

RESEARCH ARTICLE

Admission criteria in critically ill COVID-19 patients: A physiology-based approach

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Abstract

Introduction

The COVID-19 pandemic required careful management of intensive care unit (ICU) admissions, to reduce ICU overload while facing limitations in resources. We implemented a standardized, physiology-based, ICU admission criteria and analyzed the mortality rate of patients refused from the ICU.

Materials and methods

In this retrospective observational study, COVID-19 patients proposed for ICU admission were consecutively analyzed; Do-Not-Resuscitate patients were excluded. Patients presenting an oxygen peripheral saturation (SpO₂) lower than 85% and/or dyspnea and/or mental confusion resulted eligible for ICU admission; patients not presenting these criteria remained in the ward with an intensive monitoring protocol. Primary outcome was both groups' survival rate. Secondary outcome was a sub analysis correlating SpO₂ cutoff with ICU admission.

Results

From March 2020 to January 2021, 1623 patients were admitted to our Center; 208 DNR patients were excluded; 97 patients were evaluated. The *ICU-admitted* group (n = 63) mortality rate resulted 15.9% at 28 days and 27% at 40 days; the *ICU-refused* group (n = 34) mortality rate resulted 0% at both intervals (p < 0.001). With a SpO₂ cut-off of 85%, a significant correlation was found (p = 0.009), but with a 92% a cut-off there was no correlation with ICU admission (p = 0.26). A similar correlation was also found with dyspnea (p = 0.0002).

Conclusion

In COVID-19 patients, standardized ICU admission criteria appeared to safely reduce ICU overload. In the absence of dyspnea and/or confusion, a SpO₂ cutoff up to 85% for ICU

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admission was not burdened by negative outcomes. In a pandemic context, the SpO₂ cutoff of 92%, as a threshold for ICU admission, needs critical re-evaluation.

Introduction

In a dramatic situation such as the COVID-19 pandemic, a careful definition of the intensive care unit (ICU) admission criteria is required [1], with the aim to avoid inappropriate resources abuse and to provide adequate patient-tailored management. Clinicians should in fact distinguish between patients who will benefit from ICU admission and those who are unlikely to benefit from it, in order to avoid inappropriately invasive and traumatic measures in those at high risk for poor outcome despite intensive treatment [1–3]. In this regard, triage regulations based on appropriate and accepted ethical principles have been developed in Switzerland, in order to reserve ICU admission only to those who will actually benefit from an intensive medical intervention [4].

Due to the out-of-ordinary pandemic situation, with the concomitant lack of human and material resources, it was relevant to define clear guidelines for ICU admission, with rules respecting ethical principles and structured on the health-system specific medical resources and ICU limits [4]. As a consequence of this peculiar setting, restricting decisions were necessary [5].

Patients affected by SARS-CoV-2 interstitial pneumonia often present with tachypnea and desaturation without dyspnea or respiratory distress, defined as “silent hypoxemia” [6, 7]. The SpO₂ equal or less than 92%, despite maximum oxygen supplementation with a rebreathing mask, is usually defined as the indication of mechanical ventilation [8–11]. However, during the emerging pandemic, preliminary empirical experience showed that patients with SpO₂ lower than 92% presented with a good tolerance to the silent hypoxemia. For this reason, the SpO₂ threshold of 85% was arbitrarily determined by our group as definition of silent hypoxemia, which is in accord with the findings of Sohrabi C et al [6] and Harutyunyan et al [7].

We conceived and implemented a standardized procedure in our COVID-19 Center in South Switzerland, based on well-determined criteria for ICU admission, which were mainly based on patient’s respiratory pathophysiology. Aim of this study was to analyze the mortality rate and the clinical characteristics of patients assessed for eventual ICU admission, based on these established criteria.

Materials and methods

Study population and data

A retrospective analysis was conducted on consecutive patients with acute respiratory distress syndrome due to COVID-19 pneumonia, triaged for ICU admission from March 2020 to January 2021 in a single COVID-19 center. According to WHO guidelines [12], SARS-COV-2 laboratory confirmation was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) on nasal and pharyngeal swabs. After in-hospital admission, according to the Swiss Academy of Medical Sciences (SAMS) criteria [5, 8], patients were assigned a Do-Not-Resuscitate (DNR) order if they satisfied the following criteria: endotracheal intubation refusal, hypoxia-related cardiocirculatory arrest, ongoing metastatic oncological disease, end-stage neurodegenerative disease and severe, irreversible chronic diseases like heart failure NYHA IV, COPD GOLD D, liver cirrhosis Child-Pugh > 8, and severe dementia. These patients were consequently excluded from the possibility of ICU admission and were

instead followed by specialists in palliative care, as well as treated according to current standards [9]. They were not further referred for consultation regarding ICU admission during their hospital stay.

For a standardized evaluation of patients admitted to the hospital who resulted eligible for ICU admission, the Early Warning Score (EWS) was applied by nursing and medical staff [9, 10]. The daily frequency of EWS evaluation was performed based on the patients' clinical condition: for EWS less than 4, the evaluation was performed four times a day, while for EWS greater than 5, the evaluation was performed up to twice an hour [9]. For EWS equal or greater than 7, an Intensivist consultation was required.

ICU evaluation criteria

With the aim to quickly identify patients with worsened clinical conditions [5, 11] and to avoid ICU overload, the Intensivist Consultant evaluated patient's symptoms, peripheral oxygen saturation (SpO_2), blood gas analysis values and clinical status. Patients with a partial respiratory failure with a SpO_2 lower than 85% at maximum oxygen supplementation with non-rebreathing mask and new onset dyspnea (and/or new onset mental confusion) were eligible for ICU admission (*ICU-admitted* group). Dyspnea was defined as a sensation of new onset subjectively reported by the patient and confirmed with a functional assessment scales, such as MRC 5 as dyspnea at rest [13]. Patients admitted to the ICU immediately underwent endotracheal intubation and invasive mechanical ventilation as standard of care. Patients who did not meet the previously mentioned ICU inclusion criteria (*ICU-refused* group) were followed in their clinical course until the ICU criteria were met or a clinical improvement was achieved. DNR patients, as previously mentioned, were not included in these evaluations. The mortality rate of both groups at 28 and 40 days was compared thereafter. Demographics, clinical data and laboratory/radiological results collected during patient's hospitalization were extrapolated from electronic health records.

Outcomes

Primary endpoint was the determination of the survival rate in *ICU-refused* and *ICU-admitted* groups at 28 and 40 days, further comparing the mortality rate between two groups. Secondary endpoint was a comparison between the two groups in relation to clinical and biological aspects, in order to determine any predictive variables associated with ICU admission. These included demographic characteristics (such as age, gender, body-mass-index—BMI), comorbidities (such as arterial hypertension, ischemic heart disease, diabetes, obstructive sleep apnea syndrome—OSAS—and chronic obstructive pulmonary disease—COPD), hemodynamic and respiratory parameters (systolic and diastolic blood pressure, heart rate, temperature, lactate, SpO_2 , partial pressure of oxygen— pO_2 , partial pressure of carbon dioxide— pCO_2 , the need for oxygen therapy and the presence of dyspnea at ICU admission) and prognostic score system like SAPS, NEMS and SOFA. Although these scores are specific for the ICU evaluation, we applied them to the *ICU-refused* group at the day of the Intensivist Consultation to verify and stratify the severity of their disease. A specific analysis on patients' hypoxia distribution between two groups according to SpO_2 cut-offs of 92% [14–17] vs 85% was also performed.

Statistical analysis

Descriptive statistic was performed to summarize the collected clinical data. Data were presented as mean (SD) or median (IQR) for continuous variables, according to data distribution, and as absolute number (and percentage) for categorical variables; data distribution was verified by Kolmogorov-Smirnov test and Shapiro–Wilk test. Differences between patient

outcomes were studied by t-test for independent groups or by Mann-Whitney test if non-parametric analysis was required. Similarly, comparison of clinical evolution over time was performed by t-paired test or by non-parametric Wilcoxon test, depending on data distribution. Study of differences between groups of categorical data was carried out by Chi-square statistics. In order to calculate a posterior probability to ICU admission according to clinical binomial data used for patients selected during ICU consultation, a Bayesian analysis of contingency tables were performed. Kaplan-Meier analysis was used to study patients' survival with the Cox-Mantel log-rank test to ascertain differences between the groups, analyzing all event by time to ICU admission. All Intervals of Confidence (CI) were established at 99%; significance level was established to be < 0.01 . Statistical data analysis was performed using the SPSS.26 package (SPSS Inc., Armonk, NY; USA).

Ethics committee permissions

This study has been approved by the Ethics Committees of Canton Ticino (Comitato Etico Cantonale, CE_TI_3807), according to the local Federal rules. No funding has been required.

Results

During the study period 1623 patients were admitted to our COVID-19 center (Fig 1); two-hundred and eight DNR patients were excluded from the analysis. Of the remaining 1415 patients, 100 (7%) underwent Intensivist Consultation during their hospitalization; three (3%) patients refused to give informed consent to their data treatment and were therefore excluded (Fig 1). Demographics and patients' characteristics at consultation are summarized in Table 1. Of the 100 patients undergoing Intensivist consultation, sixty-three (65%) presented one or more ICU admission criteria and were therefore admitted to the ICU (*ICU-admitted* group), while thirty-four (35%), who did not present the aforementioned criteria (*ICU-refused* group), remained under strict follow-up out of ICU (Fig 1). All data groups are depicted in Table 1.

Clinical and biological comparison

In the *ICU-admitted* versus *ICU-refused* comparison (Table 1), no significant difference was found in relation to age, BMI, pO_2 , pCO_2 , lymphocytes count, CRP, creatinine kinase, total bilirubin, lactate and hemoglobin levels. There were more females in the *ICU-refused* group, with lower LDH and higher platelet counts. No significant difference was found concerning the presence of ischemic cardiomyopathy, diabetes and COPD. Concerning hemodynamics parameters at admission, such as systolic and diastolic blood pressure) and body temperature we could not find significant difference between the two groups. Patients in the *ICU-admitted* group were more prone to arterial hypertension. The rest of the collected data are reported in Table 1. In the *ICU-admitted* group the length of hospital stay (LOS) resulted 26 ± 18 days (min-max 2–79) while in the *ICU-refused* group resulted 20 ± 9 days (min-max 9–47, $p = 0.04$).

Survival rate analysis

At 28 days, the *ICU-refused* group mortality rate was 0%; all *ICU-refused* patients' clinical condition eventually improved and at forty days from the intensivist consultation some of the patients were already discharged from the hospital. For *ICU-admitted* group, the 28-days mortality rate was 15.9% (10 patients), increasing up to 27% (17 patients) at 40 days (Fig 1). Comparing the 28- and 40-days survival rate, a difference in favor of the *ICU-refused* group was found (Fig 2).

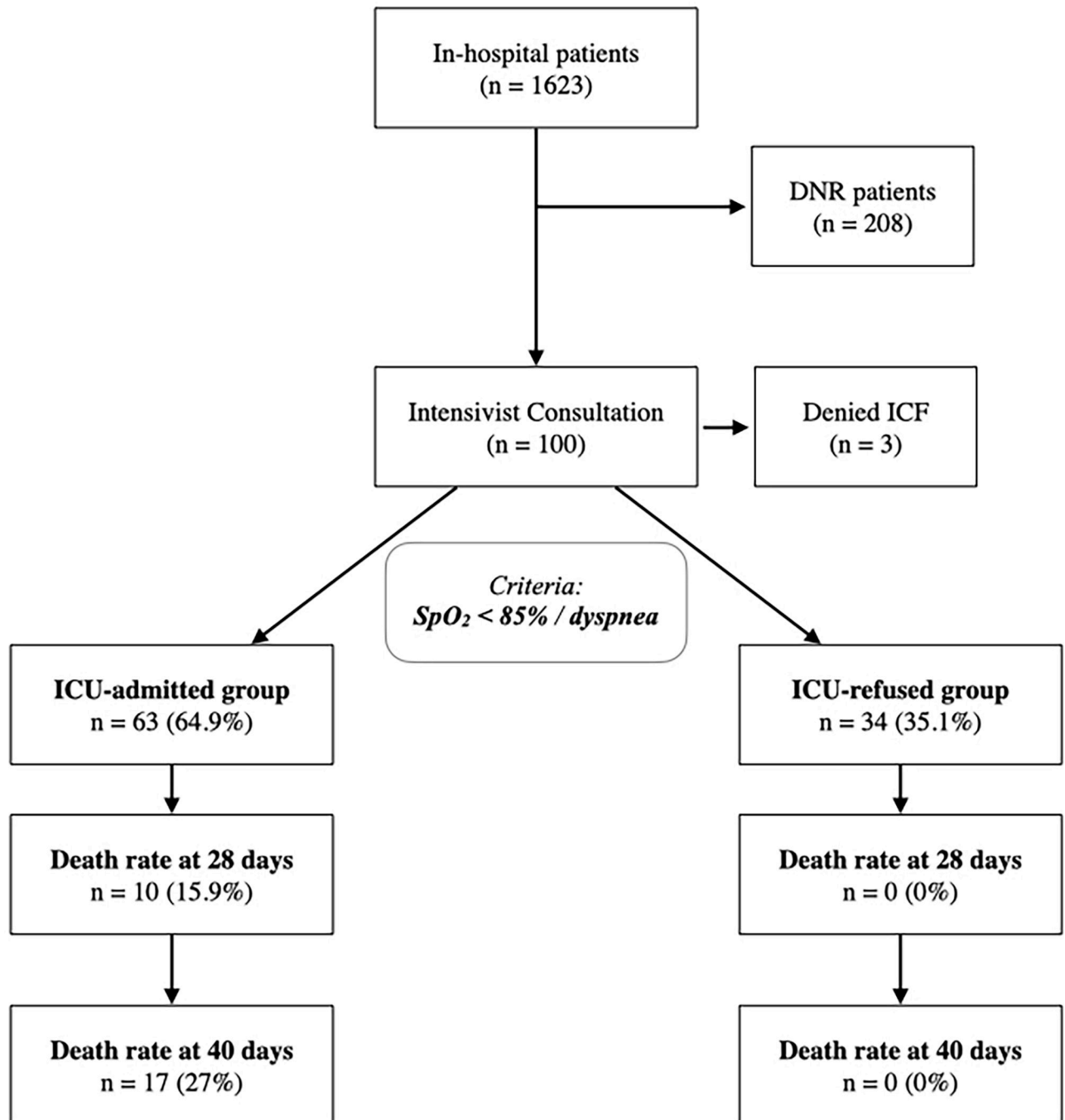


Fig 1. Study design. Management of COVID-19 patients evaluated at our COVID-19 center from March 2020 to January 2021. ICU admission was allowed according to standardized criteria. Patients not admitted followed according to EWS score, to quickly identify any change in their medical status. Death rate at 28 and 40 days is reported.

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Hypoxia distribution rate

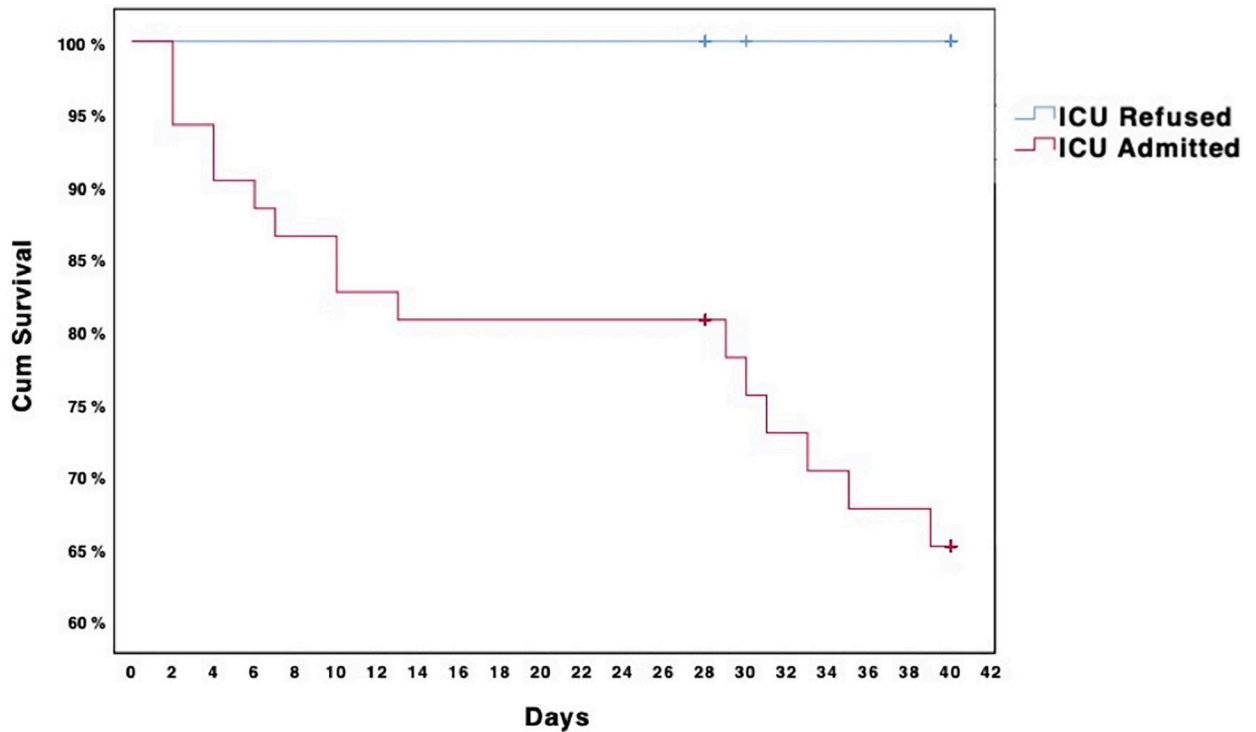
Using the SpO₂ cut-off of 92%, the distribution of the hypoxia rate in both groups did not seem to correlate with ICU admission (Table 2). In the ICU-admitted group, out of 63 patients 52 (82%) presented a SpO₂ lower than 92% (Fig 3); similarly, 24 patients (71%) of the ICU-

Table 1. Baseline characteristics at intensivist consultation.

		ICU admitted	ICU refused	p value
DEMOGRAPHIC DATA				
Number	n (%)	63 (65)	34 (35)	
Age	years	69 ± 9 (38–89)	70 ± 13 (31–93)	0.87
Male	n (%)	53 (80)	18 (53)	< 0.001*
BMI	kg/m ²	28.0 (24.6–32.3)	27.9 (24.3–31.0)	0.63
SAPS		42 (33–56)	NA	-
NEMS		31.0 ± 9.5 (18.0–39.0)	NA	-
SOFA score	points	4 (3–4)	2 (0–2)	0.02*
P/F ratio	points	4 (3–5)	2 (0–2)	0.03*
Platelets	points	0 (0–1)	0 (0–0)	0.99
Total Bilirubin	points	0 (0–0)	0 (0–0)	1
Arterial Pressure	points	0 (0–0)	0 (0–0)	1
GCS	points	0 (0–0)	0 (0–0)	1
Creatinine	points	0 (0–1)	0 (0–1)	0.99
COMORBIDITIES				
Arterial Hypertension	n (%)	42 (67)	16 (47)	< 0.001*
Ischemic cardiopathy	n (%)	18 (29)	8 (24)	0.57
Diabetes	n (%)	23 (37)	11 (32)	0.69
OSAS	n (%)	10 (15.9)	0	-
COPD	n (%)	9 (14)	6 (18)	0.59
HEMODYNAMICS				
Systolic arterial pressure	mmHg	127 (115–140)	124 (109–151)	0.61
Diastolic arterial pressure	mmHg	65 (60–72)	68 (57–74)	0.58
Heart Rate	bpm	87 (77–100)	78 (69–86)	0.13
Temperature	°C	36.8 (36.2–37.9)	36.4 (36.0–37.3)	0.15
Lactate	mmol/L	1.6 ± 1.1 (0.5–6.9)	1.2 (0.9–1.5)	0.20
RESPIRATORY				
SpO ₂	%	88 (55–100)	90 (88–93)	0.001*
pO ₂	mmHg	58 (49–81)	64 (56–76)	0.07
pCO ₂	mmHg	35 (32–44)	34.5 (31–39)	0.81
Hemoglobin	g/L	13.9 ± 1.7 (9.8–17.5)	13.4 (11.9–14.8)	0.69
LABORATORY				
ASAT	U/L	49 (44–85)	45 (34–68)	0.97
ALAT	U/L	38 (33–54)	35 (22–52)	0.59
Leucocyte	G/L	9.1 ± 2.0 (2.3–12.3)	5.8 (4.0–8.7)	0.04*
Lymphocyte	G/L	0.6 (0.4–0.6)	0.7 (0.4–1.1)	0.19
C-Reactive-Protein	mg/L	135 (116–237)	90 (53–170)	0.82
Ferritin	ng/mL	1781(1308–4320)	1397 (699–2082)	0.23
LDH	U/L	598 ± 213 (416–1048)	375 (321–468)	0.05*
Creatinine	μmol/L	110 ± 9 (50–410)	73 (60–102)	0.23
Creatinine Kinase	U/L	267 (172–573)	214 ± 330 (12–1611)	0.26
Platelets	G/L	198 (150–254)	264 (175–330)	0.03*
Total Bilirubin	μmol/L	9.1 (7.1–16.5)	7.4 (5.5–10.2)	0.21

Data comparison between *ICU-admitted* and *ICU-refused* groups regarding clinical and biological data. Continuous measurements are presented as mean ± SD (min-max), otherwise as median (25th-75th interquartile) if they are not normally distributed. Categorical variables are reported as counts and percentages.

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ICU-refused	34	34	34	34	34
ICU-admitted	66	59	56	51	49

Fig 2. Groups' survival. Kaplan-Meier survival at 40 days according to outcome of Intensivist consultation (*ICU-admitted* versus *ICU-refused*), based on the presence of dyspnea and/or confusion and/or SpO₂ less than 85%. No patients presented mental confusion as criteria for ICU admission.

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refused group presented a SpO₂ lower than 92%. An identical distribution according to SpO₂ cut-off value of 92% between the two groups was found (Chi-square 1.85, df = 1 p = 0.26). However, using the SpO₂ cut-off at 85% (Table 2), a significant correlation was found between SpO₂ < 85% distribution and ICU-admission. A similar correlation was also found between symptomatic dyspnea distribution and ICU-admission; the Chi square was 13.1 (df = 1, p = 0.0002) and the odds ratio (OR) to be admitted to the ICU in case of dyspnea resulted 4.86 (CI 95%, 1.95–12.10). In none of the patients were mental confusion present on assessment by the intensivists.

Table 2. Patients' distribution at consultation.

		ICU-admitted	ICU-refused	P value
Dyspnea	Yes	41 (42.2%)	9 (9.3%)	p = 0.0002
	No	22 (22.7%)	25 (25.8%)	
SpO ₂ < 92%	Yes	52 (53.7%)	24 (24.7%)	p = 0.26
	No	11 (11.3%)	10 (10.3%)	
SpO ₂ < 85%	Yes	23 (23.7%)	4 (4.1%)	p = 0.009
	No	40 (41.2%)	30 (30.9%)	

ICU admission criteria distribution in patients affected by COVID-19 pneumonia at the time of Intensivist consultation, according to outcome (*ICU-admitted/refused*). No patients presented mental confusion as criteria for ICU admission.

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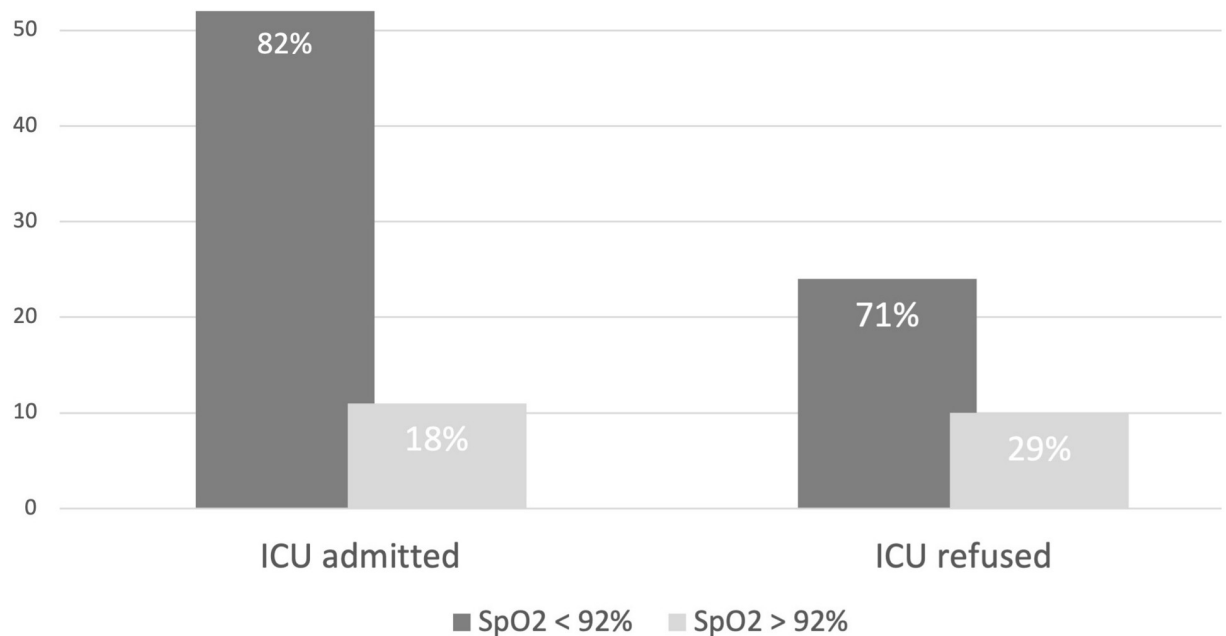


Fig 3. Patients SpO₂ distribution. Prevalence of SpO₂ distribution in patients at the Intensive Care consultation, stratified according to ICU admission (*ICU-admitted, ICU-refused*). In the *ICU-admitted* group, 52 of 63 patients (82%) presented a SpO₂ less than 92%; in the *ICU-refused* group, 24 of 34 patients (71%) presented a SpO₂ less than 92%. Chi-square analysis confirmed the identical distribution (p value = 0.26). Nearly a quarter of patients in the *ICU-refused* group presented a SpO₂ lower than 92%, without any ICU specific inclusion criteria, and their clinical conditions progressively improved.

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Using a SpO₂ of 92% as a hypothetical cut-off allowing ICU admission, the OR for patients with SpO₂ lower than 92% compared to those with SpO₂ greater than 92% resulted 1.96 (CI 95%, 0.73–5.26). Conversely, using SpO₂ of 85% as a cut-off point, the OR to be admitted to the ICU for patients with SpO₂ lower than 85% resulted 4.31 folds higher than those with SpO₂ higher than 85% (CI 95%, 1.33–13.79). According to these data, the Bayesian post-test probability predicting model indicated that the probability to be admitted to the ICU for a SpO₂ cut-off value of 92% is equal to 69.5%; the same probability increased up to 85.3% when the SpO₂ cut-off value was changed to 85%.

Discussion

Acute respiratory distress induced by SARS-CoV-2 is a critical condition associated with the COVID-19 pandemic [18, 19]. In order to minimize the high mortality rate associated with the disease, the adequate hospital management must also require a well-structured triage and frequent patients' clinical evaluations [10, 20]. With the aim to avoid ICU overload and to ensure simultaneously adequate medical care, we defined standardized ICU admission criteria based on partial respiratory failure with SpO₂ lower than 85% and/or dyspnea. To better manage patients presenting *silent hypoxemia* [6, 7], even in the case of SpO₂ lower than 92%, a conservative approach based on strict in-ward surveillance and regular EWS measurement [5, 9, 10] was implemented, until an eventual onset of dyspnea or of SpO₂ below 85% allowed ICU admission. An increased pulmonary compliance is probably the main explanation for the silent hypoxemia in these patients [9], although further mechanisms have been proposed [21, 22]. Following these criteria, none of the 34 patients not admitted to the ICU died at 28 days

follow-up; all the patients improved their clinical status and all of them were subsequently discharged.

Our data suggest that in COVID-19 patients there is a low correlation between dyspnea and SpO₂ with a cut-off value of 92%. The most interesting finding was that the *ICU-refused* and the *ICU-admitted* groups presented a similar SpO₂ lower than 92% distribution. According to the patients' distribution, the cause of ICU admission in patients with SpO₂ greater than 92% was due to the onset of either dyspnea and/or mental confusion, confirming the lack of correlation between SpO₂ values and the subjective feeling of shortness of breath. Similarly, there was a significant percentage of patients with SpO₂ lower than 92% who were not admitted to the ICU, due to the absence of dyspnea and/or confusion; all of them were subsequently discharged alive and in good general condition, with a median LOS shorter than *ICU-admitted* patients. These data allow us to speculate that, in a pandemic scenario, the criteria for ICU admission based on patient's respiratory pathophysiology resulted the more appropriate. All the collected data induce us to implement a physiology-based approach, relating to signs and/or symptoms of hypoxia together with SpO₂ values, as the more appropriate to define ICU admission criteria. Probably, we should not just look at the degree of hypoxemia, but for a better patients management we should also evaluate patients' work of breathing, respiratory mechanics and degree of respiratory distress. The presence of patients without hypoxia-related signs or symptoms despite SpO₂ less than 92%, and the absence of mortality in this group suggests that the SpO₂ cut-off of 92% as a threshold for ICU admission in the COVID-19 context requires future re-evaluation.

A further effect of this management was the reduction of ICU-workload for healthcare professionals, which has been shown to pose a great risk for ICU-healthcare burnout [23, 24], a problem gaining uttermost importance in dramatic situations such as the COVID-19 pandemic, which are subject to lack of human and material resources. A more careful management regarding ICU-admission could allow a better management both of patients that will benefit from an intensive medical intervention than patients that do not require ICU hospitalization.

One major concern regards the increased risk of peri-intubation events related to higher level of hypoxemia in *ICU-admitted* group [24], possibly induced by a prolonged observation period in the ward. Before the evaluation for ICU admission, patients were treated with oxygen therapy with mask and/or mask with reservoir bag in the ward; after ICU admission, patients were immediately intubated, using the HFNC/NIV as a bridge therapy to IMV. One could argue that in this scenario, the ICU admission was delayed but resulted earlier endotracheal intubation, where the bridge therapy allowed to achieve higher pO₂ and SaO₂ values during the peri-intubation period. This strategy could explain the reason of absence of peri-intubation major adverse events related such as profound hypoxemia and/or cardiovascular instability [24, 25]. It is also important to note that no patient had to be admitted as a delayed admission to the ICU from the *ICU-refused* group. This could be a true positive signal but may also be affected by the relatively small sample size, hence it needs further validation.

Our study has several limitations. First, it was a monocentric, observational, retrospective study, with a relatively small series of patients and a lack of direct comparison with a control group. However, a stronger evaluation of our method was supplied by its application to the two different waves of COVID-19 pandemic. Second, the two groups were not completely homogeneous, differing in male sex incidence, arterial hypertension rate and serum CRP values; however, none of these values was used as criteria for decision making during the intensivist consultation. Male sex [25], arterial hypertension [26, 27], leukocytosis [27] and LDH increase [27] may possibly be interpreted as risk factors [28] for ICU admission, rather than predicting factors; moreover, the key-message concerning the absence of mortality in the *ICU-*

refused group, whose classification criteria did not involve these non-homogeneous parameters, remains intact. Third, patients admitted to the ICU were treated immediately with IMV according to our internal protocols. Although some studies suggest other alternatives, such as HFNC and/or NIV during early ICU management for critically ill COVID-19 patients, this topic remains controversial [29, 30]. Finally, we are unable to define whether the SpO₂ cut-off of 85% was the absolute best criteria to identify patients needing ICU-admission; although our study suggests that the SpO₂ 92% threshold was unreliable in COVID-19 patients, it was not designed to specifically identify the best SpO₂ threshold for ICU admission.

Conclusion

In COVID-19 patients, standardized ICU admission criteria appeared to be a safe method to reduce ICU-admission, simultaneously guaranteeing a high standard of care. In case of silent hypoxemia, even with SpO₂ lower than 92%, a conservative approach based on strict surveillance with regular EWS measurement in the ward was not associated with increased mortality. All collected data induce us to consider a physiology-based approach to guide ICU admission as the more appropriate during pandemics. The absence of hypoxia-related signs and/or symptoms, despite SpO₂ less than 92%, suggests that this SpO₂ cut-off as the threshold for COVID-19 patients' ICU admission needs further re-evaluation.

Supporting information

S1 Table. Baseline characteristics between all ICU patients and patients admitted in ICU from Intensivist consultation.

(DOCX)

S1 Dataset.

(XLSX)

Author Contributions

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