



**Figure S1** Internal protocol indicating criteria used for triggering the evaluation for ICU admission. COVID-19, coronavirus disease 2019; RR, respiratory rate; HFNC, high-flow nasal cannulae; NEWS, National Early Warning Score; SpO<sub>2</sub>, oxygen peripheral saturation; tp, therapy; LDH, lactate dehydrogenase; BMI, body mass index; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation.

**Table S1** Baseline characteristics and process-of-care of the patients undergoing IMV during the study period with the comparison between waves

Baseline	All population (n=268)	First wave (n=78)	Second wave (n=104)	Third wave (n=86)	P value
Age (years), median [IQR]	67 [61–73]	65 [60–72]	69 [63–74]	66 [56–74]	0.116
Sex (male), n (%)	207 (77.2)	63 (80.8)	84 (80.8)	60 (69.8)	0.134
SOFA, median [IQR]	4 [4–6]	4 [3–6]	5 [4–7]	4 [4–5]	<0.001
SAPS II, median [IQR]	36 [32–43]	34 [27–40]	39 [35–46]	35 [30–39]	<0.001
BMI (kg/m <sup>2</sup> ), median [IQR]	29 [26–33]	27.8 [24.7–0.5]	29.4 [26.0–34.0]	30.5 [26–35]	0.011
D-dimer (ng/mL), median [IQR]	1,620 [890–3,180]	1,915 [965–3,525]	1,580 [840–3,565]	1,345 [840–2,590]	0.149
Lymphocyte count (cells/mL), median [IQR]	0.61 [0.43–0.89]	0.59 [0.40–0.85]	0.64 [0.46–0.90]	0.64 [0.41–0.85]	0.535
Platelet count (1,000/mm <sup>3</sup> ), median [IQR]	209 [160–284]	216 [160–286]	203 [160–264]	221 [157–294]	0.618
LDH (U/L), median [IQR]	837 [657–1,126]	803 [662–1,096]	823 [655–1,144]	915 [658–1,135]	0.595
CRP (mg/dL), median [IQR]	11.2 [3.0–19.9]	16.2 [7.6–23.8]	7.9 [1.3–18.4]	5.8 [2.2–15.1]	<0.001
PCT (ng/mL), median [IQR]	0.3 [0.1–0.9]	0.42 [0.20–1.30]	0.30 [0.12–0.80]	0.2 [0.1–0.5]	0.009
Steroids administration, n (%)	237 (88.4)	51 (65.4)	102 (98.1)	84 (97.7)	<0.001
Methylprednisolone, n (%)	154 (57.5)	51 (65.4)	61 (58.7)	42 (48.8)	0.096
Dexamethasone, n (%)	83 (31)	0 (0.0)	41 (39.4)	42 (48.8)	<0.001
Tocilizumab, n (%)	204 (76.1)	39 (50)	82 (78.8)	83 (96.5)	<0.001

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IMV, invasive mechanical ventilation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; BMI, body mass index; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin.

**Table S2** Main outcomes in patients undergoing IMV and the comparison between different waves

Outcomes	All population (n=268)	First wave (n=78)	Second wave (n=104)	Third wave (n=86)	P value
ICU mortality, n (%)	102 (38.9)	28 (35.9)	45 (43.3)	29 (33.7)	0.361
ICU-free days at day 90, median [IQR]	69.5 [0–81]	74 [0–81]	45 [0–80]	79 [0–84]	0.022
Hospital mortality, n (%)	126 (47.0)	35 (44.9)	58 (55.8)	33 (38.4)	0.052
Hospital-free days at day 90, median [IQR]	26 [0–66]	37 [0–62]	0 [0–56]	59 [0–79]	0.001
Invasive VFDs at day 30, median [IQR]	3 [0–25]	9.5 [0–25]	1 [0–21]	11 [0–26]	0.004
Tracheostomy, n (%)	84 (31.3)	15 (19.2)	40 (38.5)	29 (33.7)	0.018
Bacterial infection, n (%)	143 (53.4)	31 (39.7)	58 (55.8)	54 (62.8)	0.010

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IMV, invasive mechanical ventilation; ICU, intensive care unit; IQR, interquartile range; VFD, ventilation-free day.

**Table S3** HRs and CI obtained by unadjusted univariate and adjusted Cox regression analysis for in-hospital mortality censored at day 90 in patients undergoing IMV

Variables included in regression analysis	Survived (n=142)	Not survived (n=126)	Unadjusted HR (95% CI), P value	Adjusted HR (95% CI), P value
Age (years), median [IQR]	65 [55–72]	69 [63–75]	1.03 (1.02–1.05), <0.001	1.01 (0.99–1.03), 0.257
SAPS II score, median [IQR]	35 [30–40]	38 [35–44]	1.02 (1.01–1.04), 0.001	1.02 (0.99–1.04), 0.094
LDH (U/L), median [IQR]	803 [656–1,701]	935 [671–1,271]	1.00 (1.00–1.00), 0.008	1.00 (1.00–1.00), 0.028
Platelet count (1,000/mm <sup>3</sup> ), median [IQR]	232 [182–294]	189 [140–249]	0.99 (0.99–0.99), 0.001	0.99 (0.99–1.00), 0.015
Dexamethasone, n (%)	59 (41.5)	24 (19.0)	0.45 (0.29–0.70), <0.001	0.63 (0.38–1.02), 0.061
Tocilizumab, n (%)	120 (84.5)	99 (78.6)	0.74 (0.48–1.13), 0.157	–
Bacterial infection, n (%)	54 (38.0)	89 (70.6)	2.35 (1.60–3.45), <0.001	2.08 (1.36–3.17), 0.001
Wave, n (%)				
1 <sup>st</sup> wave (February 25 <sup>th</sup> , 2020–July 6 <sup>th</sup> , 2020)	43 (30.3)	35 (27.8)	1	1
2 <sup>nd</sup> wave (September 20 <sup>th</sup> , 2020–February 13 <sup>th</sup> , 2021)	46 (32.4)	58 (46.0)	1.19 (0.79–1.82), 0.404	0.98 (0.59–1.61), 0.928
3 <sup>rd</sup> wave (February 14 <sup>th</sup> , 2021–April 30 <sup>th</sup> , 2021)	53 (37.3)	33 (26.2)	0.74 (0.46–1.19), 0.215	0.68 (0.40–1.15), 0.149

Data for survived and not survived during hospital stay are also reported. P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. HR, hazard ratio; CI, confidence interval; IMV, invasive mechanical ventilation; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; LDH, lactate dehydrogenase.

**Table S4** Baseline characteristics and process-of-care of the patients in the propensity matched analysis with the comparison between waves

Baseline	All population (n=290)	First-second wave matched (n=145)	Third wave matched (n=145)	P value
Age (years), median [IQR]	64 [56–72]	65 [59–72]	63 [53–72]	0.122
Sex (male), n (%)	215 (74.1)	115 (79.3)	100 (69.0)	0.044
SAPS II, median [IQR]	35 [28–39]	34 [28–39]	35 [28–39]	0.840
Comorbidities, n (%)	176 (60.7)	86 (59.3)	90 (62.1)	0.631
CRP (mg/dL), median [IQR]	5.4 [1.5–15.1]	5.8 [2.0–15.3]	47 [1.3–14.6]	0.310
PCT (ng/mL), median [IQR]	0.2 [0.1–0.5]	0.2 [0.1–0.5]	0.1 [0.1–0.4]	0.970
Steroids administration, n (%)	265 (91.4)	122 (84.1)	143 (98.6)	<0.001
Dexamethasone, n (%)	128 (44.1)	39 (26.9)	89 (61.4)	<0.001
Tocilizumab, n (%)	248 (85.5)	110 (75.9)	138 (95.2)	<0.001

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; CRP, C-reactive protein; PCT, procalcitonin.

**Table S5** Main outcomes of the patients in the propensity matched analysis and the comparison between different waves

Outcomes	All population (n=290)	First-second wave matched (n=145)	Third wave (n=145)	P value
Hospital mortality, n (%)	92 (31.7)	54 (37.2)	38 (26.2)	0.044
IMV, n (%)	178 (61.4)	95 (65.5)	83 (57.2)	0.148
Invasive VFDs at day 30, median [IQR]	25 [0–30]	20 [0–30]	27 [7–30]	<0.001
Tracheostomy, n (%)	59 (20.3)	30 (20.7)	29 (20.0)	0.884
Bacterial infection, n (%)	116 (40.0)	58 (40.0)	58 (40.0)	1.000

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant:  $P < 0.05$ . IMV, invasive mechanical ventilation; VFD, ventilation-free day; IQR, interquartile range.

**Table S6** HRs and CI obtained by unadjusted univariate and adjusted Cox regression analysis for in-hospital mortality censored at day 90 of the patients in the propensity matched analysis

Variables included in regression analysis	Survived (n=198)	Not survived (n=92)	Unadjusted HR (95% CI), P value	Adjusted HR (95% CI), P value
Age (years), median [IQR]	63 [53–71]	69 [62–74]	1.04 (1.02–1.06), <0.001	1.00 (0.98–1.03), 0.929
SAPS II score, median [IQR]	33 [28–38]	36 [34–43]	1.05 (1.03–1.07), <0.001	1.03 (0.99–1.05), 0.076
Comorbidities, n (%)	112 (56.6)	64 (69.6)	1.55 (1.00–2.42), 0.053	–
CRP (mg/dL), median [IQR]	4.9 [1.5–14.4]	6.2 [1.7–17.2]	1.02 (0.99–1.04), 0.120	1.02 (0.99–1.04), 0.170
Dexamethasone, n (%)	108 (54.5)	20 (21.7)	0.31 (0.19–0.50), <0.001	0.56 (0.33–0.95), 0.033
IMV, n (%)	94 (47.5)	84 (91.3)	8.60 (4.16–17.78), <0.001	4.29 (1.99–9.25), <0.001
Bacterial infection, n (%)	47 (23.7)	69 (75.0)	5.64 (3.51–9.07), <0.001	2.69 (1.59–4.56), <0.001
Waves, n (%)				
1 <sup>st</sup> and 2 <sup>nd</sup> wave matched	91 (46.0)	54 (58.7)	1	1
3 <sup>rd</sup> wave matched	107 (54.0)	38 (41.3)	0.64 (0.42–0.97), 0.034	0.72 (0.47–1.12), 0.148

Data for survived and not survived during hospital stay are also reported. P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant:  $P < 0.05$ . HR, hazard ratio; CI, confidence interval; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; CRP, C-reactive protein; IMV, invasive mechanical ventilation.