), pneumonia severity index (PSI), FiO2 and oxygen support. IPW [17] was used to adjust for differences in the patient baseline profile between waves. Bayesian additive regression trees, entropy balancing, generalised boosted models and generalised linear models were tested as methods for weighting individuals. In the end, we chose the method with better covariate balance between waves after weighting, which was the bayesian additive regression trees method [18]. In each imputed dataset, weights were calculated with the wave as the outcome and the variables used for the full adjusted logistic model as covariates. To identify imbalances between waves after weighting, we estimated and described the standardised mean differences in baseline variables before and after weighting. We then fitted a logistic regression model for each imputation with in-hospital death as the outcome, using the stabilised weights and model-robust standard errors and adjusting for the variables that remained imbalanced between groups after weighting. We used the STROBE cohort checklist [19] when writing our report. All analyses were performed with a two-sided significance level of 0.05 using R software version 4.3.0 [20]. The main R packages used for data management and analysis were flowchart [21], REDCapDM [22], mice [15], WeightIt [23], cobalt [24] and survey [25].

203	RESULTS	5								
04	Flow ch									
5 6 7 8 9 0 1 2 3 4 5 6 7 8	were ind hospital with inc of care, hospital without the anal (Figure 1 Baseline Table 1	clude for l omp and but ceili ysis. L, Flo e cha desc	ed in the I less than lete data circumsta transferre ng of care All patier ow Chart) tracterist ribes the	VetroSuc 24 hours, on a poo ances at c ed to anc e and a to nts were cs by wa baseline	d. After ex , patients I of esser discharge other and otal of 18 followed ve character	xcluding p who dieo ntial varia) or patie treated i 31 patien up until i ristics of t	nd 2159 pa patients w d within th bles (age, nts who w n the latte ts with ce n-hospital	ho were a le first 24 sex, Char vere initial er, a total iling of ca death or	admitted t hours, pa lson score lly admitte of 3982 p re were ir hospital c	to atients e, ceili ed to atient nclude discha
			•			oles inclu	ded in the	matching	g process a	are
	describe	ed in	Supplem	entary la	able 1.					
	TABLE 1:	Pati	ent's mos	st relevan	t charact	eristics a	ccording to	o wave ar	nd ceiling	of ca
	TABLE 1:	Pati	ent's mos	t relevan	t charact	eristics a	ccording to	o wave ar	nd ceiling	of ca
	TABLE 1:	Pati	ent's mos No ceiling		t charact	eristics a	ccording to Ceiling of o		nd ceiling	of ca
	TABLE 1:	Pati		of care	t charact		Ceiling of o		nd ceiling of the wave 3,	
-	TABLE 1:	Pati	No ceiling Wave 1,	of care Wave 2,	Wave 3,	Wave 4,	Ceiling of o	care Wave 2,	Wave 3,	Wav
	TABLE 1:	Pati	No ceiling Wave 1,	of care Wave 2,	Wave 3,	Wave 4,	Ceiling of a	care Wave 2,	Wave 3,	Wav N =
		Pati	No ceiling Wave 1 , N = 2076 59 (49,	of care Wave 2 , N = 611 62 (53,	Wave 3 , N = 605 63 (53,	Wave 4 , N = 690 49 (37,	Ceiling of a Wave 1 , N = 1330 79 (72,	Wave 2 , N = 175 83 (78,	Wave 3 , N = 163 83 (78,	Wav N = 85 (8
	Age		No ceiling Wave 1 , N = 2076 59 (49,	of care Wave 2 , N = 611 62 (53,	Wave 3 , N = 605 63 (53,	Wave 4 , N = 690 49 (37,	Ceiling of a Wave 1 , N = 1330 79 (72,	Wave 2 , N = 175 83 (78, 88)	Wave 3 , N = 163 83 (78,	Wav N = 85 (8
	Age Sex		No ceiling Wave 1, N = 2076 59 (49, 69) 855	of care Wave 2, N = 611 62 (53, 71) 222	Wave 3 , N = 605 63 (53, 72) 248	Wave 4, N = 690 49 (37, 63) 242	Ceiling of a Wave 1 , N = 1330 79 (72, 85) 565	Wave 2 , N = 175 83 (78, 88)	Wave 3, N = 163 83 (78, 87)	Wav N = 85 (8 89)

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

		No ceiling	of care			Ceiling of c	are		
		Wave 1 , N = 2076	Wave 2 , N = 611	Wave 3 , N = 605	Wave 4 , N = 690	Wave 1 , N = 1330	Wave 2 , N = 175	Wave 3 , N = 163	Wave 4 , N = 163
	Other	341 (22%)	179 (31%)	73 (14%)	218 (35%)	32 (3.9%)	9 (5.2%)	4 (2.5%)	3 (1.9%)
	Unknown	529	38	68	66	503	2	5	6
	Charlson Index	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)	3.00 (1.00, 4.00)	1.00 (0.00, 3.00)	5.00 (4.00, 7.00)	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	6.00 (5.00, 7.00)
	PSI	62 (50, 79)	69 (56, 87)	66 (53, 84)	59 (46, 78)	97 (79, 123)	115 (95, 134)	103 (84, 124)	114 (96, 135)
_	Unknown	374	6	3	3	239	1	4	2

Median (IQR) for continuous variables; n (%) for categorical variables

PSI: Pneumonia severity index

Regarding age, patients with a ceiling of care were, in median, 20 years older than patients without a ceiling of care in all waves. There were no differences in the proportion of women. The most common race was Caucasian (in all waves, almost 90% of patients without ceiling of care and over 70% of patients with ceiling of care were Caucasian). Patients with a ceiling of care had a median Charlson Index more than 3 points higher than patients without a ceiling of care in all waves. PSI scores for patients with ceiling of care were more than 35 points higher in all waves (greater differences in wave 4) than PSI scores for patients without ceiling of care.

232 In-hospital mortality

The overall cumulative incidence of in-hospital mortality for patients with and withoutceiling of care in all waves is shown in Table 2.

TABLE 2: Cumulative incidence and 95% confidence interval for in-hospital mortality accordingto wave and ceiling of care.

BMJ Open

		Wave 1	Wave 2	Wave 3	Wave 4
	No ceiling of care	10.50% [9.23 to 11.92]	10.15% [7.92 to 12.89]	7.60% [5.68 to 10.09]	5.22% [3.73 to
	Ceiling of care	37.07% [34.48 to 39.74]	40.00% [32.76 to 47.69]	44.79% [37.06 to 52.76]	30.06% [23.27 37.81]
37					
38	About 1 in 1	0 patients without	ceiling of care died i	n hospital in the first a	nd second
39			•	10 patients die in hosp	
40				fourth wave (5% and 3	
41	respectively	for patients witho	ut and with a ceiling	of care).	
42					
43	Mortality in	patients without	ceiling of care		
44	Figure 2A sh	lows the balance o	f covariates before a	nd after IPW by means	of the
45	-			ithout a ceiling of care	
46				e, PSI was included in t	
47	mortality mo	odels.			-
		tios of the three m	nodels for mortality a	re shown in Figure 3A.	The results
48	The odds ra				
48 49				e same trend for all wa	
	with the thr	ee methods are co	nsistent and show th	e same trend for all wa vital than patients from	aves. Patients
49 50	with the thro from waves in the raw m	ee methods are co 2, 3 and 4 were lean nodels and in the n	nsistent and show th ss likely to die in hosp nodels adjusted for co	ital than patients from ovariates or adjusted w	aves. Patients n wave 1 both vith weights
49 50 51 52	with the thre from waves in the raw m (OR for all m	ee methods are co 2, 3 and 4 were lea nodels and in the m nodels and all wave	nsistent and show th ss likely to die in hosp nodels adjusted for co	ital than patients from	aves. Patients n wave 1 both vith weights
49 50 51 52	with the thre from waves in the raw m (OR for all m	ee methods are co 2, 3 and 4 were lean nodels and in the n	nsistent and show th ss likely to die in hosp nodels adjusted for co	ital than patients from ovariates or adjusted w	aves. Patients n wave 1 both vith weights
49 50 51 52 53	with the thre from waves in the raw m (OR for all m	ee methods are co 2, 3 and 4 were lea nodels and in the m nodels and all wave	nsistent and show th ss likely to die in hosp nodels adjusted for co	ital than patients from ovariates or adjusted w	aves. Patients n wave 1 both vith weights
49 50 51 52 53 54	with the thro from waves in the raw m (OR for all m decreases ad	ee methods are co 2, 3 and 4 were lea nodels and in the m nodels and all wave	nsistent and show th ss likely to die in hosp nodels adjusted for co es lower than 1). In ac	ital than patients from ovariates or adjusted w	aves. Patients n wave 1 both vith weights
49 50 51 52 53 54 55	with the thre from waves in the raw m (OR for all m decreases ac Mortality in	ee methods are co 2, 3 and 4 were lea nodels and in the n nodels and all wave cross waves.	insistent and show th ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care	ital than patients from ovariates or adjusted w	aves. Patients n wave 1 both vith weights e OR
49 50 51	with the thre from waves in the raw m (OR for all m decreases ad Mortality in Figure 2B sh	ee methods are co 2, 3 and 4 were lea nodels and in the n nodels and all wave cross waves. patients with ceil nows the balance o	insistent and show th ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before ar	vital than patients from ovariates or adjusted w dition, the value of th	aves. Patients n wave 1 both vith weights e OR of the SMD
49 50 51 52 53 54 55 56	with the thre from waves in the raw m (OR for all m decreases ad Mortality in Figure 2B sh in patients w difference b	ee methods are co 2, 3 and 4 were lea nodels and in the n nodels and all wave cross waves. patients with ceil nows the balance o vith a ceiling of car etween waves gre	insistent and show th ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before ar re assigned at admissi ater than 0.2. These v	vital than patients from ovariates or adjusted w dition, the value of th ad after IPW by means on. Age, PSI and race s variables were included	aves. Patients n wave 1 both vith weights e OR of the SMD showed a d as
49 50 51 52 53 54 55 56 57	with the thre from waves in the raw m (OR for all m decreases ad Mortality in Figure 2B sh in patients w difference b	ee methods are co 2, 3 and 4 were lea nodels and in the n nodels and all wave cross waves. patients with ceil nows the balance o vith a ceiling of car etween waves gre	insistent and show th ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before ar re assigned at admissi ater than 0.2. These v	vital than patients from ovariates or adjusted w Idition, the value of th ad after IPW by means on. Age, PSI and race s	aves. Patients n wave 1 both vith weights e OR of the SMD showed a d as
 49 50 51 52 53 54 55 56 57 58 59 	with the thre from waves in the raw m (OR for all m decreases ad Mortality in Figure 2B sh in patients w difference b adjustments	ee methods are co 2, 3 and 4 were lea nodels and in the m nodels and all wave cross waves. patients with ceil ows the balance o vith a ceiling of car etween waves gre s in the weighted m	insistent and show the ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before ar re assigned at admissi ater than 0.2. These w nortality model to acc	vital than patients from ovariates or adjusted w dition, the value of th ad after IPW by means on. Age, PSI and race s variables were included	aves. Patients n wave 1 both vith weights e OR of the SMD showed a d as nces.
 49 50 51 52 53 54 55 56 57 58 	with the three from waves in the raw m (OR for all m decreases ac Mortality in Figure 2B sh in patients w difference b adjustments The odds rat	ee methods are co 2, 3 and 4 were lea nodels and in the m nodels and all wave cross waves. patients with ceil ows the balance of vith a ceiling of car etween waves gre s in the weighted m tios of the three m	insistent and show the ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before ar re assigned at admissi ater than 0.2. These v nortality model to acc odels for mortality ar	ital than patients from ovariates or adjusted w dition, the value of th ad after IPW by means on. Age, PSI and race s variables were included count for these differen	aves. Patients n wave 1 both with weights e OR of the SMD showed a d as nces. No
 49 50 51 52 53 54 55 56 57 58 59 60 	with the three from waves in the raw m (OR for all m decreases ad Mortality in Figure 2B sh in patients w difference b adjustments The odds rate	ee methods are co 2, 3 and 4 were lean nodels and in the m nodels and all wave cross waves. patients with ceil nows the balance of vith a ceiling of car etween waves gre s in the weighted m tios of the three m were found betwe	insistent and show the ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before an re assigned at admissi ater than 0.2. These v nortality model to acc odels for mortality ar en 1 st and 2 nd wave p	vital than patients from ovariates or adjusted w dition, the value of th ad after IPW by means on. Age, PSI and race s variables were included count for these different re shown in Figure 3B.	of the SMD showed a d as nces. No and 3 rd wave
 49 50 51 52 53 54 55 56 57 58 59 60 61 	with the thro from waves in the raw m (OR for all m decreases ad Mortality in Figure 2B sh in patients w difference b adjustments The odds rat differences w patient (neit	ee methods are co 2, 3 and 4 were lea nodels and in the n nodels and all wave cross waves. patients with ceil nows the balance of vith a ceiling of car etween waves gre s in the weighted n tios of the three m were found betwe ther in the crude n	insistent and show the ss likely to die in hosp nodels adjusted for co es lower than 1). In ac ing of care f covariates before ar re assigned at admissi ater than 0.2. These w nortality model to acc odels for mortality ar en 1 st and 2 nd wave p or in the adjusted mo	ital than patients from ovariates or adjusted w dition, the value of th ad after IPW by means on. Age, PSI and race s variables were included count for these different e shown in Figure 3B. atients or between 1 st	of the SMD showed a d as nces. No and 3 rd wave

1 2 3 4 5 6 7 8 9 10	265 266		
10 11 12 13 14 15 16 17 18 19			
20 21 22 23 24 25 26 27 28 29			
30 31 32 33 34 35 36 37 38			
 39 40 41 42 43 44 45 46 47 48 			
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60			

2		
3	267	
4 5	268	DISCUSSION
6	269	Our multicentre cohort study compared in-hospital mortality across COVID-19 waves
7	270	between patients with and without a ceiling of care at hospital admission. We found
8 9	271	that among patients without ceiling of care, those admitted in the first wave had
10		
11	272	worse in-hospital mortality than patients hospitalised during the other waves.
12	273	Moreover, the adjusted models showed a significant decrease in mortality as the
13 14	274	waves progressed. Among patients with a ceiling of care, no differences in in-hospital
14	275	mortality were found between second and first wave patients, or between third and
16	276	first wave patients. Only in the fourth wave, patients were less likely to die than first
17	277	wave patients after adjustment for baseline risk. The magnitude of this effect on
18	278	mortality reduction observed in patients with ceiling of care in the 4 th wave was similar
19 20	279	to the effect observed among patients without ceiling of care in the same 4 th wave.
20		
22	280	It is worth noting that if the differences in mortality between waves were only due to
23	281	patient's risk profile, the mortality rates would be similar after adjustment for baseline
24 25	282	profile. However, this is not the case, as Figure 3A shows that in the adjusted and
25	283	weighted models, mortality among patients without ceiling of care decreases as waves
27	284	progress in time. The emergency situation experienced by the hospitals in the first
28	285	months of the pandemic, with a lack of organization prepared to face an emergency
29	286	such as COVID-19, partly explains the differences observed [26]. Besides, in the first
30 31	287	wave, hospital resources (such as ICU beds, number of non-invasive ventilators or high-
32	288	flow nasal oxygen therapy devices) and human resources were not sufficient to cope
33	289	with the high demand for medical care [27]. ICU capacity is known to be an important
34	290	indicator of hospital stress (health system resilience) which is associated with a
35	291	reduction in quality of care and poorer patient outcomes [28]. In addition, other
36 37	292	factors such as the increasing knowledge about the disease, facilitated by the rapid
38	293	publication of clinical trials analysing new treatments [8], or the impact of public
39	294	health surveillance measures, such as lockdowns [29] could explain this reduction in
40	295	mortality. The harvest effect could also explain this decrease in mortality, as deaths
41 42	296	that would have occurred anyway in subsequent waves may have been precipitated by
43	297	the high mortality in the first wave of COVID-19 [30]. Similarly, the aggressiveness of
44	298	SARS-CoV-2 varied between strains, and may also have played a role in the reduction
45	299	in mortality [31].
46 47	300	As expected, mortality was higher among patients with ceiling care. In this group of
47 48	301	patients, there are no differences in mortality in the first three waves, but there is a
49	302	decrease in mortality in wave 4 (Figure 3B). In Spain, this fourth wave mainly affected
50	303	young patients. Older patients, who were more likely to be assigned a ceiling of care,
51 52	304	were already vaccinated at that time [32]. A study in nursing homes in our
52 53	305	geographical area (Catalonia) [33] showed that vaccination was associated with a 95%
54	306	reduction in mortality among nursing home residents. Studies in Italy and Switzerland
55	307	also showed that the vaccine was about 95% effective against death in the general
56	308	population [30,34]. These results therefore suggest that there is no improvement in
57 58	309	medical management that affects in-hospital mortality until wave 4, which coincides
58 59	310	with the elderly vaccination campaign. The lack of a contrafactual scenario in which
60	311	people received intensive care makes it difficult to assess any potential benefit.

Further research on this topic and replication of these results in other cohorts would be needed. The high probability of a new epidemic caused by an infectious organism merits in-depth reflection by the medical and scientific community, in particular to reach a consensus on the definition of ceiling of care and to define a guideline for the management of patients who are candidates for a ceiling of care [35]. In the event of a future pandemic caused by an infectious organism, the challenge will be to improve mortality in patients with ceiling of care. To this end, the scientific community needs to develop an action plan that will enable a rapid response in terms of both human resources (by increasing the number of trained health workers), and facilities (for example, so that the ICUs can quickly increase the number of beds) [36]. Our study has some limitations that should be acknowledged. One limitation is residual confounding. Even after using all the characteristics available at admission to make the baseline status of patients comparable, there may be unobserved characteristics that make patients different between waves. For example, we knew whether a patient had pathology or not, but we could not take into account how advanced it was. A variable that collects information on patients' frailty at baseline might also be of interest for a better risk assessment. In addition, vaccines and treatments could not be used in the matching: vaccines because they did not exist in the first wave [10] and treatments because they changed drastically between waves due to increasing knowledge about the disease [7,8]. Another limitation of the study is that we assumed that the missing values in our data were at random and imputed them using standard techniques. To account for this, the analyses were repeated only with patients who had complete information on all variables, and the results were in the same line, confirming the robustness of the analysis. Moreover, we cannot guarantee that the same criteria were used to define the therapeutic ceiling of care in all hospitals. In fact, one of the challenges in clinical practice during the COVID-19 pandemic was to define the ceiling of care for infected patients. The strengths of our study are the large number of subjects included from different hospitals and from four different waves of the pandemic, and the availability of information on ceiling of care. In addition, the different methods used to compare in-hospital mortality by waves led to the same results, demonstrating the robustness of the analysis. In conclusion, in-hospital mortality was not homogeneous between waves in patients with and without ceiling of care. In patients without ceiling of care, mortality decreased over time suggesting better management and knowledge of the disease. In patients with ceiling of care, mortality remained constant, except in the last wave. In the event of a future pandemic caused by an infectious organism, it will be a challenge to harmonize and improve the clinical criteria and management of patients who might be assigned a ceiling of care.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1		
2 3 4	356	FIGURE LEGENDS
5	357	FIGURE 1: Flow-chart of the included patients without ceiling of care (left) and with
6 7	358	ceiling of care (right).
8 9	359	FIGURE 2: Maximum standardized mean differences (SMD) before (Unmatched) and
10	360	after weighting (Matched) across waves for patients without a ceiling of care (A) and
11	361	patients with ceiling of care (B). The standardized mean difference compares the
12 13	362	difference in means between all pairs of waves in standard deviation units.
14 15	363	FIGURE 3: OR for raw, adjusted and IPTW models for in-hospital mortality in patients
15 16	364	without a ceiling of care (A) and with ceiling of care (B).
17		
18	365	
19 20	366	
20		
22	367	DECLARATIONS
23	368	Ethics approval and consent to participate
24 25	369	The study was approved by the Bellvitge Hospital Research Ethics Committee with
26	370	medicines (CREm) in accordance with Spanish legislation and was performed in
27	371	accordance with the Helsinki Declaration of 1964. The need for patient informed
28	372	consent was waived by the ethics committee. Bellvitge's CREm decision was the basis
29	373	for the approval of the remaining hospital centres.
30 31	374	
32	375	
33	376	Competing interests
34	377	Cristian Tebé has received fees for speaker lectures and talks from Gedeon Richter,
35 36	378	outside the submitted work. The rest of authors declare that they have no competing
37	379	interests.
38	380	
39	381	
40 41	382	Data availability
42	383	The datasets generated during and/or analyzed during the current study are available
43	384	from the corresponding author on reasonable request.
44	385	
45 46	386	
40 47	387	Funding
48	388	This work was partially funded by Secretaria d'Universitats i Recerca del Departament
49	389	d'Empresa i Coneixement de la Generalitat de Catalunya (2020PANDE00148). The
50	390	funding was used to collect data from the 4 th wave.
51 52	391	This work has also been supported by grant 2021 SGR 01421 (GRBIO) administrated by
53	392	the Departament de Recerca i Universitats de la Generalitat de Catalunya (Spain).
54	393	
55	394	
56 57	395	Acknowledgements
57 58	396	We thank CERCA Programme/Generalitat de Catalunya for institutional support.
59	397	
60	398	

י ר	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
12	
1/	
14	
15	
10	
1/	
18	
19	
20	
21	
22	
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 37 38 37 38 37 38 37 38 39 30 31 31 31 31 31 31 31 31 31 31	
24	
25	
26	
27	
28	
29	
30	
30	
21	
⊃∠ ⊃⊃	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
47	
40 49	
49 50	
51	
52	
53	
54	
55	
56	
57	
58	
59	

399 Author's contributions

- 400 Conceptual design was performed by SV, JCa, CT, and NP.
- MetroSud cohort data was provided by SV and JCa. 401
- Statistical analysis was performed by CT and NP. 402
 - The first draft of the manuscript was written by NP and revised by JCa and CT. 403
 - All authors commented on previous versions of the manuscript. 404
- 405 All authors read and approved the final version of the manuscript. 406

1

408 409

407

410

tor occurrent only

1 2			
3	411	REFE	RENCES
4 5	412		
6			
7	413	-	Zhang SX, Arroyo Marioli F, Gao R, Wang S. A Second Wave? What Do People Mean By
8 9	414		COVID Waves? – A Working Definition of Epidemic Waves [Internet]. Rochester, NY; 2021
10	415	l	[cited 2024 Jan 8]. Available from: https://papers.ssrn.com/abstract=4456241
11	416	2. l	Unwin RJ. The 1918 Influenza Pandemic: Back to the Future? Kidney Blood Press Res.
12 13	417	2	2021;46(5):639–46.
14	418	3. \	Viboud C, Grais RF, Lafont BAP, Miller MA, Simonsen L, Multinational Influenza Seasonal
15	419		Mortality Study Group. Multinational Impact of the 1968 Hong Kong Influenza Pandemic:
16 17	420		Evidence for a Smoldering Pandemic. J Infect Dis. 2005 Jul 15;192(2):233–48.
18			
19 20	421 422		1968 flu pandemic History, Deaths, & Facts Britannica [Internet]. 2024 [cited 2024 Jan 4]. Available from: https://www.britannica.com/event/1968-flu-pandemic
21	722	_	+j. / Wallable from https:// www.bittainitea.com/event/1500 ha panaemie
22	423		National Atlas of Spain [Internet]. [cited 2024 Feb 12]. First COVID-19 cases. Available
23 24	424	f	from: http://nationalatlas.ign.es/wane/First_COVID-19_cases
25	125	۶ ۱	Wu E. Zhao S. Yu P. Chon VM. Wang W. Song ZC. et al. A new coronavirus associated with
26	425 426		Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar;579(7798):265–9.
27 28	720		
28 29	427	7. N	Mitjà O, Corbacho-Monné M, Ubals M, Tebé C, Peñafiel J, Tobias A, et al.
30	428		Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A
31	429		Randomized, Controlled Trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Dec
32 33	430	6	6;73(11):e4073–81.
34	431	8. E	Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for
35	432	t	the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 Nov 5;383(19):1813–26.
36 37	422	0 7	
38	433 434		Thakur V, Bhola S, Thakur P, Patel SKS, Kulshrestha S, Ratho RK, et al. Waves and variants of SARS-CoV-2: understanding the causes and effect of the COVID-19 catastrophe.
39	434		Infection. 2022 Apr;50(2):309–25.
40 41			
42	436		EMA recommends first COVID-19 vaccine for authorisation in the EU European
43	437		Medicines Agency [Internet]. [cited 2024 Jan 4]. Available from:
44 45	438		https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine- authorisation-eu
45 46	439	c	autionsation-eu
47	440	11. 5	Stein C, Nassereldine H, Sorensen RJD, Amlag JO, Bisignano C, Byrne S, et al. Past SARS-
48	441		CoV-2 infection protection against re-infection: a systematic review and meta-analysis.
49 50	442	٦	The Lancet. 2023 Mar 11;401(10379):833–42.
50		40 -	Relley's N. Tabé C. Abalanda Alamas C. Davida da A. Ostable St
52	443		Pallarès N, Tebé C, Abelenda-Alonso G, Rombauts A, Oriol I, Simonetti AF, et al.
53	444 445		Characteristics and Outcomes by Ceiling of Care of Subjects Hospitalized with COVID-19 During Four Waves of the Pandemic in a Metropolitan Area: A Multicenter Cohort Study.
54 55	445 446		Infect Dis Ther. 2023 Jan;12(1):273–89.
55 56	- -1 0		
57	447		Straw S, McGinlay M, Drozd M, Slater TA, Cowley A, Kamalathasan S, et al. Advanced care
58	448		planning during the COVID-19 pandemic: ceiling of care decisions and their implications
59 60	449	f	for observational data. BMC Palliat Care. 2021 Jan 11;20(1):10.
00			

3	450	14	Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap
4	451	14.	consortium: Building an international community of software platform partners. J Biomed
5	452		Inform. 2019;95:103208.
6	452		
7	453	15.	Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained
8	454		Equations in R. J Stat Softw. 2011 Dec 12;45:1–67.
9 10			
10	455	16.	Statistical Analysis with Missing Data Wiley Series in Probability and Statistics [Internet].
12	456		[cited 2023 Aug 17]. Available from:
13	457		https://onlinelibrary.wiley.com/doi/book/10.1002/9781119013563
14	107		
15	458	17.	Austin PC, Stuart EA. Moving towards best practice when using inverse probability of
16	459		treatment weighting (IPTW) using the propensity score to estimate causal treatment
17	460		effects in observational studies. Stat Med. 2015;34(28):3661–79.
18			
19	461	18.	Hu L, Gu C, Lopez M, Ji J, Wisnivesky J. Estimation of causal effects of multiple treatments
20	462		in observational studies with a binary outcome. Stat Methods Med Res. 2020
21 22	463		Nov;29(11):3218–34.
22			
24	464	19.	von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The
25	465		Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
26	466		statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008
27	467		Apr;61(4):344–9.
28	-		
29	468	20.	R: The R Project for Statistical Computing [Internet]. [cited 2022 Jul 12]. Available from:
30	469		https://www.r-project.org/
31 32			
33	470	21.	Satorra P, Carmezim J, Pallarés N, Tebé C. flowchart: Tidy Flowchart Generator [Internet].
34	471		2024 [cited 2024 Mar 4]. Available from: https://cran.r-
35	472		project.org/web/packages/flowchart/index.html
36			
37	473	22.	Carmezim J, Satorra P, Peñafiel J, García-Lerma E, Pallarès N, Santos N, et al. REDCapDM:
38	474		An R package with a set of data management tools for a REDCap project. BMC Med Res
39	475		Methodol. 2024 Mar 1;24(1):55.
40			
41 42	476	23.	Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies [Internet].
42 43	477		2023 [cited 2023 Aug 17]. Available from: https://cran.r-
44	478		project.org/web/packages/Weightlt/index.html
45		_	
46	479	24.	Greifer N. cobalt: Covariate Balance Tables and Plots [Internet]. 2023 [cited 2023 Aug 17].
47	480		Available from: https://cran.r-project.org/web/packages/cobalt/index.html
48			
49	481	25.	CRAN - Package survey [Internet]. [cited 2023 Oct 23]. Available from: https://cran.r-
50	482		project.org/web/packages/survey/index.html
51 52	400	20	Causia Causatana D. Marawaa Causaa O. Cil Deiata D. Cil da Mita al A. Haavitalia ti
52 53	483	26.	Garcia-Carretero R, Vazquez-Gomez O, Gil-Prieto R, Gil-de-Miguel A. Hospitalization
53 54	484		burden and epidemiology of the COVID-19 pandemic in Spain (2020–2021). BMC Infect
55	485		Dis. 2023 Jul 18;23(1):476.
56		-	
57	486	27.	Osorio J, Madrazo Z, Videla S, Sainz B, Rodríguez-Gonzalez A, Campos A, et al. Use of
58	487		failure-to-rescue after emergency surgery as a dynamic indicator of hospital resilience
59	488		during the COVID-19 pandemic. A multicenter retrospective propensity score-matched
60	489		cohort study. Int J Surg Lond Engl. 2022 Oct;106:106890.

1			
2 3	400	20	Marlay C. Unwin M. Datarran C.M. Stankovich I. Kinsman I. Emerganov department
4	490 491	28.	Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PLoS ONE. 2018
5	491		Aug 30;13(8):e0203316.
6	492		Aug 50,15(8).00205510.
7	493	29.	Siqueira CA dos S, de Freitas YNL, Cancela M de C, Carvalho M, Oliveras-Fabregas A, de
8 9	494		Souza DLB. The effect of lockdown on the outcomes of COVID-19 in Spain: An ecological
9 10	495		study. PLoS ONE. 2020 Jul 29;15(7):e0236779.
11			
12	496	30.	Riou J, Hauser A, Fesser A, Althaus CL, Egger M, Konstantinoudis G. Direct and indirect
13	497		effects of the COVID-19 pandemic on mortality in Switzerland. Nat Commun. 2023 Jan
14	498		6;14(1):90.
15 16	400	24	
17	499	31.	Comparing the risk of death involving coronavirus (COVID-19) by variant, England - Office
18	500		for National Statistics [Internet]. [cited 2024 Feb 14]. Available from:
19	501		https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofd
20	502		eath/articles/comparingtheriskofdeathinvolvingcoronaviruscovid19byvariantengland/dece
21	503		mber2021
22 23	504	32	Belvis F, Aleta A, Padilla-Pozo Á, Pericàs JM, Fernández-Gracia J, Rodríguez JP, et al. Key
23	505	52.	epidemiological indicators and spatial autocorrelation patterns across five waves of
25	506		COVID-19 in Catalonia. Sci Rep. 2023 Jun 15;13(1):9709.
26			
27	507	33.	Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations
28	508		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death
29 30	509		with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort
30	510		study. BMJ. 2021 Aug 18;374:n1868.
32			
33	511	34.	Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination
34	512		programme effectiveness against SARS-CoV-2 related infections, hospital admissions and
35 36	513		deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022
30	514		Nov 3;12:18597.
38	515	35	Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones
39	516	55.	éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la
40	517		situación excepcional de crisis por la pandemia por COVID-19: revisión rápida y consenso
41	518		de expertos. Med Intensiva. 2020 Oct;44(7):439–45.
42 43			
44	519	36.	Grant R, Benamouzig D, Catton H, Cheng VCC, Dhingra N, Laxminarayan R, et al. COVID-19
45	520		pandemic: a catalyst for accelerating global action on patient safety. Lancet Infect Dis.
46	521		2023 Oct;23(10):1108–10.
47	500		
48 49	522		
49 50			
51			
52			
53			
54 55			
55 56			
57			
58			
59			
60			
			18

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

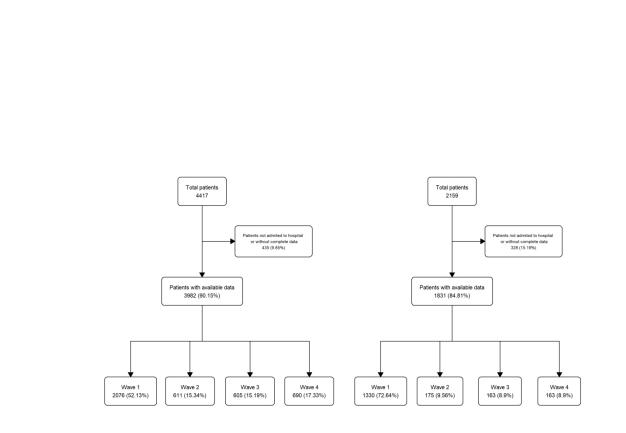


FIGURE 1: Flow-chart of the included patients without ceiling of care (left) and with ceiling of care (right).

249x199mm (300 x 300 DPI)

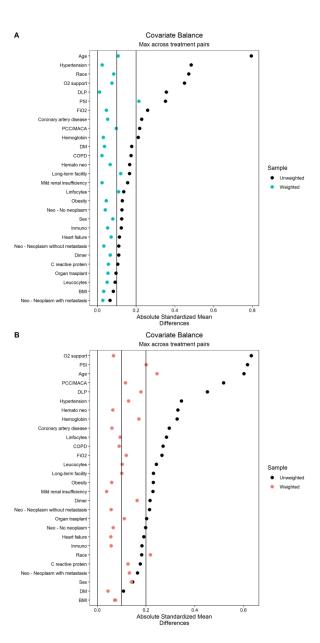


FIGURE 2: Maximum standardized mean differences (SMD) before (Unmatched) and after weighting (Matched) across waves for patients without a ceiling of care (A) and patients with ceiling of care (B). The standardized mean difference compares the difference in means between all pairs of waves in standard deviation units.

199x399mm (300 x 300 DPI)

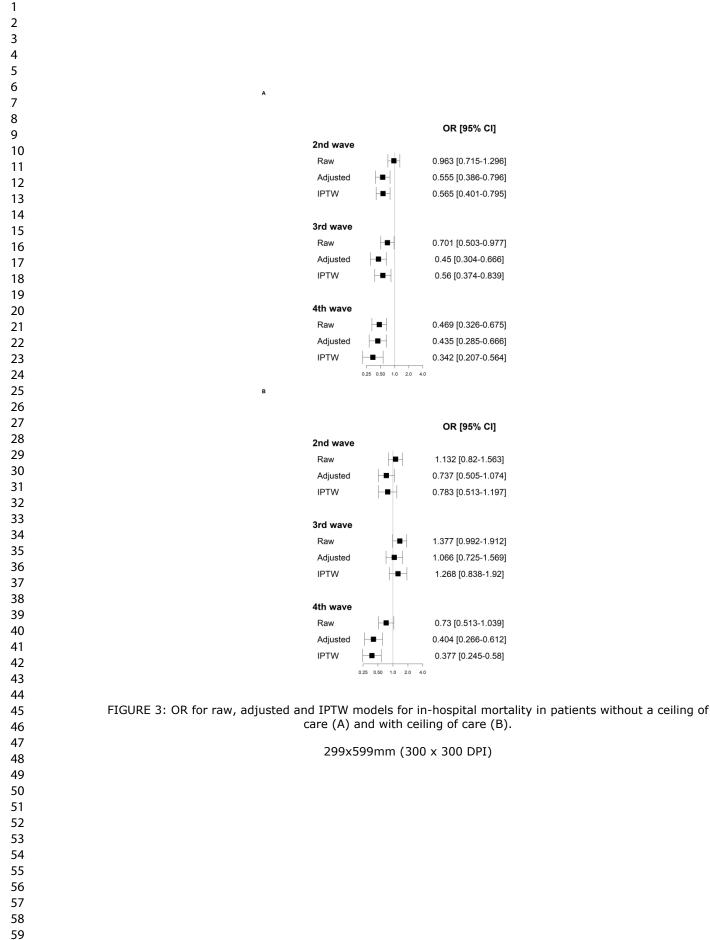


Table S1: Variables used in the matching procedure according to wave and ceiling of care

076 4 .1%) 3.9 5.9, 2.2) 36	Wave 2, N = 611 19 (3.1%) 29.2 (26.4, 32.6) 103 32 (5.2%)	Wave 3, N = 605 17 (2.8%) 29.4 (26.6, 32.9) 72 72	Wave 4, N = 690 4 (0.6%) 29.7 (26.4, 33.6) 177 9 (1.3%)	1330 223 (17%) 28.1 (25.4, 31.3) 456 290	N = 175 20 (11%) 28.7 (25.8, 31.5) 22	Wave 3, N = 163 20 (12%) 29.3 (26.0, 31.5) 19	
.1%) 3.9 5.9, 2.2) 36	 (3.1%) 29.2 (26.4, 32.6) 103 32 	 (2.8%) 29.4 (26.6, 32.9) 72 15 	29.7 (26.4, 33.6) 177	 (17%) 28.1 (25.4, 31.3) 456 290 	28.7 (25.8, 31.5) 22	29.3 (26.0, 31.5)	(9.2%) 27.6 (24.8, 31.8)
.1%) 3.9 5.9, 2.2) 36	 (3.1%) 29.2 (26.4, 32.6) 103 32 	 (2.8%) 29.4 (26.6, 32.9) 72 15 	29.7 (26.4, 33.6) 177	 (17%) 28.1 (25.4, 31.3) 456 290 	28.7 (25.8, 31.5) 22	29.3 (26.0, 31.5)	(9.2%) 27.6 (24.8, 31.8)
5.9, 2.2) 36	(26.4, 32.6) 103 32	(26.6, 32.9) 72 15	(26.4, 33.6) 177	(25.4, 31.3) 456 290	(25.8, 31.5) 22	(26.0, 31.5)	(24.8, 31.8)
3	32	15		290		19	17
			9 (1.3%)				
			9 (1.3%)				
				(22%)	80 (46%)	47 (29%)	57 (35
	124 (20%)	126 (21%)	96 (14%)	414 (31%)	61 (35%)	54 (33%)	59 (36
	108 (18%)	119 (20%)	110 (16%)	325 (24%)	54 (31%)	49 (30%)	60 (37
	18	27 (4 5%)	25 (3.6%)	194 (15%)	37 (21%)	31 (19%)	36 (22
3	3%)	18	3%) (18%) (20%) 18 27	18 27 25 (18%) (20%) (16%)	3%) (18%) (20%) (16%) (24%) 18 27 25 194	3%) (18%) (20%) (16%) (24%) ⁵⁴ (31%) 18 27 25 194 37 (21%)	3%) (18%) (20%) (16%) (24%) 54 (31%) 49 (30%)

Hypertension

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

	NI 11					6		
	No ceilin	g of care			Ceiling o	t care		
	Wave 1 , N = 2076	Wave 2 , N = 611	Wave 3 , N = 605	Wave 4 , N = 690	Wave 1 , N = 1330	Wave 2 , N = 175	Wave 3 , N = 163	Wave 4 , N = 163
Yes	792 (38%)	266 (44%)	295 (49%)	176 (26%)	881 (66%)	137 (78%)	124 (76%)	132 (81%)
Obesity								
Yes	579 (35%)	221 (36%)	248 (41%)	248 (36%)	285 (29%)	51 (29%)	65 (40%)	50 (31%)
Unknown	404	0	0	0	361	0	0	0
Dyslipidemia								
Yes	698 (34%)	223 (36%)	239 (40%)	158 (23%)	502 (38%)	105 (60%)	92 (56%)	83 (51%)
Mild renal insufficiency								
Yes	83 (4.0%)	27 (4.4%)	42 (6.9%)	25 (3.6%)	234 (18%)	42 (24%)	26 (16%)	41 (25%)
Coronary artery disease								
Yes	91 (4.4%)	33 (5.4%)	28 (4.6%)	7 (1.0%)	112 (8.4%)	26 (15%)	30 (18%)	19 (12%)
Haematological neoplasm								
Yes	12 (0.6%)	16 (2.6%)	7 (1.2%)	12 (1.7%)	27 (2.0%)	8 (4.6%)	7 (4.3%)	15 (9.2%)
Organ transplant								
Yes	20 (1.0%)	13 (2.1%)	6 (1.0%)	13 (1.9%)	12 (0.9%)	0 (0%)	3 (1.8%)	1 (0.6%)

	No ceilin	g of care			Ceiling o	f care		
	Wave 1 , N = 2076	Wave 2 , N = 611	Wave 3 , N = 605	Wave 4 , N = 690	Wave 1 , N = 1330	Wave 2 , N = 175	Wave 3 , N = 163	Wave 4 , N = 163
Immunology								
Yes	72 (3.5%)	32 (5.2%)	17 (2.8%)	32 (4.6%)	50 (3.8%)	6 (3.4%)	11 (6.7%)	5 (3.1%)
Neoplasm								
No neoplasm	1991 (96%)	578 (95%)	563 (93%)	656 (95%)	1160 (87%)	141 (81%)	136 (83%)	130 (80%)
Neoplasm without metastasis	78 (3.8%)	30 (4.9%)	37 (6.1%)	30 (4.3%)	145 (11%)	26 (15%)	22 (13%)	30 (18%
Neoplasm with metastasis	7 (0.3%)	3 (0.5%)	5 (0.8%)	4 (0.6%)	25 (1.9%)	8 (4.6%)	5 (3.1%)	3 (1.8%)
D-dimer	570 (316, 1050)	530 (284, 970)	500 (266, 895)	365 (250, 690)	722 (378, 1608)	689 (356, 1438)	471 (280, 969)	451 (276, 895)
Unknown	488	55	62	59	384	19	29	19
C reactive protein	80 (34, 149)	84 (39, 143)	76 (39, 128)	85 (41, 144)	92 (47, 160)	86 (41, 144)	96 (44, 148)	69 (30, 155)
Unknown	161	30	54	36	102	6	24	8
Haemoglobin	13.90 (12.90, 14.90)	13.60 (12.50, 14.80)	13.90 (12.80, 15.00)	14.05 (13.10, 15.10)	13.30 (12.00, 14.43)	12.50 (11.00, 14.40)	12.80 (11.60, 13.60)	12.50 (11.20, 13.80)
Unknown	150	21	40	24	82	6	15	5
Lymphocytes	0.98 (0.72, 1.33)	0.91 (0.66, 1.26)	0.91 (0.64, 1.23)	0.93 (0.66, 1.24)	0.90 (0.63, 1.24)	0.85 (0.57, 1.18)	0.80 (0.54, 1.13)	0.90 (0.59, 1.36)
Unknown	137	21	40	28	105	6	15	5

	No ceilin	g of care			Ceiling o	f care		
	Wave 1 , N = 2076	Wave 2 , N = 611		Wave 4 , N = 690	Wave 1 , N = 1330		Wave 3 , N = 163	Wave 4 , N = 163
Leucocytes	6.5 (5.0, 8.7)	6.5 (5.0, 9.0)	6.4 (5.0, 8.6)	6.2 (4.6, 8.6)	6.9 (5.2, 9.2)	7.2 (5.4, 9.4)	6.5 (5.0, 8.7)	6.9 (5.4, 9.6)
Unknown	109	23	40	26	71	6	15	6
FiO2	21 (21, 21)	21 (21, 28)	21 (21, 28)	21 (21, 31)	21 (21, 24)	21 (21, 28)	21 (21, 35)	24 (21, 31)
Unknown	2	0	0	0	3	0	0	0
Need for oxygen support	511 (25%)	193 (32%)	234 (39%)	316 (46%)	345 (26%)	69 (39%)	77 (47%)	92 (56%)
Unknown	2	0	0	0	3	0	0	0

Median (IQR) for continuous variables; n (%) for categorical variables

BMI: Body mass index

COPD: Chronic obstructive pulmonary disease

PCC: chronic complex patient

MACA: advanced chronic disease patient

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

BMJ Open

Impact of ceiling of care on mortality across four COVID-19 epidemic waves in Catalonia: a multicentre prospective cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-091249.R1
Article Type:	Original research
Date Submitted by the Author:	07-Apr-2025
Complete List of Authors:	Pallarès, Natàlia; Germans Trias i Pujol Research Institute and Hospital (IGTP), Biostatistics Support and Research Unit; University of Barcelona, Basic Clinical Practice Videla, Sebastià; Germans Trias i Pujol University Hospital, Department of Clinical Pharmacology; University of Barcelona, Department of Pathology and Experimental Therapeutics Carratala, Jordi; Hospital Universitari de Bellvitge, Infectious Diseases; Bellvitge Biomedical Research Institute; Instituto de Salud Carlos III, Centro de Investigación en Red de Enfermedades Infecciosas (CIBERINFEC) Tebé, Cristian; Germans Trias i Pujol Research Institute and Hospital (IGTP), Biostatistics Support and Research Unit
Primary Subject Heading :	Infectious diseases
Secondary Subject Heading:	Palliative care, Epidemiology
Keywords:	COVID-19, INFECTIOUS DISEASES, PALLIATIVE CARE, Epidemiology < INFECTIOUS DISEASES

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies



3 4 5	1 2	Impact of ceiling of care on mortality across four COVID-19 epidemic waves in Catalonia: a multicentre prospective cohort study
6 7 8	3 4	Pallarès N ^{1,2} MSc, Videla S ^{3,4} MD PhD, Carratalà J ^{5,6,7,8} MD PhD, Tebé C ¹ MPH PhD, on behalf of the MetroSud study group and the Divine study group
9 10 11	5 6	1) Biostatistics Support and Research Unit, Germans Trias i Pujol Research Institute and Hospital (IGTP), Badalona, Barcelona, Spain
12 13 14	7 8	2) Department of Basic Clinical Practice, School of Medicine and Health Sciences, University of Barcelona, Spain
15 16 17	9 10	3) Clinical Research Support Area, Department of Clinical Pharmacology, Germans Trias i Pujol University Hospital, Badalona, Spain
18 19 20	11 12	4) Department of Pathology and Experimental Therapeutics, School of Medicine and Health Sciences, University of Barcelona, Spain
21	13	5) Department of Infectious Diseases, Bellvitge University Hospital, Barcelona, Spain
22 23	14	6) Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
24	15	7) Centro de Investigación en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de
25 26	16	Salud Carlos III, Madrid, Spain.
27 28	17	8) Department of Clinical Sciences, School of Medicine and Health Sciences, University of
29	18	Barcelona, Spain
30 31	19	
32	20	MetroSud Study group: Gabriela Abelenda-Alonso, Alexander Rombauts, Isabel Oriol,
33	21	Antonella F. Simonetti, Alejandro Rodríguez-Molinero, Elisenda Izquierdo, Vicens Díaz-Brito,
34 35	22	Carlota Gudiol, Judit Aranda-Lobo, Marta Arroyo, Carlos Pérez-López, Montserrat Sanmartí,
36	23	Encarna Moreno, Maria C Alvarez, Ana Faura, Martha González, Paula Cruz, Mireia Colom,
37	24	Andrea Perez, Laura Serrano.
38	25	
39	26	DIVINE Study group: Mireia Besalú, Erik Cobo, Jordi Cortés, Daniel Fernández, Leire
40	27	Garmendia, Guadalupe Gómez, Pilar Hereu, Klaus Langohr, Gemma Molist, Núria Pérez-
41 42	28	Álvarez, Xavier Piulachs.
42	29	
44	30	
45	31	
46	32	Corresponding author Natàlia Pallarès, MSc
47	33 34	Biostatistics Support and Research Unit
48 49	34 35	Germans Trias i Pujol Research Institute and Hospital (IGTP)
49 50	36	Campus Can Ruti. Carretera de Can Ruti, Camí de les Escoles s/n. 08916 Badalona, Barcelona,
51	37	Spain
52 53	38	Span
54 55	39	
56 57	40	
58 59	41	
60	42	

1

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2	
3	43
4	
5 6	44
7	45
8	46
9 10	
11	47
12	48
13 14	49
15	50
16 17	51
18	52
19	53
20	54
21 22	55
23	56
24	57
25 26	58
27	59
28	60
29 30	61
31	62
32	63
33 34	64
35	
36	65
37	66
38 39	67
40	68
41	69
42 43	70
44	71
45 46	72
47	73
48	73
49 50	74
50 51	75
52 53	76
53 54	77
55	78
56	79
57 58	80
58 59	81
	01

43 ABSTRACT

- 44 **Objective:** The aim of this study was to compare in-hospital mortality across waves in
 45 patients without and with a ceiling of care at hospital admission.
- 46 **Design :** A multicentre prospective cohort study
- 47 Setting: Five tertiary hospitals in Catalonia, Spain, during four waves of the COVID-19
 48 pandemic. Data from the first wave embraced from March to April 2020, second wave
- 48 pandemic. Data from the first wave embraced from March to April 2020, second wav 49 from October to November 2020, third wave from January to February 2021 and
- 50 fourth wave from July to August 2021.

Participants: All consecutive adult subjects (older than 18 years old) admitted to any of
the five aforementioned centers. All subjects had a confirmed SARS-CoV-2 infection
(with a positive PCR test or antigen test) and an overnight hospital stay. Ceiling of care
defined as the highest level of care that a patient will receive during medical treatment
was assessed at hospital admission for all patients.

- 57 **Primary measure:** In-hospital mortality
- Results: A total of 3982 hospitalized patients without ceiling of care and 1831
 hospitalized patients with ceiling of care were included in the analysis. The adjusted
 odds ratio (OR) of in-hospital mortality in the second wave were 0.57 (95%CI 0.40 to
 0.80), in the third 0.56 (95%CI 0.37 to 0.84) and in the fourth 0.34 (95%CI 0.21 to 0.56)
 compared with the first wave in subjects without ceiling of care. The adjusted odds
 ratio were significantly lower in the fourth (0.38 95%CI 0.25 to 0.58) wave compared to
 the first wave in subjects with ceiling of care.
 - 65 Conclusions: In patients without ceiling of care, mortality decreased over time
 66 suggesting better disease knowledge and management. In ceiling of care, only fourth67 wave patients were less likely to die than first-wave patients. In a future infectious
 68 disease pandemic, it will be a challenge to improve the management of patients with
 69 ceiling of care.
- 70
 70
 71
 72 Keywords
 73 COVID-19, Infectious diseases, Palliative care, Epidemiology
 74
 75 Strengths and limitations of this study
 76 This is multicontrip study with a large number of subjects inc
 - This is multicentric study with a large number of subjects included from four different waves of the COVID-19 pandemic.
 - Several methods were used to compare in-hospital mortality between waves to
 increase the robustness of the estimated effects.
- 80
 Despite the inverse probability weighting analysis, there may be unobserved
 81
 60
 81
 61

82 83	• The national vaccination campaign started for the elderly subjects before fourth wave so it could not be used in the adjustment analysis.
05	fourth wave so it could not be used in the adjustment analysis.

Despite the lack of definition in epidemiology, the term epidemic wave implies a natural pattern of peaks and troughs in the incidence of cases or hospitalizations due to an outbreak [1]. Epidemics often occur in local or global waves, each one with variations in severity or in transmission dynamics [2–4].

Following a similar pattern, the COVID-19 pandemic began in Wuhan, China, in December 2019, and spread rapidly across Europe, with the first outbreak in Italy in February 2020. During the course of the pandemic, countries and regions experienced several waves with distinct peaks in cases. In Spain, 7 waves of the pandemic have been recorded between March 2020 and September 2023, with almost 14 million confirmed cases and more than 120.000 deaths [5]. Throughout this period, knowledge of the disease has progressively increased with the sequencing of the virus [6], clinical trials to assess treatments efficacy [7,8], the identification of different strains of the virus [9] and the development of vaccines [10]. All these factors, together with the natural immunity protection against COVID-19 [11], lead to a reduction in the need for hospitalization, in-hospital mortality and complications.

The therapeutic ceiling of care refers to the highest level of care that a patient will receive during medical treatment. In general, in a non-pandemic setting, decisions about the ceiling of care are common practice when dealing with patients with a critical prognosis and have implications for the use of life-sustaining measures such as intubation, mechanical ventilation, and cardiopulmonary resuscitation. However, in the peaks of the COVID-19 pandemic, decisions about the maximum level of care that each patient should receive, besides of the critical prognosis of the patient, were made in a scenery of emergency with excess demand for critical care and limited availability of clinical resources. Previously published data [12,13] suggest that COVID-19 hospitalized patients who had a ceiling of care were mainly older, had more comorbidities and higher incidence of in-hospital death. In-hospital mortality has been shown to decrease over time [14,15]. However, little is known about the impact of ceiling of care on mortality in hospitalized patients with COVID-19 across pandemic waves. Stratifying by care limitations helps to distinguish whether the reduction in mortality was due to advances in intensive care unit management, improved general hospital care, or shifts in decision making. This approach addresses a gap in previous research, which has often overlooked how changes in patient selection for intensive care can bias mortality trends. Understanding these dynamics can inform clinical decision-making and ensure optimal management for all patients, regardless of their care limitations.

Our hypothesis is that the decrease in in-hospital mortality over time is different in
patients with and without ceiling of care. The aim of this study was to compare inhospital mortality across four COVID-19 waves between patients with and without a
ceiling of care at hospital admission.

METHODS Study design and setting The MetroSud study is an observational multicenter study conducted in five centers located in the southern metropolitan area of Barcelona (Catalonia, Spain), to characterise all patients with COVID-19 admitted to these hospitals during four waves of the pandemic from March 2020 to August 2021. Analized data of the first wave of COVID-19 pandemic embraced from March to April 2020, second wave from October to November 2020, third wave from January to February 2021 and fourth wave from July to August 2021 [16]. MetroSud cohort has been previously described [12]. **Eligibility criteria**

The MetroSud cohort included all consecutive adult subjects (older than 18 years old)
admitted to any of the five aforementioned centers. All subjects had a proven SARSCoV-2 infection (with a positive PCR test or antigen test).

143 Data sources and study variables

An electronic case report form in REDCap [17] was designed in March 2020 to collect study data. Demographic data (age, sex, race), comorbidities and other relevant findings on medical history, previous medications, clinical symptoms, vital signs (body temperature, FiO2, O2 saturation, blood pressure, pulse, and respiratory rate), laboratory results (D dimer, C-reactive protein, lactat dehydrogenase, leukocytes, and others) and respiratory exploration (wheezing, rhoncus), Pneumonia severity index (PSI) and ceiling of care were collected at baseline by the attending physicians.

The presence or absence of ceiling of care was decided at the emergency room by the attending physicians according to their criteria, taking into account the patient's potential benefit of intensive treatments. In the beginning of the first wave, due to the ICU demand and capacity, the availability of resources at each participating hospital was also taken into account. Patients without a ceiling of care would have access to an ICU or could receive invasive mechanical ventilation (IMV). Otherwise, patients assigned to ceiling of care would have limited access to the ICU and, if they required any respiratory support, it would be non-rebreather mask, high-flow nasal cannula or NIMV.

48 161 49 162 **Outcome variable**

The outcome variable was in-hospital mortality defined as death by any cause during
 hospitalization and was registered in the electronic case report form.

166
 55 167 The study was approved by the Bellvitge Hospital Research Ethics Committee with
 56 168 medicines (CREm), with reference PR140/20 and code HUB-INF-COHORT·HUB·COVID,
 57 169 in accordance with Spanish legislation and was performed in accordance with the
 58 170 Helsinki Declaration of 1964. The need for patient informed consent was waived by the

ethics committee. Bellvitge's CREm decision was the basis for the approval of the
remaining hospital centers.

174 Statistical methods

To describe cohort characteristics, categorical variables were presented as the number
of cases and percentage, while continuous variables were expressed as the mean and
standard deviation (SD) or median and interquartile range (IQR). All analyses were
presented by wave and stratified by ceiling of care.

A pool of essential variables to describe the baseline profile of patients was defined.
 This pool included age, sex, Charlson score, ceiling of care, and circumstances at
 discharge. Patients who had incomplete data on this pool of variables were discarded
 from the analysis.

Once the variables to be used to match patients were identified, multiple imputation with chained equations (MICE) [18] was used to create five datasets with complete data. Missing data were assumed to be at random. Predictive mean matching was used to impute continuous variables and binomial logistic regression was used to impute binary variables. Information on age, sex and baseline comorbidities (completed for all patients after exclusions) was used to impute missing values for obesity, body mass index (BMI), race, pneumonia severity Index (PSI), FiO₂, oxygen support, D-dimer, C-reactive protein, leukocytes, haemoglobin and lymphocytes. Final estimates were adjusted for variability between the five imputed datasets according to the Rubin rules [19] to obtain the final model.

With the database with all the missing data imputed, three models were constructed
 With the database with all the missing data imputed, three models were constructed
 to study the association between in-hospital mortality and wave: 1) a crude logistic
 regression model using wave as a covariate, 2) a fully adjusted logistic regression
 model and 3) an inverse probability weighting (IPW) logistic regression model.

After discussion with clinicians, the variables included in the fully adjusted logistic regression model to minimize confounding and make patients comparable between waves were baseline variables that define the patient's status at hospital admission: age, sex, race, BMI, obesity, long-term facility, comorbidities (diabetes mellitus, COPD, heart failure, hypertension, renal insufficiency, dyslipidemia, coronary heart disease, haematological neoplasm, solid neoplasm, organ transplantation, immunosuppressive treatment, chronic complex patient (PCC) and patients with advanced chronic disease (MACA), baseline laboratory values (dimer, C-reactive protein, leukocytes, haemoglobin, lymphocytes), pneumonia severity index (PSI), FiO2 and oxygen support. IPW [20] was used to adjust for differences in the patient baseline profile between waves. Bayesian additive regression trees, entropy balancing, generalised boosted models and generalised linear models were tested as methods for weighting individuals. In the end, we chose the method with better covariate balance between

59 210 waves after weighting, which was the bayesian additive regression trees method [21].

2		
3	211	In each imputed dataset, weights were calculated with the wave as the outcome and
4 5	212	the variables used for the full adjusted logistic model as covariates.
6 7	213	To identify imbalances between waves after weighting, we estimated and described
8	214	the standardised mean differences in baseline variables before and after weighting.
9	215	We then fitted a logistic regression model for each imputation with in-hospital death
10 11	216	as the outcome, using the stabilised weights and model-robust standard errors and
12	217	adjusting for the variables that remained imbalanced between groups after weighting.
13 14	218	To overcome the limitation of assuming missing at random, a sensitivity analysis was
15	219	performed by repeating the analyses using only those patients who had complete
16	220	information on all variables.
17	220	
18 19	221	We used the STROBE cohort checklist [22] when writing our report. All analyses were
20	222	performed with a two-sided significance level of 0.05 using R software version 4.3.0
21	223	[23]. The main R packages used for data management and analysis were flowchart
22 23	224	[24], REDCapDM [25], mice [18], WeightIt [26], cobalt [27] and survey [28].
24	225	
25 26		\sim
20 27	226	Patient and public involvement
28	227	There was no patient or public involvement in the development of the research design
29	228	or in conducting the study.
30 31	229	
32		
33	230	
34		
35 36		
37		
38		
39 40		
40		
42		
43		
44 45		
45 46		
47		
48		
49 50		
50		
52		
53		
54 55		
55 56		
57		
58		
59 60		

231	RESULTS								
232	Flow chart								
233	A total of 4	417 patien	ts withou	ut ceiling	of care a	nd 2159 p	atients wi	ith ceiling	of care
234	were includ	led in the l	MetroSuc	d. After ex	cluding p	oatients w	ho were a	admitted ⁻	to
235	hospital for	less than	24 hours,	, patients	who died	d within tł	ne first 24	hours, pa	atients
236	with incom	plete data	on a poo	l of esser	ntial varia	bles (age,	sex, Char	lson score	e, ceiling
237	of care, and	l circumsta	ances at o	discharge) or patie	nts who w	vere initia	lly admitt	ed to one
238	hospital bu ⁻	t transferr	ed to and	other and	treated i	n the latte	er, a total	of 3982 p	atients
239	without cei	ling of care	e and a to	otal of 18	31 patien	ts with ce	iling of ca	re were in	ncluded i
240	the analysis	s. All patier	nts were	followed	up until i	n-hospita	l death or	hospital of	discharge
241	(Figure 1, F	low Chart)							
242									
243									
244	Baseline ch	aracterist	ics by wa	ve					
245	Table 1 des	cribes the	baseline	characte	ristics of t	the includ	ed patien	ts by wav	e and
246	stratified by	ceiling of	care. Otl	ner variat	oles inclu	ded in the	matching	g process	are
247	described in	n Supplem	entary Ta	ble 1.					
		••	,						
248									
249	TABLE 1: Pa	tient's mos	st relevan	t characte	eristics a	ccording t	o wave ar	nd ceiling	of care.
249 250	TABLE 1: Pa	tient's mos	st relevan	t charact	eristics a	ccording t	o wave ar	nd ceiling	of care.
	TABLE 1: Pa	tient's mos No ceiling		t charact	eristics a	ccording t		nd ceiling	of care.
	TABLE 1: Pa			t charact	eristics ad	-		nd ceiling	of care.
	TABLE 1: Pa	No ceiling	of care		Wave 4	Ceiling of	care	-	
	TABLE 1: Pa	No ceiling Wave 1	of care Wave 2	Wave 3	Wave 4 (July-	Ceiling of Wave 1	care Wave 2	Wave 3	Wave 4
	TABLE 1: Pa	No ceiling	of care Wave 2		Wave 4	Ceiling of	care	-	Wave 4
	TABLE 1: Pa	No ceiling Wave 1 (Mar-Apr	of care Wave 2 (Oct-Nov	Wave 3 (Jan-Feb	Wave 4 (July- Aug	Ceiling of Wave 1 (Mar-Apr	care Wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb	Wave 4 (July-Au
		No ceiling Wave 1 (Mar-Apr 2020)	of care Wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb 2021)	Wave 4 (July- Aug 2021)	Ceiling of Wave 1 (Mar-Apr 2020)	care Wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb 2021)	Wave 4 (July-Aug 2021)
	TABLE 1: Pa	No ceiling Wave 1 (Mar-Apr 2020) N = 2076	of care Wave 2 (Oct-Nov 2020) N = 611	Wave 3 (Jan-Feb 2021) N = 605	Wave 4 (July- Aug 2021) N = 690	Ceiling of Wave 1 (Mar-Apr 2020) N = 1330	Wave 2 (Oct-Nov 2020) N = 175	Wave 3 (Jan-Feb 2021) N = 163	Wave 4 (July-Aug 2021) N = 163
		No ceiling Wave 1 (Mar-Apr 2020) N = 2076 59 (49,	of care Wave 2 (Oct-Nov 2020) N = 611	Wave 3 (Jan-Feb 2021) N = 605 63 (53,	Wave 4 (July- Aug 2021) N = 690 49 (37,	Ceiling of Wave 1 (Mar-Apr 2020) N = 1330 79 (72,	Wave 2 (Oct-Nov 2020) N = 175 83 (78,	Wave 3 (Jan-Feb 2021) N = 163 83 (78,	Wave 4 (July-Aug 2021) N = 163 85 (80,
	Age Sex	No ceiling Wave 1 (Mar-Apr 2020) N = 2076 59 (49,	of care Wave 2 (Oct-Nov 2020) N = 611	Wave 3 (Jan-Feb 2021) N = 605 63 (53,	Wave 4 (July- Aug 2021) N = 690 49 (37,	Ceiling of Wave 1 (Mar-Apr 2020) N = 1330 79 (72,	Care Wave 2 (Oct-Nov 2020) N = 175 83 (78, 88)	Wave 3 (Jan-Feb 2021) N = 163 83 (78, 87)	Wave 4 (July-Aug 2021) N = 163 85 (80, 89)
	Age	No ceiling Wave 1 (Mar-Apr 2020) N = 2076 59 (49, 69)	of care Wave 2 (Oct-Nov 2020) N = 611 62 (53, 71)	Wave 3 (Jan-Feb 2021) N = 605 63 (53, 72)	Wave 4 (July- Aug 2021) N = 690 49 (37, 63)	Ceiling of Wave 1 (Mar-Apr 2020) N = 1330 79 (72, 85)	Care Wave 2 (Oct-Nov 2020) N = 175 83 (78, 88)	Wave 3 (Jan-Feb 2021) N = 163 83 (78,	Wave 4 (July-Aug 2021) N = 163 85 (80, 89)

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1 2	
3	
4	
5	
4 5 6 7 8 9 10 11 12	
8	
9	
10	
11	
13	
14	
15	
10	
18	
19	
20	
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 4 35 36 37	
23	
24	
25 26	
20	
28	
29	
30 31	
32	
33	
34 35 36 37 38	
35 36	
37	
39	
40 41	
42	
43	
44 45	
45 46	
47	
48	
49 50	
50 51	
52	
53 54	
54 55	
56	
57	
58 59	
59 60	
55	

1

	No ceiling	of care			Ceiling of o	care		
	Wave 1 (Mar-Apr 2020) N = 2076	Wave 2 (Oct-Nov 2020) N = 611	Wave 3 (Jan-Feb 2021) N = 605	Wave 4 (July- Aug 2021) N = 690	Wave 1 (Mar-Apr 2020) N = 1330	Wave 2 (Oct-Nov 2020) N = 175	Wave 3 (Jan-Feb 2021) N = 163	Wave 4 (July-Aug 2021) N = 163
Caucasian	1206 (78%)	394 (69%)	464 (86%)	406 (65%)	795 (96%)	164 (95%)	154 (97%)	154 (98%)
Other	341 (22%)	179 (31%)	73 (14%)	218 (35%)	32 (3.9%)	9 (5.2%)	4 (2.5%)	3 (1.9%)
Unknown	529	38	68	66	503	2	5	6
Charlson Index	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)	3.00 (1.00, 4.00)	1.00 (0.00, 3.00)	5.00 (4.00, 7.00)	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	6.00 (5.00, 7.00)
PSI	62 (50, 79)	69 (56, 87)	66 (53, 84)	59 (46, 78)	97 (79, 123)	115 (95, 134)	103 (84, 124)	114 (96, 135)
Unknown	374	6	3	3	239	1	4	2

Median (IQR) for continuous variables; n (%) for categorical variables

PSI: Pneumonia severity index

251 Regarding age, patients with a ceiling of care were, in median, 20 years older than 252 patients without a ceiling of care in all waves. There were no differences in the proportion of women. The most common race was Caucasian (in all waves, almost 90% 253 254 of patients without ceiling of care and over 70% of patients with ceiling of care were 255 Caucasian). Patients with a ceiling of care had a median Charlson Index more than 3 256 points higher than patients without a ceiling of care in all waves. PSI scores for patients 257 with ceiling of care were more than 35 points higher in all waves (greater differences in 258 wave 4) than PSI scores for patients without ceiling of care.

7

259

59 260 In-hospital mortality

261 The overall cumulative incidence of in-hospital mortality for patients with and without

262 ceiling of care in all waves is shown in Table 2.

TABLE 2: Cumulative incidence and 95% confidence interval for in-hospital mortality accordingto wave and ceiling of care.

	Wave 1	Wave 2	Wave 3	Wave 4
	(Mar-Apr 2020)	(Oct-Nov 2020)	(Jan-Feb 2021)	(July-Aug 2021)
No ceiling of care	10.50% [9.23 to 11.92]	10.15% [7.92 to 12.89]	7.60% [5.68 to 10.09]	5.22% [3.73 to 7.22]
Ceiling of	37.07% [34.48 to	40.00% [32.76 to	44.79% [37.06 to	30.06% [23.27 to
care	39.74]	47.69]	52.76]	37.81]

About 1 in 10 patients without ceiling of care died in hospital in the first and second waves. In patients with a ceiling of care, about 4 in 10 patients die in hospital in the first three waves. The percentages are lower in the fourth wave (5% and 30% respectively for patients without and with a ceiling of care).

271 Mortality in patients without ceiling of care

Figure 2A shows the balance of covariates before and after IPW by means of the
standardised mean differences (SMD) in patients without a ceiling of care. The SMD for
PSI remains above 0.2. To correct for this imbalance, PSI was included in the weighted
mortality models.

The odds ratios of the three models for mortality are shown in Figure 3A. The results with the three methods are consistent and show the same trend for all waves. Patients from waves 2, 3 and 4 were less likely to die in hospital than patients from wave 1 both in the raw models and in the models adjusted for covariates or adjusted with weights (OR for all models and all waves lower than 1). In addition, the value of the OR decreases across waves.

51 282

53 283 Mortality in patients with ceiling of care 54

Figure 2B shows the balance of covariates before and after IPW by means of the SMD
 in patients with a ceiling of care assigned at admission. Age, PSI and race showed a
 difference between waves greater than 0.2. These variables were included as

adjustments in the weighted mortality model to account for these differences.

2		
3	288	The odds ratios of the three models for mortality are shown in Figure 3B. No
4 5	289	differences were found between 1 st and 2 nd wave patients or between 1 st and 3 rd wave
6	290	patient (neither in the crude nor in the adjusted models). For wave 4 th , both adjusted
7	291	and IPW models showed that, given two patients with the same baseline profile, a
8	292	wave 4 patient was less likely to die in hospital than a wave 1 patient.
9	252	wave 4 patient was less intery to die in nospital than a wave 1 patient.
10 11	293	
12	294	
13		
14		
15 16		
17		
18		
19		
20		
21 22		
23		
24		
25		
26 27		
28		
29		
30		
31 32		
33		
34		
35		
36 37		
38		
39		
40		
41 42		
43		
44		
45		
46 47		
48		
49		
50		
51 52		
52 53		
54		
55		
56 57		
57 58		
59		
60		

2		
3	295	
4 5	296	DISCUSSION
6	297	Our multicentre cohort study compared in-hospital mortality across COVID-19 waves
7	298	between patients with and without a ceiling of care at hospital admission. We found
8 9	299	that among patients without ceiling of care, those admitted in the first wave had
10		
11	300	worse in-hospital mortality than patients hospitalized during the other waves.
12	301	Moreover, the adjusted models showed a significant decrease in mortality as the
13	302	waves progressed. Among patients with a ceiling of care, no differences in in-hospital
14 15	303	mortality were found between second and first wave patients, or between third and
16	304	first wave patients. Only in the fourth wave, patients were less likely to die than first
17	305	wave patients after adjustment for baseline risk. The magnitude of this effect on
18	306	mortality reduction observed in patients with ceiling of care in the 4 th wave was similar
19 20	307	to the effect observed among patients without ceiling of care in the same 4 th wave.
21	200	
22	308	It is worth noting that if the differences in mortality between waves were only due to
23	309	patient's risk profile, the mortality rates would be similar after adjustment for baseline
24 25	310	profile. However, this is not the case, as Figure 3A shows that in the adjusted and
26	311	weighted models, mortality among patients without ceiling of care decreases as waves
27	312	progress in time (OR decreasing from 0.56 (second and third wave) to 0.34 (fourth
28	313	wave) when comparing with first wave)). The emergency situation experienced by the
29 30	314	hospitals in the first months of the pandemic, with a lack of organization prepared to
30	315	face an emergency such as COVID-19, partly explains the differences observed [29].
32	316	Besides, in the first wave, hospital resources (such as ICU beds, number of non-invasive
33	317	ventilators or high-flow nasal oxygen therapy devices) and human resources were not
34 35	318	sufficient to cope with the high demand for medical care [30]. ICU capacity is known to
36	319 320	be an important indicator of hospital stress (health system resilience) which is
37	320 321	associated with a reduction in quality of care and poorer patient outcomes [31]. In addition, other factors such as the increasing knowledge about the disease, facilitated
38		by the rapid publication of clinical trials analysing new treatments [8], or the impact of
39 40	322 323	public health surveillance measures, such as lockdowns [32] could explain this
40 41	323	reduction in mortality. The harvest effect could also explain this decrease in mortality,
42	325	as deaths that would have occurred anyway in subsequent waves may have been
43	326	precipitated by the high mortality in the first wave of COVID-19 [33]. Similarly, the
44 45	327	aggressiveness of SARS-CoV-2 varied between strains, and may also have played a role
45 46	328	in the reduction in mortality [34].
47		
48	329	As expected, mortality was higher among patients with ceiling care. In this group of
49	330	patients, there are no differences in mortality in the first three waves, but there is a
50 51	331	decrease in mortality in wave 4 (OR 0.38 95%CI 0.25 to 0.58) (Figure 3B). In Spain, this
52	332	fourth wave mainly affected young patients. Older patients, who were more likely to
53	333	be assigned a ceiling of care, were already vaccinated at that time [35]. A study in
54	334	nursing homes in our geographical area (Catalonia) [36] showed that vaccination was
55 56	335	associated with a 95% reduction in mortality among nursing home residents. Studies in
57	336	Italy and Switzerland also showed that the vaccine was about 95% effective against
58	337	death in the general population [33,37]. These results therefore suggest that there is
59	338	no improvement in medical management that affects in-hospital mortality until wave
60	339	4, which coincides with the elderly vaccination campaign. The lack of a contrafactual

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

scenario in which people received intensive care makes it difficult to assess any potential benefit. Further research on this topic and replication of these results in other cohorts would be needed. Moreover, it will be of interest to study the management of ceiling of care in other cultural settings. It would also be interesting to investigate whether the impact of ceiling of care is the same on other outcomes, such as complications or length of hospital stay.

The high probability of a new epidemic caused by an infectious organism merits in-depth reflection by the medical and scientific community, in particular to reach a consensus on the definition of ceiling of care and to define a guideline for the management of patients who are candidates for a ceiling of care [38]. In the event of a future pandemic caused by an infectious organism, the challenge will be to improve mortality in patients with ceiling of care. To this end, the scientific community needs to develop an action plan that will enable a rapid response in terms of both human resources (by increasing the number of trained health workers), and facilities (for example, so that the ICUs can quickly increase the number of beds) [39].

Our study has some limitations that should be acknowledged. One limitation is residual confounding. Even after using all the characteristics available at admission to make the baseline status of patients comparable, there may be unobserved characteristics that make patients different between waves. For example, we knew whether a patient had pathology or not, but we could not take into account how advanced it was. A variable that collects information on patients' frailty at baseline might also be of interest for a better risk assessment. In addition, vaccines and treatments could not be used in the matching: vaccines because they did not exist in the first wave [10] and treatments because they changed drastically between waves due to increasing knowledge about the disease [7,8]. Moreover, we do not have data on the follow-up of patients with regard to treatments received during hospitalization, which could help to understand some of the differences in mortality. Another limitation of the study is that we assumed that the missing values in our data were at random and imputed them using standard techniques. To account for this, a sensitivity analysis was performed repeating the analysis only with patients who had complete information on all variables, and the results were in the same line, confirming the robustness of the analysis. Moreover, we cannot guarantee that the same criteria were used to define the therapeutic ceiling of care in all hospitals. In fact, one of the challenges in clinical practice during the COVID-19 pandemic was to define the ceiling of care for infected patients. Even though the definition of ceiling of care is not a standardized one, the definition in the MetroSud cohort was a pragmatic one which would be readable and understood by clinician teams involved in reaching these decisions. Our definition is consistent with that used in the Leeds cohort [13] and with the one used in a multicentre study to identify factors influencing ceiling of treatment in an Emergency Department [40]. In addition, when the study protocol was written, little was known about COVID-19, including the lack of immunity and the possibility of reinfection. Before the emergence of the Omicron strain, the incidence of COVID-19 reinfection leading to hospitalization was very low (<1%) [41]. Our last wave included patients from July to August 2021, when the Omicron strain had not yet reach Spain and the incidence of reinfection was still very low. However, we could not rule out the possibility that some subjects from the 3rd or 4th wave had previously been included

pandemics.

in the study. Due to data protection laws, we did not have access to patients' clinical records, which prevented verification. Nevertheless, participating physicians were aware of this possibility and took measures to avoid case duplication. The strengths of our study are the large number of subjects included from different hospitals and from four different waves of the pandemic, and the availability of information on ceiling of care. In addition, the different methods used to compare in-hospital mortality by waves led to the same results, demonstrating the robustness of the analysis. In conclusion, knowing that the evolution of in-hospital mortality through waves is ev vithou anagemer, idemic scenar i-care profession. different in patients with and without ceiling of care could help the scientific community to address the management of patients with ceiling of care to improve their outcomes in a new pandemic scenario. The lessons learned from the COVID-19

pandemic could help health-care professional and health policy-makers to face future

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1 2		
2 3 4	404	FIGURE LEGENDS
5	405	FIGURE 1: Flow-chart of the included patients without ceiling of care (left) and with
6 7	406	ceiling of care (right).
8	407	FIGURE 2: Maximum standardized mean differences (SMD) before (Unmatched) and
9 10	408	after weighting (Matched) across waves for patients without a ceiling of care (A) and
11	409	patients with ceiling of care (B). The standardized mean difference compares the
12	410	difference in means between all pairs of waves in standard deviation units.
13 14	411	FIGURE 3: OR for raw, adjusted and IPTW models for in-hospital mortality in patients
15	411	without a ceiling of care (A) and with ceiling of care (B).
16 17	412	without a centrig of care (A) and with centrig of care (B).
17	413	
19		
20	414	
21 22	415	DECLARATIONS
23		
24	416	Ethics approval and consent to participate
25	417	The study was approved by the Bellvitge Hospital Research Ethics Committee with
26	418	medicines (CREm) in accordance with Spanish legislation and was performed in
27 29	419	accordance with the Helsinki Declaration of 1964. The need for patient informed
28 29	420	consent was waived by the ethics committee. Bellvitge's CREm decision was the basis
30	421	for the approval of the remaining hospital centres.
31	422	
32	423	
33	424	Competing interests
34 35	425	Cristian Tebé has received fees for speaker lectures and talks from Gedeon Richter,
36	426	outside the submitted work. The rest of authors declare that they have no competing
37	427	interests.
38	428	
39	429	
40	430	Data availability
41 42	431	The datasets generated during and/or analyzed during the current study are available
43	432	from the corresponding author on reasonable request.
44	433	in one corresponding dather on reasonable request
45	434	
46	435	Funding
47 48	435	This work was partially funded by Secretaria d'Universitats i Recerca del Departament
40 49	430	d'Empresa i Coneixement de la Generalitat de Catalunya (2020PANDE00148). The
50		funding was used to collect data from the 4 th wave.
51	438	
52	439	This work has also been supported by grant 2021 SGR 01421 (GRBIO) administrated by
53	440	the Departament de Recerca i Universitats de la Generalitat de Catalunya (Spain).
54 55	441	
56	442	
57	443	Acknowledgements
58	444	We thank CERCA Programme/Generalitat de Catalunya for institutional support.
59	445	
60	446	

1 2 3 447 4 448 5 449 7 450 8 451 9 452 10 453 12 454 13 455 14 456 15 457 16 457 17 458 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	<text><text><text><text><text></text></text></text></text></text>
--	---

1 2			
3	459	RFE	ERENCES
4	455	NLI	
5	460		
6 7	461	1.	Zhang SX, Arroyo Marioli F, Gao R, Wang S. A Second Wave? What Do People Mean By
8	461	1.	COVID Waves? – A Working Definition of Epidemic Waves [Internet]. Rochester, NY; 2021
9	463		[cited 2024 Jan 8]. Available from: https://papers.ssrn.com/abstract=4456241
10	105		
11	464	2.	Unwin RJ. The 1918 Influenza Pandemic: Back to the Future? Kidney Blood Press Res.
12 13	465		2021;46[5]:639–46.
14		-	
15	466	3.	
16	467		Mortality Study Group. Multinational Impact of the 1968 Hong Kong Influenza Pandemic:
17	468		Evidence for a Smoldering Pandemic. J Infect Dis. 2005 Jul 15;192[2]:233–48.
18 19	469	4.	1968 flu pandemic History, Deaths, & Facts Britannica [Internet]. 2024 [cited 2024 Jan
20	470		4]. Available from: https://www.britannica.com/event/1968-flu-pandemic
21			
22	471	5.	National Atlas of Spain [Internet]. [cited 2024 Feb 12]. First COVID-19 cases. Available
23 24	472		from: http://nationalatlas.ign.es/wane/First_COVID-19_cases
25	473	6.	Wu E Zhao S Yu P Chan VM Wang W Song ZC at al. A new coronavirus accosisted with
26	475 474	0.	Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar;579[7798]:265–9.
27	4/4		
28 29	475	7.	Mitjà O, Corbacho-Monné M, Ubals M, Tebé C, Peñafiel J, Tobias A, et al.
30	476		Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A
31	477		Randomized, Controlled Trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Dec
32	478		6;73[11]:e4073–81.
33	470	0	
34 35	479	8.	Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for
36	480		the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 Nov 5;383[19]:1813–26.
37	481	9.	Thakur V, Bhola S, Thakur P, Patel SKS, Kulshrestha S, Ratho RK, et al. Waves and variants
38	482		of SARS-CoV-2: understanding the causes and effect of the COVID-19 catastrophe.
39 40	483		Infection. 2022 Apr;50[2]:309–25.
40			
42	484	10.	EMA recommends first COVID-19 vaccine for authorisation in the EU European
43	485		Medicines Agency [Internet]. [cited 2024 Jan 4]. Available from:
44 45	486 487		https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine- authorisation-eu
46	407		
47	488	11.	Stein C, Nassereldine H, Sorensen RJD, Amlag JO, Bisignano C, Byrne S, et al. Past SARS-
48	489		CoV-2 infection protection against re-infection: a systematic review and meta-analysis.
49 50	490		The Lancet. 2023 Mar 11;401[10379]:833–42.
50 51			
52	491	12.	Pallarès N, Tebé C, Abelenda-Alonso G, Rombauts A, Oriol I, Simonetti AF, et al.
53	492		Characteristics and Outcomes by Ceiling of Care of Subjects Hospitalized with COVID-19
54	493 494		During Four Waves of the Pandemic in a Metropolitan Area: A Multicenter Cohort Study. Infect Dis Ther. 2023 Jan;12[1]:273–89.
55 56	494		וווכנו טוא ווופו. 2025 אוו,12[1].275-05.
57	495	13.	Straw S, McGinlay M, Drozd M, Slater TA, Cowley A, Kamalathasan S, et al. Advanced care
58	496		planning during the COVID-19 pandemic: ceiling of care decisions and their implications
59	497		for observational data. BMC Palliat Care. 2021 Jan 11;20[1]:10.
60			

1 2			
2	498	1/ [Roso-Llorach A, Serra-Picamal X, Cos FX, Pallejà-Millán M, Mateu L, Rosell A, et al. Evolving
4	498 499		mortality and clinical outcomes of hospitalized subjects during successive COVID-19 waves
5	499 500		in Catalonia, Spain. Glob Epidemiol. 2022 Dec;4:100071.
6	300	I	in Catalonia, Spain. Glob Epidemiol. 2022 Dec,4.100071.
7	501	15 H	Hedberg P, Parczewski M, Serwin K, Marchetti G, Bai F, Jensen BEO, et al. In-hospital
8	501		mortality during the wild-type, alpha, delta, and omicron SARS-CoV-2 waves: a
9	502		multinational cohort study in the EuCARE project. Lancet Reg Health – Eur [Internet]. 2024
10 11	503 504		Mar 1 [cited 2024 Aug 6];38. Available from:
12	504 505		https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(24)00021-8/fulltext
13	303	I	
14	506	16 I	Dades COVID [Internet]. [cited 2024 May 13]. Available from: https://dadescovid.cat
15	500	10. 1	
16	507	17. H	Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap
17	508		consortium: Building an international community of software platform partners. J Biomed
18	509		Inform. 2019;95:103208.
19 20			
20 21	510	18. E	Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained
21	511		Equations in R. J Stat Softw. 2011 Dec 12;45:1–67.
23			
24	512	19. 9	Statistical Analysis with Missing Data Wiley Series in Probability and Statistics [Internet].
25	513	[[cited 2023 Aug 17]. Available from:
26	514	ł	https://onlinelibrary.wiley.com/doi/book/10.1002/9781119013563
27			
28	515	20. A	Austin PC, Stuart EA. Moving towards best practice when using inverse probability of
29	516	t	treatment weighting (IPTW) using the propensity score to estimate causal treatment
30 31	517	e	effects in observational studies. Stat Med. 2015;34[28]:3661–79.
32			
33	518		Hu L, Gu C, Lopez M, Ji J, Wisnivesky J. Estimation of causal effects of multiple treatments
34	519		n observational studies with a binary outcome. Stat Methods Med Res. 2020
35	520	1	Nov;29[11]:3218–34.
36			
37	521		von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The
38 39	522		Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
39 40	523		statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008
41	524	4	Apr;61[4]:344–9.
42	ГЭГ	-	P. The D Draiget for Statistical Computing [Internet] [sited 2022 [u] 12] Augilable from
43	525		R: The R Project for Statistical Computing [Internet]. [cited 2022 Jul 12]. Available from:
44	526	I	https://www.r-project.org/
45	527	2/ 9	Satorra P, Carmezim J, Pallarés N, Tebé C. flowchart: Tidy Flowchart Generator [Internet].
46	528		2024 [cited 2024 Mar 4]. Available from: https://cran.r-
47 48	528		project.org/web/packages/flowchart/index.html
40 49	525	ł	broject.org/ web/packages/nowchart/index.ntm
50	530	25. (Carmezim J, Satorra P, Peñafiel J, García-Lerma E, Pallarès N, Santos N, et al. REDCapDM:
51	531		An R package with a set of data management tools for a REDCap project. BMC Med Res
52	532		Methodol. 2024 Mar 1;24[1]:55.
53	552	'	
54	533	26. (Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies [Internet].
55	534		2023 [cited 2023 Aug 17]. Available from: https://cran.r-
56	535		project.org/web/packages/WeightIt/index.html
57 58		1	
58 59	536	27. (Greifer N. cobalt: Covariate Balance Tables and Plots [Internet]. 2023 [cited 2023 Aug 17].
60	537		Available from: https://cran.r-project.org/web/packages/cobalt/index.html
-			

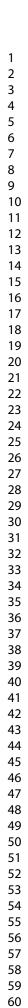
3	538	28.	CRAN - Package survey [Internet]. [cited 2023 Oct 23]. Available from: https://cran.r-
4	539		project.org/web/packages/survey/index.html
5			
6	540	29.	Garcia-Carretero R, Vazquez-Gomez O, Gil-Prieto R, Gil-de-Miguel A. Hospitalization
7	541		burden and epidemiology of the COVID-19 pandemic in Spain (2020–2021). BMC Infect
8	542		Dis. 2023 Jul 18;23[1]:476.
9 10	0.1		
11	543	30.	Osorio J, Madrazo Z, Videla S, Sainz B, Rodríguez-Gonzalez A, Campos A, et al. Use of
12	544		failure-to-rescue after emergency surgery as a dynamic indicator of hospital resilience
13	545		during the COVID-19 pandemic. A multicenter retrospective propensity score-matched
14	546		cohort study. Int J Surg Lond Engl. 2022 Oct;106:106890.
15	540		
16	547	31	Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department
17	548	51.	crowding: A systematic review of causes, consequences and solutions. PLoS ONE. 2018
18	549		Aug 30;13[8]:e0203316.
19	545		Aug 50,15[8].e0205510.
20	550	27	Siqueira CA dos S, de Freitas YNL, Cancela M de C, Carvalho M, Oliveras-Fabregas A, de
21	550	52.	Souza DLB. The effect of lockdown on the outcomes of COVID-19 in Spain: An ecological
22			
23	552		study. PLoS ONE. 2020 Jul 29;15[7]:e0236779.
24 25	FF 2	22	Diau L. Hauser A. Fasser A. Althous Cl. Eggar M. Konstantingudis C. Direct and indirect
25 26	553	55.	Riou J, Hauser A, Fesser A, Althaus CL, Egger M, Konstantinoudis G. Direct and indirect
20 27	554		effects of the COVID-19 pandemic on mortality in Switzerland. Nat Commun. 2023 Jan
28	555		6;14[1]:90.
29		24	
30	556	34.	Comparing the risk of death involving coronavirus (COVID-19) by variant, England - Office
31	557		for National Statistics [Internet]. [cited 2024 Feb 14]. Available from:
32	558		https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofd
33	559		eath/articles/comparing the risk of deathin volving coronavirus covid 19 by variant england/dece
34	560		mber2021
35			
36	561	35.	Belvis F, Aleta A, Padilla-Pozo Á, Pericàs JM, Fernández-Gracia J, Rodríguez JP, et al. Key
37	562		epidemiological indicators and spatial autocorrelation patterns across five waves of
38	563		COVID-19 in Catalonia. Sci Rep. 2023 Jun 15;13[1]:9709.
39			
40	564	36	
41	E C E	50.	Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations
12	565	50.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death
42 43	565 566	50.	
43		50.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death
43 44	566		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort
43 44 45	566		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort
43 44	566 567		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868.
43 44 45 46	566 567 568		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination
43 44 45 46 47	566 567 568 569		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and
43 44 45 46 47 48 49 50	566 567 568 569 570		of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022
43 44 45 46 47 48 49 50 51	566 567 568 569 570	37.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597.
43 44 45 46 47 48 49 50 51 52	566 567 568 569 570 571	37.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022
43 44 45 46 47 48 49 50 51 52 53	566 567 568 569 570 571 572 573	37.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la
43 44 45 46 47 48 49 50 51 52 53 54	566 567 568 569 570 571 572 573 573	37.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la situación excepcional de crisis por la pandemia por COVID-19: revisión rápida y consenso
43 44 45 46 47 48 49 50 51 52 53 54 55	566 567 568 569 570 571 572 573	37.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la
43 44 45 46 47 48 49 50 51 52 53 54 55 56	566 567 568 569 570 571 572 573 574 575	37. 38.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la situación excepcional de crisis por la pandemia por COVID-19: revisión rápida y consenso de expertos. Med Intensiva. 2020 Oct;44[7]:439–45.
43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	566 567 568 569 570 571 572 573 574 575 576	37. 38.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la situación excepcional de crisis por la pandemia por COVID-19: revisión rápida y consenso de expertos. Med Intensiva. 2020 Oct;44[7]:439–45. Grant R, Benamouzig D, Catton H, Cheng VCC, Dhingra N, Laxminarayan R, et al. COVID-19
43 44 45 46 47 48 49 50 51 52 53 54 55 56	566 567 568 569 570 571 572 573 574 575	37. 38.	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ. 2021 Aug 18;374:n1868. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination programme effectiveness against SARS-CoV-2 related infections, hospital admissions and deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022 Nov 3;12:18597. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la situación excepcional de crisis por la pandemia por COVID-19: revisión rápida y consenso de expertos. Med Intensiva. 2020 Oct;44[7]:439–45.

579	40. Walzl N, Jameson J, Kinsella J, Lowe DJ. Ceilings of treatment: a qualitative study in the
580	emergency department. BMC Emerg Med. 2019 Jan 17;19[1]:9.

581 41. Lin W, Kung KH, Chan CL, Chuang SK, Au KW. Characteristics and risk factors associated
582 with COVID-19 reinfection in Hong Kong: a retrospective cohort study. Epidemiol Infect.
583 2025 Feb 7;153:e30.

for oper teries only

BMJ Open: first published as 10.1136/bmjopen-2024-091249 on 30 May 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.



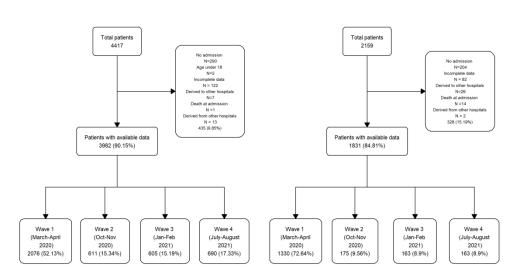


FIGURE 1: Flow-chart of the included patients without ceiling of care (left) and with ceiling of care (right).

249x199mm (300 x 300 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

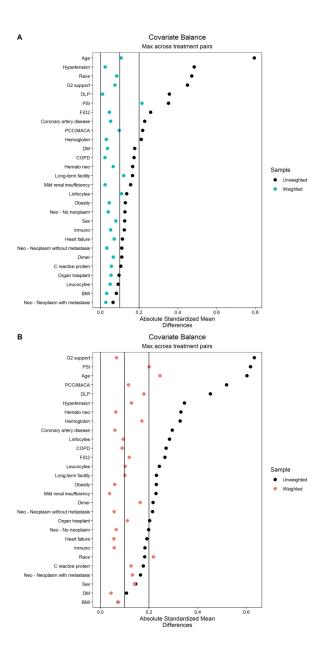
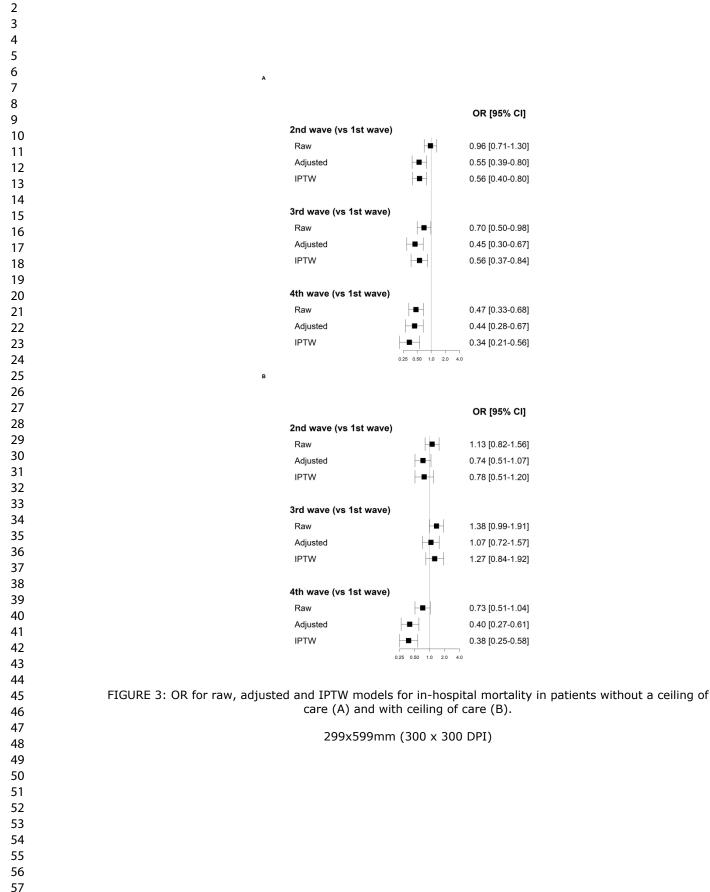


FIGURE 2: Maximum standardized mean differences (SMD) before (Unmatched) and after weighting (Matched) across waves for patients without a ceiling of care (A) and patients with ceiling of care (B). The standardized mean difference compares the difference in means between all pairs of waves in standard deviation units.

199x399mm (300 x 300 DPI)



60

Table S1: Variables used in the matching procedure according to wave and ceiling of care

	No cellin	ig of care			Ceiling o	r care		
	Wave 1 (Mar- Apr 2020) N =	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave 4 (July- Aug 2021)	Wave 1 (Mar- Apr 2020) N =	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wa (J 20
	2076	N = 611	N = 605	N = 690	1330	N = 175	N = 163	N =
Long-term facility								
Yes	64 (3.1%)	19 (3.1%)	17 (2.8%)	4 (0.6%)	223 (17%)	20 (11%)	20 (12%)	15 (9.2
BMI	28.9 (25.9, 32.2)	29.2 (26.4, 32.6)	29.4 (26.6, 32.9)	29.7 (26.4, 33.6)	28.1 (25.4, 31.3)	28.7 (25.8, 31.5)	29.3 (26.0, 31.5)	27.0 (24 31.3
Unknown	636	103	72	177	456	22	19	17
PCC/MACA								
PCC/MACA	93 (4.5%)	32 (5.2%)	15 (2.5%)	9 (1.3%)	290 (22%)	80 (46%)	47 (29%)	57
Diabetes mellitus	5							
Yes	418 (20%)	124 (20%)	126 (21%)	96 (14%)	414 (31%)	61 (35%)	54 (33%)	59
COPD								
Yes	274 (13%)	108 (18%)	119 (20%)	110 (16%)	325 (24%)	54 (31%)	49 (30%)	60

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

	No ceilin	g of care			Ceiling o	f care		
	Wave 1 (Mar- Apr 2020) N =	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave 4 (July- Aug 2021)	Wave 1 (Mar- Apr 2020) N =	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave 4 (July- Aug 2021)
Yes	2076 50 (2.4%)	N = 611 18 (2.9%)	N = 605 27 (4.5%)	N = 690 25 (3.6%)	1330 194 (15%)	N = 175 37 (21%)	N = 163 31 (19%)	N = 163 36 (22%)
Hypertension								
Yes	792 (38%)	266 (44%)	295 (49%)	176 (26%)	881 (66%)	137 (78%)	124 (76%)	132 (81%)
Obesity								
Yes	579 (35%)	221 (36%)	248 (41%)	248 (36%)	285 (29%)	51 (29%)	65 (40%)	50 (31%)
Unknown	404	0	0	0	361	0	0	0
Dyslipidemia								
Yes	698 (34%)	223 (36%)	239 (40%)	158 (23%)	502 (38%)	105 (60%)	92 (56%)	83 (51%)
Mild renal insufficiency								
Yes	83 (4.0%)	27 (4.4%)	42 (6.9%)	25 (3.6%)	234 (18%)	42 (24%)	26 (16%)	41 (25%)
Coronary artery disease								
Yes	91 (4.4%)	33 (5.4%)	28 (4.6%)	7 (1.0%)	112 (8.4%)	26 (15%)	30 (18%)	19 (12%)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	No ceilin	g of care			Ceiling o	t care		
	Wave 1				Wave 1			
	(Mar- Apr 2020)	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave 4 (July- Aug 2021)	(Mar- Apr 2020)	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave (July Aug 2021
	N = 2076	N = 611	N = 605	N = 690	N = 1330	N = 175	N = 163	N = 16
Haematological neoplasm								
Yes	12 (0.6%)	16 (2.6%)	7 (1.2%)	12 (1.7%)	27 (2.0%)	8 (4.6%)	7 (4.3%)	15 (9.2%)
Organ transplant								
Yes	20 (1.0%)	13 (2.1%)	6 (1.0%)	13 (1.9%)	12 (0.9%)	0 (0%)	3 (1.8%)	1 (0.6%
Immunology								
Yes	72 (3.5%)	32 (5.2%)	17 (2.8%)	32 (4.6%)	50 (3.8%)	6 (3.4%)	11 (6.7%)	5 (3.1%
Neoplasm								
No neoplasm	1991 (96%)	578 (95%)	563 (93%)	656 (95%)	1160 (87%)	141 (81%)	136 (83%)	130 (80%)
Neoplasm without metastasis	78 (3.8%)	30 (4.9%)	37 (6.1%)	30 (4.3%)	145 (11%)	26 (15%)	22 (13%)	30 (18
Neoplasm with metastasis	7 (0.3%)	3 (0.5%)	5 (0.8%)	4 (0.6%)	25 (1.9%)	8 (4.6%)	5 (3.1%)	3 (1.8%
D-dimer	570 (316, 1050)	530 (284, 970)	500 (266, 895)	365 (250, 690)	722 (378, 1608)	689 (356, 1438)	471 (280, 969)	451 (276, 895)
Unknown	488	55	62	59	384	19	29	19

	No ceilir	ig of care			Ceiling o	f care		
	Wave 1 (Mar- Apr 2020) N = 2076	Wave 2 (Oct- Nov 2020) N = 611	Wave 3 (Jan- Feb 2021) N = 605	Wave 4 (July- Aug 2021) N = 690	Wave 1 (Mar- Apr 2020) N = 1330	Wave 2 (Oct- Nov 2020) N = 175	Wave 3 (Jan- Feb 2021) N = 163	Wave 4 (July- Aug 2021) N = 163
C reactive protein	80 (34, 149)	84 (39, 143)	76 (39, 128)	85 (41, 144)	92 (47, 160)	86 (41, 144)	96 (44, 148)	69 (30, 155)
Unknown	161	30	54	36	102	6	24	8
Haemoglobin	13.90 (12.90, 14.90)	13.60 (12.50, 14.80)	13.90 (12.80, 15.00)	14.05 (13.10, 15.10)	13.30 (12.00, 14.43)	12.50 (11.00, 14.40)	12.80 (11.60, 13.60)	12.50 (11.20, 13.80)
Unknown	150	21	40	24	82	6	15	5
Lymphocytes	0.98 (0.72, 1.33)	0.91 (0.66, 1.26)	0.91 (0.64, 1.23)	0.93 (0.66, 1.24)	0.90 (0.63, 1.24)	0.85 (0.57, 1.18)	0.80 (0.54, 1.13)	0.90 (0.59, 1.36)
Unknown	137	21	40	28	105	6	15	5
Leucocytes	6.5 (5.0, 8.7)	6.5 (5.0, 9.0)	6.4 (5.0, 8.6)	6.2 (4.6, 8.6)	6.9 (5.2, 9.2)	7.2 (5.4, 9.4)	6.5 (5.0, 8.7)	6.9 (5.4, 9.6)
Unknown	109	23	40	26	71	6	15	6
FiO2	21 (21, 21)	21 (21, 28)	21 (21, 28)	21 (21, 31)	21 (21, 24)	21 (21, 28)	21 (21, 35)	24 (21, 31)
Unknown	2	0	0	0	3	0	0	0
Need for oxygen support	511 (25%)	193 (32%)	234 (39%)	316 (46%)	345 (26%)	69 (39%)	77 (47%)	92 (56%)
Unknown	2	0	0	0	3	0	0	0

Median (IQR) for continuous variables; n (%) for categorical variables

1									
2									
3		No ceilin	g of care			Ceiling o	f care		
4 5									
6		Wave 1				Wave 1			
7		(Mar-	Wave 2	Wave 3	Wave 4	(Mar-	Wave 2	Wave 3	Wave 4
8		-				-			
9 10		Apr	(Oct-	(Jan-	(July-	Apr	(Oct-	(Jan-	(July-
11		2020)	Nov	Feb	Aug	2020)	Nov	Feb	Aug
12		N =	2020)	2021)	2021)	N =	2020)	2021)	2021)
13			N = 0.14	N - 005	N - 000		N - 475	N = 400	N - 400
14		2076	N = 611	N = 605	N = 690	1330	N = 175	N = 163	N = 163
15 16									
17	BMI: Body mass in	dex							
18	COPD: Chronic ob	octructivo p	ulmonony d	licoaco					
19		psiluctive p	unnonary u	lisease					
20 21	PCC: chronic comp	olex patient	:						
22									
23	MACA: advanced of	chronic dise	ease patien	t					
24									
25									
26 27									
28									
29									
30			ease patien						
31 32									
33									
34									
35									
36									
37 38									
39									
40									
41									
42 43									
44									
45									
46									
47 48									
48									
50									
51									
52 53									
53 54									
55									
56									
57									
58 59									
59 60									

BMJ Open

BMJ Open

Impact of ceiling of care on mortality across four COVID-19 epidemic waves in Catalonia: a multicentre prospective cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-091249.R2
Article Type:	Original research
Date Submitted by the Author:	14-May-2025
Complete List of Authors:	Pallarès, Natàlia; Germans Trias i Pujol Research Institute and Hospital (IGTP), Biostatistics Support and Research Unit; University of Barcelona, Basic Clinical Practice Videla, Sebastià; Germans Trias i Pujol University Hospital, Department of Clinical Pharmacology; University of Barcelona, Department of Pathology and Experimental Therapeutics Carratala, Jordi; Hospital Universitari de Bellvitge, Infectious Diseases; Bellvitge Biomedical Research Institute; Instituto de Salud Carlos III, Centro de Investigación en Red de Enfermedades Infecciosas (CIBERINFEC) Tebé, Cristian; Germans Trias i Pujol Research Institute and Hospital (IGTP), Biostatistics Support and Research Unit the MetroSud and the Divine study groups, On behalf of; IGTP,
Primary Subject Heading :	Infectious diseases
Secondary Subject Heading:	Palliative care, Epidemiology
Keywords:	COVID-19, INFECTIOUS DISEASES, PALLIATIVE CARE, Epidemiology < INFECTIOUS DISEASES

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2		
3	1	Impact of ceiling of care on mortality across four COVID-19 epidemic waves in Catalonia: a
4	2	multicentre prospective cohort study
5		
6 7	3	Pallarès N ^{1,2} MSc, Videla S ^{3,4} MD PhD, Carratalà J ^{5,6,7,8} MD PhD, Tebé C ¹ MPH PhD, on behalf of
8	4	the MetroSud study group and the Divine study group
9 10 11	5 6	1) Biostatistics Support and Research Unit, Germans Trias i Pujol Research Institute and Hospital (IGTP), Badalona, Barcelona, Spain
12 13 14	7 8	2) Department of Basic Clinical Practice, School of Medicine and Health Sciences, University of Barcelona, Spain
15	9	3) Clinical Research Support Area, Department of Clinical Pharmacology, Germans Trias i Pujol
16 17	10	University Hospital, Badalona, Spain
18 19 20	11 12	4) Department of Pathology and Experimental Therapeutics, School of Medicine and Health Sciences, University of Barcelona, Spain
21 22	13	5) Department of Infectious Diseases, Bellvitge University Hospital, Barcelona, Spain
23	14	6) Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
24 25	15	7) Centro de Investigación en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de
26	16	Salud Carlos III, Madrid, Spain.
27	17	a) Department of Clinical Coloneas Coloral of Madicine and Health Coloneas Haiversity of
28	17 18	8) Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Spain
29	10	
30	19	
31 32	20	
33	20	MetroSud Study group: Gabriela Abelenda-Alonso, Alexander Rombauts, Isabel Oriol,
34	21	Antonella F. Simonetti, Alejandro Rodríguez-Molinero, Elisenda Izquierdo, Vicens Díaz-Brito,
35	22	Carlota Gudiol, Judit Aranda-Lobo, Marta Arroyo, Carlos Pérez-López, Montserrat Sanmartí,
36	23	Encarna Moreno, Maria C Alvarez, Ana Faura, Martha González, Paula Cruz, Mireia Colom,
37	24 25	Andrea Perez, Laura Serrano.
38	25 26	DIVINE Study group, Miroja Pasalý, Erik Caba, Jardi Cartás, Daniel Fornándoz, Jaira
39 40	26 27	DIVINE Study group: Mireia Besalú, Erik Cobo, Jordi Cortés, Daniel Fernández, Leire Garmendia, Guadalupe Gómez, Pilar Hereu, Klaus Langohr, Gemma Molist, Núria Pérez-
40 41	27	Álvarez, Xavier Piulachs.
42	28 29	
43	30	Corresponding author
44	31	Corresponding author
45	32	Natàlia Pallarès, MSc
46	33	Biostatistics Support and Research Unit
47	33 34	Germans Trias i Pujol Research Institute and Hospital (IGTP)
48 49	35	Campus Can Ruti. Carretera de Can Ruti, Camí de les Escoles s/n. 08916 Badalona, Barcelona,
49 50	36	Spain
51	37	Span
52	57	
53	38	
54		
55 56	39	
57	40	
58		
59 60	41	

2	
3 4	42
5	43
6 7	44
, 8 9	45
10	46
11 12	40
12 13	48
14	49
15 16	
17	50 51
18 19	52
20	53
21	54
22	55
23 24	56
25	
26 27	57
27 28	58
29	59
30	60
31 32	61
33	62
34	63
35 36	64
37	65
38	66
39 40	67
41	68
42	69
43 44	70
45	70
46	/1
47 48	72
49	73
50 51	74
52	75
53 54	76
55	77
56	78
57 58	79
58 59	80
60	80

- 43 **Objective:** The aim of this study was to compare in-hospital mortality across waves in
 44 patients without and with a ceiling of care at hospital admission.
- 45 **Design:** A multicentre prospective cohort study
- 46 Setting: Five tertiary hospitals in Catalonia, Spain, during four waves of the COVID-19
 - 47 pandemic. Data from the first wave embraced from March to April 2020, second wave
- 48 from October to November 2020, third wave from January to February 2021 and
 49 fourth wave from July to August 2021.
- Participants: All consecutive adult subjects (older than 18 years old) admitted to any of
 the five aforementioned centers. All subjects had a confirmed SARS-CoV-2 infection
 (with a positive PCR test or antigen test) and an overnight hospital stay. Ceiling of care
 defined as the highest level of care that a patient will receive during medical treatment
 was assessed at hospital admission for all patients.
- 56 **Primary measure:** In-hospital mortality
- **Results:** A total of 3982 hospitalized patients without ceiling of care and 1831
 hospitalized patients with ceiling of care were included in the analysis. The adjusted
 odds ratio (OR) of in-hospital mortality in the second wave were 0.57 (95%CI 0.40 to
 0.80), in the third 0.56 (95%CI 0.37 to 0.84) and in the fourth 0.34 (95%CI 0.21 to 0.56)
 compared with the first wave in subjects without ceiling of care. The adjusted odds
 ratio were significantly lower in the fourth (0.38 95%CI 0.25 to 0.58) wave compared to
 the first wave in subjects with ceiling of care.
- 64 Conclusions: In patients without ceiling of care, mortality decreased over time
 65 suggesting better disease knowledge and management. In ceiling of care, only fourth66 wave patients were less likely to die than first-wave patients. In a future infectious
 67 disease pandemic, it will be a challenge to improve the management of patients with
 68 ceiling of care.
- 2369470571Keywords6772COVID-19, Infectious diseases, Palliative care, Epidemiology77373074Strengths and limitations of this study
 - This is multicentric study with a large number of subjects included from four different waves of the COVID-19 pandemic.
 Several methods were used to compare in-hospital mortality between waves to
- 78 increase the robustness of the estimated effects.
 79 Despite the inverse probability weighting analysis, there may be unobserved characteristics that lead to residual confounding.

81 82	• The national vaccination campaign started for the elderly subjects before fourth wave so it could not be used in the adjustment analysis.
02	fourth wave so it could not be used in the dujustment undrysis.

Despite the lack of definition in epidemiology, the term epidemic wave implies a natural pattern of peaks and troughs in the incidence of cases or hospitalizations due to an outbreak [1]. Epidemics often occur in local or global waves, each one with variations in severity or in transmission dynamics [2–4].

Following a similar pattern, the COVID-19 pandemic began in Wuhan, China, in December 2019, and spread rapidly across Europe, with the first outbreak in Italy in February 2020. During the course of the pandemic, countries and regions experienced several waves with distinct peaks in cases. In Spain, 7 waves of the pandemic have been recorded between March 2020 and September 2023, with almost 14 million confirmed cases and more than 120.000 deaths [5]. Throughout this period, knowledge of the disease has progressively increased with the sequencing of the virus [6], clinical trials to assess treatments efficacy [7,8], the identification of different strains of the virus [9] and the development of vaccines [10]. All these factors, together with the natural immunity protection against COVID-19 [11], lead to a reduction in the need for hospitalization, in-hospital mortality and complications.

The therapeutic ceiling of care refers to the highest level of care that a patient will receive during medical treatment. In general, in a non-pandemic setting, decisions about the ceiling of care are common practice when dealing with patients with a critical prognosis and have implications for the use of life-sustaining measures such as intubation, mechanical ventilation, and cardiopulmonary resuscitation. However, in the peaks of the COVID-19 pandemic, decisions about the maximum level of care that each patient should receive, besides of the critical prognosis of the patient, were made in a scenery of emergency with excess demand for critical care and limited availability of clinical resources. Previously published data [12,13] suggest that COVID-19 hospitalized patients who had a ceiling of care were mainly older, had more comorbidities and higher incidence of in-hospital death. In-hospital mortality has been shown to decrease over time [14,15]. However, little is known about the impact of ceiling of care on mortality in hospitalized patients with COVID-19 across pandemic waves. Stratifying by care limitations helps to distinguish whether the reduction in mortality was due to advances in intensive care unit management, improved general hospital care, or shifts in decision making. This approach addresses a gap in previous research, which has often overlooked how changes in patient selection for intensive care can bias mortality trends. Understanding these dynamics can inform clinical decision-making and ensure optimal management for all patients, regardless of their care limitations.

Our hypothesis is that the decrease in in-hospital mortality over time is different in
patients with and without ceiling of care. The aim of this study was to compare inhospital mortality across four COVID-19 waves between patients with and without a
ceiling of care at hospital admission.

127 METHODS

128 Study design and setting

The MetroSud study is an observational multicenter study conducted in five centers located in the southern metropolitan area of Barcelona (Catalonia, Spain), to characterise all patients with COVID-19 admitted to these hospitals during four waves of the pandemic from March 2020 to August 2021. COVID-19 epidemic waves followed a pattern of peaks and troughs in the incidence of cases or hospitalizations. There is no official date for the start or end of a wave in Catalonia, but recruitment in the MetroSud cohort occurred during peaks in the incidence of cases or hospitalizations in our hospitals. The Infectious Diseases Unit of Bellvitge's Hospital developed the protocol for this study as soon as the first cases appeared. After the first wave, and with the experience gained, the protocol and data collection were reactivated when early epidemiological indicators signaled the arrival of the second wave. This approach was continued in subsequent waves. Analized data of the first wave of COVID-19 pandemic embraced from March to April 2020, second wave from October to November 2020, third wave from January to February 2021 and fourth wave from July to August 2021 [16]. MetroSud cohort has been previously described [12].

145 Eligibility criteria

The MetroSud cohort included all consecutive adult subjects (older than 18 years old)
admitted to any of the five aforementioned centers. All subjects had a proven SARSCoV-2 infection (with a positive PCR test or antigen test).

150 Data sources and study variables

An electronic case report form (eCRF) in REDCap [17] was designed in March 2020 to
collect study data: in-hospital mortality as main outcome, ceiling of care and epidemic
wave as main independent variables, and subjects clinical profile to adjust for potential
confounding.

Demographic data (age, sex, race), comorbidities and other relevant findings on medical history, previous medications, clinical symptoms, vital signs (body temperature, FiO2, O2 saturation, blood pressure, pulse, and respiratory rate), laboratory results (D dimer, C-reactive protein, lactat dehydrogenase, leukocytes, and others) and respiratory exploration (wheezing, rhoncus), Pneumonia severity index (PSI) and ceiling of care were collected at baseline by the attending physicians. Patient status at hospital discharge was also recorded in the eCRF. No variables were transformed, and ranges of pausible values for continuous variables were indicated in the eCRF to ensure data quality.

The presence or absence of ceiling of care was decided at the emergency room by the attending physicians according to their criteria, taking into account the patient's potential benefit of intensive treatments. In the beginning of the first wave, due to the ICU demand and capacity, the availability of resources at each participating hospital was also taken into account. Patients without a ceiling of care would have access to an

1		
2 3	171	10
4 5	172	а
6	173	а
7	174	Ν
8 9	175	а
9 10	176	fı
11	177	_
12	178	C
13 14	179	Т
15	180	h
16	181	h
17	182	-
18 19	183	Т
20	184	n
21	185	ir
22	186	Н
23 24	187 188	e re
24	180	11
26	109	
27 28	190	S
29	191	Т
30 31	192	0
32	193	S
33	194	р
34 35	195	А
36	196	Т
37 38	197	d
39	198	fı
40 41	199	С
42	200	W
43	201	d
44 45	202	te
46	203	b
47	204	p
48	205	۲ ir
49 50	205	
51	200	r
52		a r
53 54	208	[1
55	209	V
56	210	t
57 58	211	r
58 59	212	n
60		

ICU or could receive invasive mechanical ventilation (IMV). Otherwise, patients
assigned to ceiling of care would have limited access to the ICU and, if they required
any respiratory support, it would be non-rebreather mask, high-flow nasal cannula or
NIMV. Information about ceiling of care was registered in the eCRF at hospital
admission. Patients without information on ceiling of care assigned were excluded
from the analysis.

178 **Outcome variable**

The outcome variable was in-hospital mortality defined as death by any cause during
hospitalization and was registered in the eCRF. Patients without information on inhospital mortality were excluded from the analysis.

The study was approved by the Bellvitge Hospital Research Ethics Committee with medicines (CREm), with reference PR140/20 and code HUB-INF-COHORT·HUB·COVID, in accordance with Spanish legislation and was performed in accordance with the Helsinki Declaration of 1964. The need for patient informed consent was waived by the ethics committee. Bellvitge's CREm decision was the basis for the approval of the remaining hospital centers.

7 190 Statistical methods

191 To describe cohort characteristics, categorical variables were presented as the number 192 of cases and percentage, while continuous variables were expressed as the mean and 193 standard deviation (SD) or median and interquartile range (IQR). All analyses were 194 presented by wave and stratified by ceiling of care.

A pool of essential variables to describe the baseline profile of patients was defined. This pool included age, sex, Charlson score, ceiling of care, and circumstances at discharge. Patients who had incomplete data on this pool of variables were discarded from the analysis.

Once the variables to be used to match patients were identified, multiple imputation
 with chained equations (MICE) [18] was used to create five datasets with complete
 data. Missing data were assumed to be at random. Predictive mean matching was used
 to impute continuous variables and binomial logistic regression was used to impute
 binary variables. Information on age, sex and baseline comorbidities (completed for all
 patients after exclusions) was used to impute missing values for obesity, body mass
 index (BMI), race, pneumonia severity Index (PSI), FiO₂, oxygen support, D-dimer, C reactive protein, leukocytes, haemoglobin and lymphocytes. Final estimates were
 adjusted for variability between the five imputed datasets according to the Rubin rules
 [19] to obtain the final model.

With the database with all the missing data imputed, three models were constructed to study the association between in-hospital mortality and wave: 1) a crude logistic regression model using wave as a covariate, 2) a fully adjusted logistic regression model and 3) an inverse probability weighting (IPW) logistic regression model.

After discussion with clinicians, the variables included in the fully adjusted logistic regression model to minimize confounding and make patients comparable between waves were baseline variables that define the patient's status at hospital admission: age, sex, race, BMI, obesity, long-term facility, comorbidities (diabetes mellitus, COPD, heart failure, hypertension, renal insufficiency, dyslipidemia, coronary heart disease, haematological neoplasm, solid neoplasm, organ transplantation, immunosuppressive treatment, chronic complex patient (PCC) and patients with advanced chronic disease (MACA), baseline laboratory values (dimer, C-reactive protein, leukocytes, haemoglobin, lymphocytes), pneumonia severity index (PSI), FiO2 and oxygen support. IPW [20] was used to adjust for differences in the patient baseline profile between waves. Bayesian additive regression trees, entropy balancing, generalised boosted models and generalised linear models were tested as methods for weighting individuals. In the end, we chose the method with better covariate balance between waves after weighting, which was the bayesian additive regression trees method [21]. In each imputed dataset, weights were calculated with the wave as the outcome and the variables used for the full adjusted logistic model as covariates. To identify imbalances between waves after weighting, we estimated and described the standardised mean differences in baseline variables before and after weighting. We then fitted a logistic regression model for each imputation with in-hospital death as the outcome, using the stabilised weights and model-robust standard errors and adjusting for the variables that remained imbalanced between groups after weighting. To overcome the limitation of assuming missing at random, a sensitivity analysis was performed by repeating the analyses using only those patients who had complete information on all variables. We used the STROBE cohort checklist [22] when writing our report. All analyses were performed with a two-sided significance level of 0.05 using R software version 4.3.0 [23]. The main R packages used for data management and analysis were flowchart [24], REDCapDM [25], mice [18], WeightIt [26], cobalt [27] and survey [28]. Patient and public involvement There was no patient or public involvement in the development of the research design or in conducting the study.

247	RESULTS								
248	Flow chart								
		417 potion	±		-f	ad 2150 m	-+:	the acilian	ofooro
249 250	A total of 4 were incluc			-				-	
250	of admissio						-		
252	purposes o	•						•	
253	within 24 h	ours, it wa	s assume	d that the	eir clinica	l conditio	n may hav	ve been m	ore
254	appropriate			•	-				•
255	variables w				•	-	-		
256	the analysis								
257 258	Charlson sc who were i						0,1	<i>,</i> ,	
258	the latter (f			•					
260	ceiling of ca								
261	analysis. Al			•		-			
262	(Figure 1, F	low Chart)							
263									
264									
265	Baseline ch	aracteristi	ics by wa	ve					
266	Table 1 des	cribes the	baseline	character	istics of t	the includ	ed patient	ts by wave	e and
.67	stratified by	y ceiling of	care. Ot	ner variat	les inclu	ded in the	matching	; process a	are
68	described in	n Supplem	entary Ta	ble 1.					
69									
		tiont's mor	st rolovan						
270	IADLE I. Fa	110111 5 11105	stielevali	t characte	eristics a	ccording to	o wave an	d ceiling	of care.
	TABLE I. F a		lielevali	t characte	eristics a	ccording to	o wave an	id ceiling	of care.
	TADLE 1. F a	uent s mos	lieievaii	t characte	eristics a	ccording to	o wave ar	nd ceiling	of care.
270 271	TADLE I. F a	No ceiling		t characte	eristics ad	Ceiling of o		id ceiling	of care.
	TABLE 1. F a			t characte	eristics ad Wave 4	2		nd ceiling	of care.
	TABLE 1. F a			t characte Wave 3		2		id ceiling of Wave 3	of care. Wave 4
	TABLE 1. F a	No ceiling	of care		Wave 4	Ceiling of d	care		
	TABLE 1. F a	No ceiling Wave 1	of care Wave 2	Wave 3	Wave 4 (July-	Ceiling of o	care Wave 2	Wave 3	Wave 4
	TABLE 1. F a	No ceiling Wave 1 (Mar-Apr	of care Wave 2 (Oct-Nov	Wave 3 (Jan-Feb	Wave 4 (July- Aug	Ceiling of o Wave 1 (Mar-Apr	care Wave 2 (Oct-Nov	Wave 3 (Jan-Feb	Wave 4 (July-Aug
		No ceiling Wave 1 (Mar-Apr 2020)	of care Wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb 2021)	Wave 4 (July- Aug 2021)	Ceiling of o Wave 1 (Mar-Apr 2020)	wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb 2021)	Wave 4 (July-Aug 2021)
	Age	No ceiling Wave 1 (Mar-Apr 2020) N = 2076	of care Wave 2 (Oct-Nov 2020) N = 611	Wave 3 (Jan-Feb 2021) N = 605	Wave 4 (July- Aug 2021) N = 690	Ceiling of o Wave 1 (Mar-Apr 2020) N = 1330	Wave 2 (Oct-Nov 2020) N = 175	Wave 3 (Jan-Feb 2021) N = 163	Wave 4 (July-Aug 2021) N = 163

	No ceiling of care			Ceiling of care				
	Wave 1 (Mar-Apr 2020)	Wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb 2021)	Wave 4 (July- Aug 2021)	Wave 1 (Mar-Apr 2020)	Wave 2 (Oct-Nov 2020)	Wave 3 (Jan-Feb 2021)	Wave 4 (July-Aug 2021)
	N = 2076	N = 611	N = 605	N = 690	N = 1330	N = 175	N = 163	N = 163
Women	855 (41%)	222 (36%)	248 (41%)	242 (35%)	565 (42%)	75 (43%)	81 (50%)	75 (46%)
Race								
Caucasian	1206 (78%)	394 (69%)	464 (86%)	406 (65%)	795 (96%)	164 (95%)	154 (97%)	154 (98%)
Other	341 (22%)	179 (31%)	73 (14%)	218 (35%)	32 (3.9%)	9 (5.2%)	4 (2.5%)	3 (1.9%)
Unknown	529	38	68	66	503	2	5	6
Charlson Index	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)	3.00 (1.00, 4.00)	1.00 (0.00, 3.00)	5.00 (4.00, 7.00)	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	6.00 (5.00, 7.00)
PSI	62 (50, 79)	69 (56, 87)	66 (53, 84)	59 (46, 78)	97 (79, 123)	115 (95, 134)	103 (84, 124)	114 (96, 135)
Unknown	374	6	3	3	239	1	4	2

Median (IQR) for continuous variables; n (%) for categorical variables

PSI: Pneumonia severity index

Regarding age, patients with a ceiling of care were, in median, 20 years older than patients without a ceiling of care in all waves. There were no differences in the proportion of women. The most common race was Caucasian (in all waves, almost 90% of patients without ceiling of care and over 70% of patients with ceiling of care were Caucasian). Patients with a ceiling of care had a median Charlson Index more than 3 points higher than patients without a ceiling of care in all waves. PSI scores for patients

with ceiling of care were more than 35 points higher in all waves (greater differences inwave 4) than PSI scores for patients without ceiling of care.

281 In-hospital mortality

The overall cumulative incidence of in-hospital mortality for patients with and withoutceiling of care in all waves is shown in Table 2.

TABLE 2: Cumulative incidence and 95% confidence interval for in-hospital mortality accordingto wave and ceiling of care.

	Wave 1	Wave 2	Wave 3	Wave 4
	(Mar-Apr 2020)	(Oct-Nov 2020)	(Jan-Feb 2021)	(July-Aug 2021)
No ceiling of care	10.50% [9.23 to 11.92]	10.15% [7.92 to 12.89]	7.60% [5.68 to 10.09]	5.22% [3.73 to 7.22]
Ceiling of care	37.07% [34.48 to	40.00% [32.76 to	44.79% [37.06 to	30.06% [23.27 to
	39.74]	47.69]	52.76]	37.81]

About 1 in 10 patients without ceiling of care died in hospital in the first and second waves. In patients with a ceiling of care, about 4 in 10 patients die in hospital in the first three waves. The percentages are lower in the fourth wave (5% and 30% respectively for patients without and with a ceiling of care).

292 Mortality in patients without ceiling of care

Figure 2A shows the balance of covariates before and after IPW by means of the standardised mean differences (SMD) in patients without a ceiling of care. The SMD for PSI remains above 0.2. To correct for this imbalance, PSI was included in the weighted mortality models.

The odds ratios of the three models for mortality are shown in Figure 3A. The results with the three methods are consistent and show the same trend for all waves. Patients from waves 2, 3 and 4 were less likely to die in hospital than patients from wave 1 both in the raw models and in the models adjusted for covariates or adjusted with weights (OR for all models and all waves lower than 1). In addition, the value of the OR decreases across waves.

⁶⁰ 304 Mortality in patients with ceiling of care

Figure 2B shows the balance of covariates before and after IPW by means of the SMD in patients with a ceiling of care assigned at admission. Age, PSI and race showed a difference between waves greater than 0.2. These variables were included as adjustments in the weighted mortality model to account for these differences. The odds ratios of the three models for mortality are shown in Figure 3B. No

differences were found between 1st and 2nd wave patients or between 1st and 3rd wave patient (neither in the crude nor in the adjusted models). For wave 4th, both adjusted and IPW models showed that, given two patients with the same baseline profile, a wave 4 patient was less likely to die in hospital than a wave 1 patient.

Sensitivity analysis

To account for the assumption of missing at random, we perform a sensitivity analysis using only those patients who had all the variables completed. The results were in the same direction as for the imputed database. In patients with ceiling of care, the effect of the wave in mortality was the same in patients with and without complete data. In patients without ceiling of care the effect was also similar, but as the sample size of the cohort with complete data was smaller, the odds ratio for the 2nd and 3rd waves did not reach statistical significance. Liez

DISCUSSION

Our multicentre cohort study compared in-hospital mortality across COVID-19 waves between patients with and without a ceiling of care at hospital admission. We found that among patients without ceiling of care, those admitted in the first wave had worse in-hospital mortality than patients hospitalized during the other waves. Moreover, the adjusted models showed a significant decrease in mortality as the waves progressed. Among patients with a ceiling of care, no differences in in-hospital mortality were found between second and first wave patients, or between third and first wave patients. Only in the fourth wave, patients were less likely to die than first wave patients after adjustment for baseline risk. The magnitude of this effect on mortality reduction observed in patients with ceiling of care in the 4th wave was similar to the effect observed among patients without ceiling of care in the same 4th wave.

It is worth noting that if the differences in mortality between waves were only due to patient's risk profile, the mortality rates would be similar after adjustment for baseline profile. However, this is not the case, as Figure 3A shows that in the adjusted and weighted models, mortality among patients without ceiling of care decreases as waves progress in time (OR decreasing from 0.56 (second and third wave) to 0.34 (fourth

wave) when comparing with first wave)). The emergency situation experienced by the hospitals in the first months of the pandemic, with a lack of organization prepared to face an emergency such as COVID-19, partly explains the differences observed [29]. Besides, in the first wave, hospital resources (such as ICU beds, number of non-invasive ventilators or high-flow nasal oxygen therapy devices) and human resources were not sufficient to cope with the high demand for medical care [30]. ICU capacity is known to be an important indicator of hospital stress (health system resilience) which is associated with a reduction in quality of care and poorer patient outcomes [31]. In addition, other factors such as the increasing knowledge about the disease, facilitated by the rapid publication of clinical trials analysing new treatments [8], or the impact of public health surveillance measures, such as lockdowns [32] could explain this reduction in mortality. The harvest effect could also explain this decrease in mortality, as deaths that would have occurred anyway in subsequent waves may have been precipitated by the high mortality in the first wave of COVID-19 [33]. Similarly, the aggressiveness of SARS-CoV-2 varied between strains, and may also have played a role in the reduction in mortality [34].

As expected, mortality was higher among patients with ceiling care. In this group of patients, there are no differences in mortality in the first three waves, but there is a decrease in mortality in wave 4 (OR 0.38 95%CI 0.25 to 0.58) (Figure 3B). In Spain, this fourth wave mainly affected young patients. Older patients, who were more likely to be assigned a ceiling of care, were already vaccinated at that time [35]. A study in nursing homes in our geographical area (Catalonia) [36] showed that vaccination was associated with a 95% reduction in mortality among nursing home residents. Studies in Italy and Switzerland also showed that the vaccine was about 95% effective against death in the general population [33,37]. These results therefore suggest that there is no improvement in medical management that affects in-hospital mortality until wave 4, which coincides with the elderly vaccination campaign. The lack of a contrafactual scenario in which people received intensive care makes it difficult to assess any potential benefit. Further research on this topic and replication of these results in other cohorts would be needed. Moreover, it will be of interest to study the management of ceiling of care in other cultural settings. It would also be interesting to investigate whether the impact of ceiling of care is the same on other outcomes, such as complications or length of hospital stay.

The high probability of a new epidemic caused by an infectious organism merits in-depth reflection by the medical and scientific community, in particular to reach a consensus on the definition of ceiling of care and to define a guideline for the management of patients who are candidates for a ceiling of care [38]. In the event of a future pandemic caused by an infectious organism, the challenge will be to improve mortality in patients with ceiling of care. To this end, the scientific community needs to develop an action plan that will enable a rapid response in terms of both human resources (by increasing the number of trained health workers), and facilities (for example, so that the ICUs can quickly increase the number of beds) [39].

Our study has some limitations that should be acknowledged. Excluding subjects who
 were discharged or died within 24 hours of admission may introduce selection bias by
 systematically omitting individuals with atypically short hospital stays. This limitation

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

should be considered when interpreting the generalizability of the study findings. Moreover, we could have residual confounding because even after using all the characteristics available at admission to make the baseline status of patients comparable, there may be unobserved characteristics that make patients different between waves. For example, we knew whether a patient had pathology or not, but we could not take into account how advanced it was. A variable that collects information on patients' frailty at baseline might also be of interest for a better risk assessment. In addition, vaccines and treatments could not be used in the matching: vaccines because they did not exist in the first wave [10] and treatments because they changed drastically between waves due to increasing knowledge about the disease [7,8]. Moreover, we do not have data on the follow-up of patients with regard to treatments received during hospitalization, which could help to understand some of the differences in mortality. Another limitation of the study is that we assumed that the missing values in our data were at random and imputed them using standard techniques. To account for this, a sensitivity analysis was performed repeating the analysis only with patients who had complete information on all variables, and the results were in the same line, confirming the robustness of the analysis. Moreover, we cannot guarantee that the same criteria were used to define the therapeutic ceiling of care in all hospitals. In fact, one of the challenges in clinical practice during the COVID-19 pandemic was to define the ceiling of care for infected patients. Even though the definition of ceiling of care is not a standardized one, the definition in the MetroSud cohort was a pragmatic one which would be readable and understood by clinician teams involved in reaching these decisions. Our definition is consistent with that used in the Leeds cohort [13] and with the one used in a multicentre study to identify factors influencing ceiling of treatment in an Emergency Department [40]. In addition, when the study protocol was written, little was known about COVID-19, including the lack of immunity and the possibility of reinfection. Before the emergence of the Omicron strain, the incidence of COVID-19 reinfection leading to hospitalization was very low (<1%) [41]. Our last wave included patients from July to August 2021, when the Omicron strain had not yet reach Spain and the incidence of reinfection was still very low. However, we could not rule out the possibility that some subjects from the 3rd or 4th wave had previously been included in the study. Due to data protection laws, we did not have access to patients' clinical records, which prevented verification. Nevertheless, participating physicians were aware of this possibility and took measures to avoid case duplication. The strengths of our study are the large number of subjects included from different hospitals and from four different waves of the pandemic, and the availability of information on ceiling of care. In addition, the different methods used to compare in-hospital mortality by waves led to the same results, demonstrating the robustness of the analysis. In conclusion, knowing that the evolution of in-hospital mortality through waves is different in patients with and without ceiling of care could help the scientific community to address the management of patients with ceiling of care to improve their outcomes in a new pandemic scenario. The lessons learned from the COVID-19

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4 5	434 435 436	pandemic could help health-care professional and health policy-makers to face future pandemics.
10 11 12 13 14 15 16 17 18		
19 20 21 22 23 24 25 26 27 28		
29 30 31 32 33 34 35 36 37		
38 39 40 41 42 43 44 45 46		
47 48 49 50 51 52 53 54 55 56 57 58 59 60		

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1		
2 3	437	DECLARATIONS
4 5		
6	438 439	Ethics approval and consent to participate The study was approved by the Bellvitge Hospital Research Ethics Committee with
7	439 440	medicines (CREm), with reference PR140/20 and code HUB-INF-COHORT-HUB-COVID ,
8	440 441	in accordance with Spanish legislation and was performed in accordance with the
9 10	441	Helsinki Declaration of 1964. The need for patient informed consent was waived by the
10	443	ethics committee. Bellvitge's CREm decision was the basis for the approval of the
12	444	remaining hospital centres.
13	445	
14 15	446	
16	447	Competing interests
17	448	Cristian Tebé has received fees for speaker lectures and talks from Gedeon Richter,
18	449	outside the submitted work. The rest of authors declare that they have no competing
19 20	450	interests.
20	451	
22	452	
23	453	Data availability
24	454	The datasets generated during and/or analyzed during the current study are available
25 26	455	from the corresponding author on reasonable request.
27	456	
28	457	
29	458	Funding
30 31	459	This work was partially funded by Secretaria d'Universitats i Recerca del Departament
31	460	d'Empresa i Coneixement de la Generalitat de Catalunya (2020PANDE00148). The
33	461	funding was used to collect data from the 4 th wave.
34	462	This work has also been supported by grant 2021 SGR 01421 (GRBIO) administrated by
35	463	the Departament de Recerca i Universitats de la Generalitat de Catalunya (Spain).
36 37	464	
38	465	
39	466	Acknowledgements
40	467	We thank CERCA Programme/Generalitat de Catalunya for institutional support.
41 42	468	
43	469	Author's contributions
44	470	Author's contributions
45	471	Conceptual design was performed by SV, JCa, CT, and NP.
46 47	472	MetroSud cohort data was provided by SV and JCa.
47 48	473	Statistical analysis was performed by CT and NP.
49	474	The first draft of the manuscript was written by NP and revised by JCa and CT.
50	475	All authors commented on previous versions of the manuscript.
51 52	476	All authors read and approved the final version of the manuscript.
52 53	477	CT is the guarantor.
54	478	
55	479	
56 57	480	
57 58	481	
59	482	
60	-102	

1 2		
3	483	REFERENCES
4 5	484	
6	404	
7	485	1. Zhang SX, Arroyo Marioli F, Gao R, Wang S. A Second Wave? What Do People Mean By
8 9	486	COVID Waves? – A Working Definition of Epidemic Waves [Internet]. Rochester, NY; 2021
9 10	487	[cited 2024 Jan 8]. Available from: https://papers.ssrn.com/abstract=4456241
11	488	2. Unwin RJ. The 1918 Influenza Pandemic: Back to the Future? Kidney Blood Press Res.
12	489	2021;46(5):639–46.
13 14		
15	490	3. Viboud C, Grais RF, Lafont BAP, Miller MA, Simonsen L, Multinational Influenza Seasonal
16	491 492	Mortality Study Group. Multinational Impact of the 1968 Hong Kong Influenza Pandemic: Evidence for a Smoldering Pandemic. J Infect Dis. 2005 Jul 15;192(2):233–48.
17 18	452	
19	493	4. 1968 flu pandemic History, Deaths, & Facts Britannica [Internet]. 2024 [cited 2024 Jan
20	494	4]. Available from: https://www.britannica.com/event/1968-flu-pandemic
21 22	495	5. National Atlas of Spain [Internet]. [cited 2024 Feb 12]. First COVID-19 cases. Available
23	495 496	from: http://nationalatlas.ign.es/wane/First_COVID-19_cases
24	450	nom. http://hationalatias.ign.cs/wane/hist_covid_is_cases
25 26	497	6. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with
20	498	human respiratory disease in China. Nature. 2020 Mar;579(7798):265–9.
28	499	7. Mitjà O, Corbacho-Monné M, Ubals M, Tebé C, Peñafiel J, Tobias A, et al.
29	499 500	Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A
30 31	501	Randomized, Controlled Trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Dec
32	502	6;73(11):e4073–81.
33		
34 35	503	8. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for
36	504	the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 Nov 5;383(19):1813–26.
37	505	9. Thakur V, Bhola S, Thakur P, Patel SKS, Kulshrestha S, Ratho RK, et al. Waves and variants
38 39	506	of SARS-CoV-2: understanding the causes and effect of the COVID-19 catastrophe.
39 40	507	Infection. 2022 Apr;50(2):309–25.
41	F09	10 ENA recommends first COVID 10 vacains for outborisation in the EUL European
42	508 509	 EMA recommends first COVID-19 vaccine for authorisation in the EU European Medicines Agency [Internet]. [cited 2024 Jan 4]. Available from:
43 44	510	https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-
45	511	authorisation-eu
46		
47 48	512	11. Stein C, Nassereldine H, Sorensen RJD, Amlag JO, Bisignano C, Byrne S, et al. Past SARS-
40	513 514	CoV-2 infection protection against re-infection: a systematic review and meta-analysis. The Lancet. 2023 Mar 11;401(10379):833–42.
50	514	THE LANCEL 2023 WAI 11,401(103/3).033-42.
51 52	515	12. Pallarès N, Tebé C, Abelenda-Alonso G, Rombauts A, Oriol I, Simonetti AF, et al.
52 53	516	Characteristics and Outcomes by Ceiling of Care of Subjects Hospitalized with COVID-19
54	517	During Four Waves of the Pandemic in a Metropolitan Area: A Multicenter Cohort Study.
55 56	518	Infect Dis Ther. 2023 Jan;12(1):273–89.
56 57	519	13. Straw S, McGinlay M, Drozd M, Slater TA, Cowley A, Kamalathasan S, et al. Advanced care
58	520	planning during the COVID-19 pandemic: ceiling of care decisions and their implications
59	521	for observational data. BMC Palliat Care. 2021 Jan 11;20(1):10.
60		
4		

1 ว			
2 3	522	1 1	Dess Hersch & Course Discourse V. Cos EV. Dellait Millán M. Mateur L. Dessell & at al. Evoluting
4	522	14.	Roso-Llorach A, Serra-Picamal X, Cos FX, Pallejà-Millán M, Mateu L, Rosell A, et al. Evolving
5	523		mortality and clinical outcomes of hospitalized subjects during successive COVID-19 waves
6	524		in Catalonia, Spain. Glob Epidemiol. 2022 Dec;4:100071.
7	гог	1 Г	Hadharr D. Darazowski M. Carwin K. Marchatti C. Dai F. Jansan DEO, at al. In hasnital
8	525	15.	Hedberg P, Parczewski M, Serwin K, Marchetti G, Bai F, Jensen BEO, et al. In-hospital
9	526		mortality during the wild-type, alpha, delta, and omicron SARS-CoV-2 waves: a
10	527		multinational cohort study in the EuCARE project. Lancet Reg Health – Eur [Internet]. 2024
11	528		Mar 1 [cited 2024 Aug 6];38. Available from:
12	529		https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(24)00021-8/fulltext
13			
14 15	530	16.	Dades COVID [Internet]. [cited 2024 May 13]. Available from: https://dadescovid.cat
16	504	4 7	
17	531	17.	Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap
18	532		consortium: Building an international community of software platform partners. J Biomed
19	533		Inform. 2019;95:103208.
20			
21	534	18.	Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained
22	535		Equations in R. J Stat Softw. 2011 Dec 12;45:1–67.
23			
24	536	19.	Statistical Analysis with Missing Data Wiley Series in Probability and Statistics [Internet].
25	537		[cited 2023 Aug 17]. Available from:
26	538		https://onlinelibrary.wiley.com/doi/book/10.1002/9781119013563
27			
28 29	539	20.	Austin PC, Stuart EA. Moving towards best practice when using inverse probability of
29 30	540		treatment weighting (IPTW) using the propensity score to estimate causal treatment
31	541		effects in observational studies. Stat Med. 2015;34(28):3661–79.
32			
33	542	21.	Hu L, Gu C, Lopez M, Ji J, Wisnivesky J. Estimation of causal effects of multiple treatments
34	543		in observational studies with a binary outcome. Stat Methods Med Res. 2020
35	544		Nov;29(11):3218–34.
36			
37	545	22.	von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The
38	546		Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
39	547		statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008
40	548		Apr;61(4):344–9.
41 42			
42 43	549	23.	R: The R Project for Statistical Computing [Internet]. [cited 2022 Jul 12]. Available from:
44	550		https://www.r-project.org/
45			
46	551	24.	Satorra P, Carmezim J, Pallarés N, Tebé C. flowchart: Tidy Flowchart Generator [Internet].
47	552		2024 [cited 2024 Mar 4]. Available from: https://cran.r-
48	553		project.org/web/packages/flowchart/index.html
49			
50	554	25.	Carmezim J, Satorra P, Peñafiel J, García-Lerma E, Pallarès N, Santos N, et al. REDCapDM:
51	555		An R package with a set of data management tools for a REDCap project. BMC Med Res
52	556		Methodol. 2024 Mar 1;24(1):55.
53			
54 55	557	26.	Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies [Internet].
55 56	558		2023 [cited 2023 Aug 17]. Available from: https://cran.r-
50 57	559		project.org/web/packages/WeightIt/index.html
58			
59	560	27.	Greifer N. cobalt: Covariate Balance Tables and Plots [Internet]. 2023 [cited 2023 Aug 17].
60	561		Available from: https://cran.r-project.org/web/packages/cobalt/index.html

1			
2 3	562	3. CRAN - Package survey [Internet]. [cited 2023 Oct 23]. Available from: https://cran.r-	
4 5	563	project.org/web/packages/survey/index.html	
6	564	9. Garcia-Carretero R, Vazquez-Gomez O, Gil-Prieto R, Gil-de-Miguel A. Hospitalization	
7	565	burden and epidemiology of the COVID-19 pandemic in Spain (2020–2021). BMC Infect	
8 9	566	Dis. 2023 Jul 18;23(1):476.	
9 10			
11	567). Osorio J, Madrazo Z, Videla S, Sainz B, Rodríguez-Gonzalez A, Campos A, et al. Use of	
12	568	failure-to-rescue after emergency surgery as a dynamic indicator of hospital resilience	
13	569	during the COVID-19 pandemic. A multicenter retrospective propensity score-matched	
14 15	570	cohort study. Int J Surg Lond Engl. 2022 Oct;106:106890.	
16	571	. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department	
17 18	572	crowding: A systematic review of causes, consequences and solutions. PLoS ONE. 2018	
18	573	Aug 30;13(8):e0203316.	
20		Circuster CA des C de Ensites VAU. Consels Made C. Conselles M. Oliveres Estenses A. de	
21	574 575	2. Siqueira CA dos S, de Freitas YNL, Cancela M de C, Carvalho M, Oliveras-Fabregas A, de	
22	575 576	Souza DLB. The effect of lockdown on the outcomes of COVID-19 in Spain: An ecological	
23 24	576	study. PLoS ONE. 2020 Jul 29;15(7):e0236779.	
24 25	577	3. Riou J, Hauser A, Fesser A, Althaus CL, Egger M, Konstantinoudis G. Direct and indirect	
26	578	effects of the COVID-19 pandemic on mortality in Switzerland. Nat Commun. 2023 Jan	
27	579	6;14(1):90.	
28	0.0		
29	580	I. Comparing the risk of death involving coronavirus (COVID-19) by variant, England - Office	
30 21	581	for National Statistics [Internet]. [cited 2024 Feb 14]. Available from:	
31 32	582	https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofd	
33	583	eath/articles/comparingtheriskofdeathinvolvingcoronaviruscovid19byvariantengland/dece	
34	584	mber2021	
35			
36	585	5. Belvis F, Aleta A, Padilla-Pozo Á, Pericàs JM, Fernández-Gracia J, Rodríguez JP, et al. Key	
37 38	586	epidemiological indicators and spatial autocorrelation patterns across five waves of	
38 39	587	COVID-19 in Catalonia. Sci Rep. 2023 Jun 15;13(1):9709.	
40	588	5. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina F, et al. Associations	
41	589	of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death	
42	590	with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort	
43	591	study. BMJ. 2021 Aug 18;374:n1868.	
44 45	221		
45 46	592	7. Homan T, Mazzilli S, Chieti A, Musa A, Roth A, Fortunato F, et al. Covid-19 vaccination	
47	593	programme effectiveness against SARS-CoV-2 related infections, hospital admissions and	
48	594	deaths in the Apulia region of Italy: a one-year retrospective cohort study. Sci Rep. 2022	
49	595	Nov 3;12:18597.	
50			
51 52	596	3. Rubio O, Estella A, Cabre L, Saralegui-Reta I, Martin MC, Zapata L, et al. Recomendaciones	
52 53	597	éticas para la toma de decisiones difíciles en las unidades de cuidados intensivos ante la	
54	598	situación excepcional de crisis por la pandemia por COVID-19: revisión rápida y consenso	
55	599	de expertos. Med Intensiva. 2020 Oct;44(7):439–45.	
56	600		
57	600 601). Grant R, Benamouzig D, Catton H, Cheng VCC, Dhingra N, Laxminarayan R, et al. COVID-19	
58	601	pandemic: a catalyst for accelerating global action on patient safety. Lancet Infect Dis.	
59 60	602	2023 Oct;23(10):1108–10.	
00			

- 40. Walzl N, Jameson J, Kinsella J, Lowe DJ. Ceilings of treatment: a qualitative study in the
 emergency department. BMC Emerg Med. 2019 Jan 17;19(1):9.
- 41. Lin W, Kung KH, Chan CL, Chuang SK, Au KW. Characteristics and risk factors associated
 with COVID-19 reinfection in Hong Kong: a retrospective cohort study. Epidemiol Infect.
 2025 Feb 7;153:e30.

611 FIGURE LEGENDS

FIGURE 1: Flow-chart of the included patients without ceiling of care (left) and withceiling of care (right).

- 614 FIGURE 2: Maximum standardized mean differences (SMD) before (Unmatched) and
- 615 after weighting (Matched) across waves for patients without a ceiling of care (A) and
- 616 patients with ceiling of care (B). The standardized mean difference compares the
- 617 difference in means between all pairs of waves in standard deviation units.
- FIGURE 3: OR for raw, adjusted and IPTW models for in-hospital mortality in patientswithout a ceiling of care (A) and with ceiling of care (B).

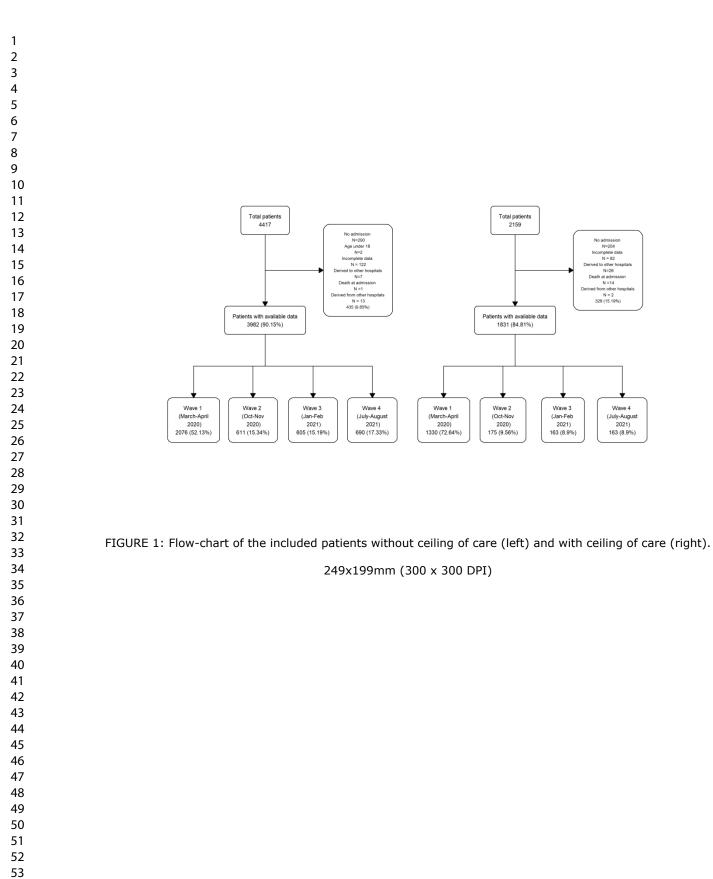
No admis N=2(

N =14

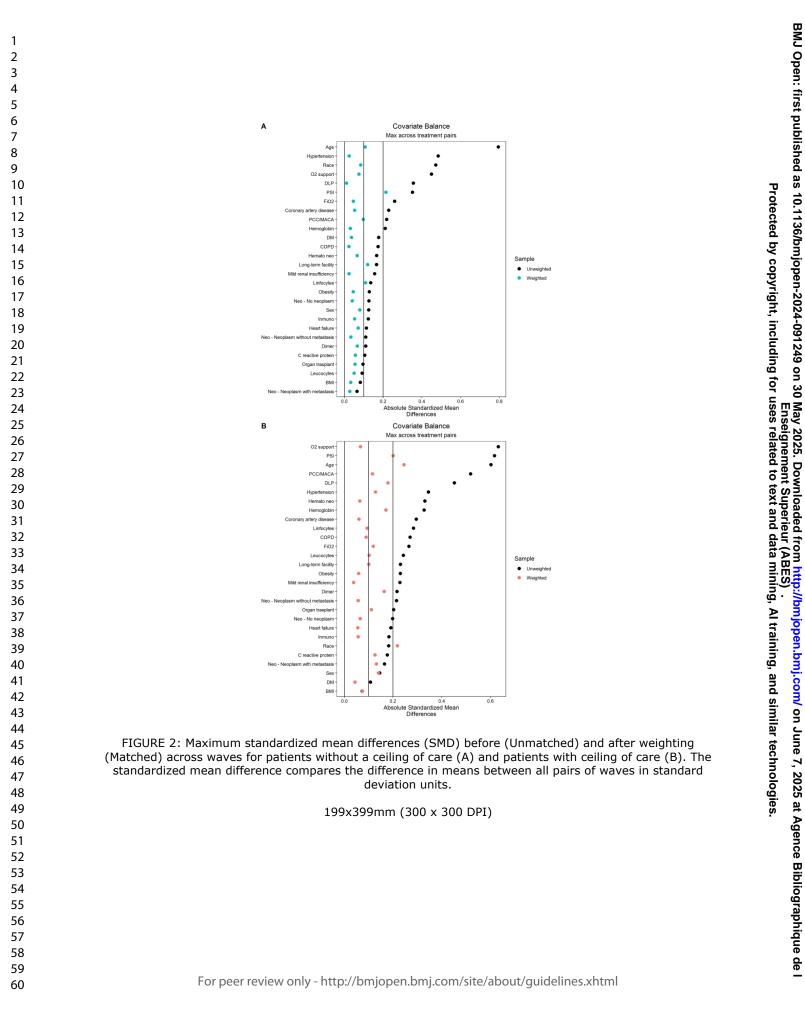
Wave 4 (July-August 2021)

163 (8.9%)

328 (15



59 60



3			
4			
5 6			
6 7	Α		
8 9			OR [95% CI]
	2nd wave (vs 1st wav	e)	
10	Raw	· ++-	0.96 [0.71-1.30]
11	Adjusted	- ■ - '	0.55 [0.39-0.80]
12	IPTW	¦-∎-	0.56 [0.40-0.80]
13			
14	3rd wave (vs 1st wave	a)	
15	Raw	, ⊢∎-∣	0.70 [0.50-0.98]
16	Adjusted		0.45 [0.30-0.67]
17	IPTW	┝┻┤	
18	IF I VV		0.56 [0.37-0.84]
19			
20	4th wave (vs 1st wave	1 1	
21	Raw	╞╋┤	0.47 [0.33-0.68]
22	Adjusted	-■-	0.44 [0.28-0.67]
23	IPTW		0.34 [0.21-0.56]
24		0.25 0.50 1.0 2.0	4.0
25	В		
26			
27			OR [95% CI]
28	2nd wave (vs 1st wav	e)	
29	Raw	, =-	1.13 [0.82-1.56]
30	Adjusted	-∎-	0.74 [0.51-1.07]
31	IPTW	┝╼┤	0.78 [0.51-1.20]
32		1 - 1	
33	3rd wave (vs 1st wave	a)	
34	Raw	c) ∟∎	1 28 [0 00 1 01]
35			1.38 [0.99-1.91] 1.07 [0.72-1.57]
36	Adjusted		
37	IPTW	╞╼	1.27 [0.84-1.92]
38			
39	4th wave (vs 1st wave		
40	Raw	-■-	0.73 [0.51-1.04]
41	Adjusted		0.40 [0.27-0.61]
42	IPTW		0.38 [0.25-0.58]
43		0.25 0.50 1.0 2.0	4.0
44			
45	FIGURE 3: OR for raw, adjusted and IPTW mode	ls for in-hos	pital mortality in patients without a ceiling of
46	care (A) and v	vith ceiling o	f care (B).
47			
48	299x599m	m (300 x 30	00 DPI)
49			
50			
51			
52			
53			
55			
55			
55			
57			
58			

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

SUPPLEMENTAL MATERIAL

Table S1: Variables used in the matching procedure according to wave and ceiling of care

	No ceilir	ng of care						
	Wave 1				Wave 1			
	(Mar-	Wave 2	Wave 3	Wave 4	(Mar-	Wave 2	Wave 3	Wave
	Apr	(Oct-	(Jan-	(July-	Apr	(Oct-	(Jan-	(July
	2020)	Nov	Feb	Aug	2020)	Nov	Feb	Aug
	N =	2020)	2021)	2021)	N =	2020)	2021)	2021
	2076	N = 611	N = 605	N = 690	1330	N = 175	N = 163	N = 16
Long-term facility								
Yes	64 (3.1%)	19 (3.1%)	17 (2.8%)	4 (0.6%)	223 (17%)	20 (11%)	20 (12%)	15 (9.2%)
	28.9	29.2	29.4	29.7	28.1	28.7	29.3	27.6
BMI	(25.9, 32.2)	(26.4, 32.6)	(26.6, 32.9)	(26.4, 33.6)	(25.4, 31.3)	(25.8, 31.5)	(26.0, 31.5)	(24.8, 31.8)
Unknown	636	103	72	177	456	22	19	17
PCC/MACA								
PCC/MACA	93 (4.5%)	32 (5.2%)	15 (2.5%)	9 (1.3%)	290 (22%)	80 (46%)	47 (29%)	57 (35
Diabetes mellitu	IS							
Yes	418 (20%)	124 (20%)	126 (21%)	96 (14%)	414 (31%)	61 (35%)	54 (33%)	59 (369
COPD								
				110	325			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	No ceilin	g of care			Ceiling o	f care		
	Wave 1 (Mar- Apr 2020) N = 2076	Wave 2 (Oct- Nov 2020) N = 611	Wave 3 (Jan- Feb 2021) N = 605	Wave 4 (July- Aug 2021) N = 690	Wave 1 (Mar- Apr 2020) N = 1330	Wave 2 (Oct- Nov 2020) N = 175	Wave 3 (Jan- Feb 2021) N = 163	Wav (Jul Au 202 N = 1
Yes	50 (2.4%)	18 (2.9%)	27 (4.5%)	25 (3.6%)	194 (15%)	37 (21%)	31 (19%)	36 (2
Hypertension								
Yes	792 (38%)	266 (44%)	295 (49%)	176 (26%)	881 (66%)	137 (78%)	124 (76%)	132 (81%)
Obesity								
Yes	579 (35%)	221 (36%)	248 (41%)	248 (36%)	285 (29%)	51 (29%)	65 (40%)	50 (3
Unknown	404	0	0	0	361	0	0	0
Dyslipidemia								
Yes	698 (34%)	223 (36%)	239 (40%)	158 (23%)	502 (38%)	105 (60%)	92 (56%)	83 (5
Mild renal insufficiency								
Yes	83 (4.0%)	27 (4.4%)	42 (6.9%)	25 (3.6%)	234 (18%)	42 (24%)	26 (16%)	41 (2
Coronary artery disease								
Yes	91 (4.4%)	33 (5.4%)	28 (4.6%)	7 (1.0%)	112 (8.4%)	26 (15%)	30 (18%)	19 (1

	No ceilin	g of care			Ceiling o	f care		
	Wave 1 (Mar- Apr 2020) N = 2076	Wave 2 (Oct- Nov 2020) N = 611	Wave 3 (Jan- Feb 2021) N = 605	Wave 4 (July- Aug 2021) N = 690	Wave 1 (Mar- Apr 2020) N = 1330	Wave 2 (Oct- Nov 2020) N = 175	Wave 3 (Jan- Feb 2021) N = 163	Wave 4 (July- Aug 2021) N = 163
Haematological neoplasm								
Yes	12 (0.6%)	16 (2.6%)	7 (1.2%)	12 (1.7%)	27 (2.0%)	8 (4.6%)	7 (4.3%)	15 (9.2%)
Organ transplant								
Yes	20 (1.0%)	13 (2.1%)	6 (1.0%)	13 (1.9%)	12 (0.9%)	0 (0%)	3 (1.8%)	1 (0.6%)
Immunology								
Yes	72 (3.5%)	32 (5.2%)	17 (2.8%)	32 (4.6%)	50 (3.8%)	6 (3.4%)	11 (6.7%)	5 (3.1%)
Neoplasm								
No neoplasm	1991 (96%)	578 (95%)	563 (93%)	656 (95%)	1160 (87%)	141 (81%)	136 (83%)	130 (80%)
Neoplasm without metastasis	78 (3.8%)	30 (4.9%)	37 (6.1%)	30 (4.3%)	145 (11%)	26 (15%)	22 (13%)	30 (18%
Neoplasm with metastasis	7 (0.3%)	3 (0.5%)	5 (0.8%)	4 (0.6%)	25 (1.9%)	8 (4.6%)	5 (3.1%)	3 (1.8%)
D-dimer	570 (316, 1050)	530 (284, 970)	500 (266, 895)	365 (250, 690)	722 (378, 1608)	689 (356, 1438)	471 (280, 969)	451 (276, 895)
Unknown	488	55	62	59	384	19	29	19

	No ceilin	g of care			Ceiling o	f care		
	Wave 1				Wave 1			
	(Mar-	Wave 2	Wave 3	Wave 4	(Mar-	Wave 2	Wave 3	Wave
	Apr	(Oct-	(Jan-	(July-	Apr	(Oct-	(Jan-	(July-
	2020)	Nov	Feb	Aug	2020)	Nov	Feb	Aug
	N =	2020)	2021)	2021)	N =	2020)	2021)	2021)
	2076	N = 611	N = 605	N = 690	1330	N = 175	N = 163	N = 163
C reactive protein	80 (34, 149)	84 (39, 143)	76 (39, 128)	85 (41, 144)	92 (47, 160)	86 (41, 144)	96 (44, 148)	69 (30, 155)
Unknown	161	30	54	36	102	6	24	8
	13.90	13.60	13.90	14.05	13.30	12.50	12.80	12.50
Haemoglobin	(12.90,	(12.50,	(12.80,	(13.10,	(12.00,	(11.00,	(11.60,	(11.20,
	14.90)	14.80)	15.00)	15.10)	14.43)	14.40)	13.60)	13.80)
Unknown	150	21	40	24	82	6	15	5
	0.98	0.91	0.91	0.93	0.90	0.85	0.80	0.90
Lymphocytes	(0.72,	(0.66,	(0.64,	(0.66,	(0.63,	(0.57,	(0.54,	(0.59,
	1.33)	1.26)	1.23)	1.24)	1.24)	1.18)	1.13)	1.36)
Unknown	137	21	40	28	105	6	15	5
1	6.5 (5.0,	6.5 (5.0,	6.4 (5.0,	6.2 (4.6,	6.9 (5.2,	7.2 (5.4,	6.5 (5.0,	6.9 (5.4
Leucocytes	8.7)	9.0)	8.6)	8.6)	9.2)	9.4)	8.7)	9.6)
Unknown	109	23	40	26	71	6	15	6
FiO2	21 (21,	21 (21,	21 (21,	21 (21,	21 (21,	21 (21,	21 (21,	24 (21,
	21)	28)	28)	31)	24)	28)	35)	31)
Unknown	2	0	0	0	3	0	0	0
Need for oxygen	511 (25%)	193 (32%)	234 (39%)	316 (46%)	345 (26%)	69 (39%)	77 (47%)	92 (569
support	(2)/0)	(3270)	(0/0)	(4070)	(2070)			
Unknown	2	0	0	0	3	0	0	0

Median (IQR) for continuous variables; n (%) for categorical variables

1									
2 3 4		No ceilir	ng of care			Ceiling c	of care		
5 6 7 8 9 10 11 12		Wave 1 (Mar- Apr 2020) N =	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave 4 (July- Aug 2021)	Wave 1 (Mar- Apr 2020) N =	Wave 2 (Oct- Nov 2020)	Wave 3 (Jan- Feb 2021)	Wave 4 (July- Aug 2021)
13 14 15		2076	N = 611	N = 605	N = 690	1330	N = 175	N = 163	N = 163
16 17	BMI: Body m	nass index							
18 19	COPD: Chro	onic obstructive p	oulmonary d	lisease					
20 21	PCC: chronic	c complex patien	t						
22 23 24	MACA: adva	inced chronic dis	ease patien	t					
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41			ease patien						
42 43 44 45 46 47 48 49 50 51 51 52 53 54 55 56									