

Low-PEEP Mechanical Ventilation and P/F Ratio Evolution in COVID-19 Patients

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Research Article

Keywords: Adult Respiratory Distress Syndrome, COVID-19, Mechanical Ventilation, PaO₂/FiO₂, Positive-End-Expiratory Respiration

Posted Date: May 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-443459/v1>

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Version of Record: A version of this preprint was published at SN Comprehensive Clinical Medicine on July 24th, 2021. See the published version at <https://doi.org/10.1007/s42399-021-01031-x>.

Abstract

Background Critically ill COVID-19 patients are burdened by high mortality. Evaluation to improve patients' management was performed using strict patient criteria for Intensive Care Unit (ICU) admission, a low- positive end-expiratory pressure (PEEP) setting and standard thromboembolism treatment.

Objectives of this study was to report the effects of this strategy on P/F-ratio evolution during mechanical ventilation (MV), ICU length of stay (LOS) and MV length.

Methods A retrospective analysis was conducted on all consecutive patients with acute respiratory distress due to COVID-19 pneumonia admitted into ICU from March 2nd to January 15th, 2021.

Patients were treated with a low-PEEP strategy (PEEP 10 cmH₂O if BMI < 30 Kg m⁻², PEEP 12 cmH₂O if BMI 30-50 Kg m⁻², PEEP 15 cmH₂O if BMI > 50 Kg m⁻²) and therapeutic anticoagulation in case of thrombosis or D-dimer greater than 1'500 ng ml⁻¹.

Results 79 patients were on invasive MV. Average applied PEEP was 11 ± 2.9 cmH₂O for BMI < 30 Kg m⁻², 16 ± 3.18 cmH₂O for BMI > 30 Kg m⁻². After low-PEEP application, patients' P/F ratio presented daily improvement from admission during next 72 hours (p<0.001; CI 99%) that resulted statistically significant for each single day after oro-tracheal intubation (OTI). Median ICU length of stay (LOS) was 15 days (10–28); median duration of MV was 12 days (8–26). The ICU mortality rate was 31.6%.

Conclusions A combination of low-PEEP treatment resulted in P/F persistent daily ratio improvement during first 72 hours after OTI. A low-PEEP strategy could be beneficial in hemodynamic than respiratory terms.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of COVID-19, a pandemic that has affected more than 109,000,000 individuals and caused nearly 2,500,000 deaths since initial detection of the virus at the end of January 2019 [1].

Epidemiologic data underline the severity of the syndrome, with a critical load for intensive care units (ICU) and a high mortality [2]. Detailed reports describe appropriate management for COVID-19 patients admitted to the ICU, which is relevant both for a better clinical characterization [3] and for guiding decision making in relation to the severe hypoxemia affecting these subjects [4]. In particular, relevant pathophysiological understanding of the disease, as reported by Cronin [5], Nieman [6], Gattinoni [7] and Bendjelid [8], are of uttermost importance for a better clinical evaluation and management. On the basis of these evidences and with the aim to improve COVID-19 patients management in life-threatening conditions, we conceived and implemented a targeted management based on the following: specific criteria for ICU admission (paper in progress), intermediate-intensity anticoagulation [9] for Venous

Thromboembolism (VTE) and low-PEEP management in patients undergoing mechanical ventilation (MV).

Invasive MV is the gold standard treatment in patients with severe respiratory distress, including critically ill COVID-19 patients; however, barotrauma, volotrauma or biotrauma can occur when MV setting is extremely aggressive and/or prolonged [10–12]. The implementation of high PEEP values, which is often used in patients with Acute Respiratory Distress Syndrome (ARDS), has been suggested also for COVID-19 patients [13, 14]. However, more recent evidences reported that a less aggressive approach, implementing a “low-PEEP strategy” may be favourable in critically ill COVID-19 patients [13, 15, 16], who tend to present higher lung compliance when compared to “classic” ARDS patients [7, 8, 13, 14, 17–19]. The PaO₂/FiO₂-ratio (P/F ratio) determines patients` respiratory efficiency, acting as a primary clinical indicator of hypoxemia and of ventilation setting`s efficiency [20] and thus allowing to properly evaluate changes in patients` respiratory status.

Aim of this project was to report and analyze the P/F ratio evolution in a case series of consecutive critically ill COVID-19 patients admitted to our ICU and undergoing MV, strategically managed with the implementation of low-PEEP, with further report of biological, respiratory and clinical data.

Methods

After approval by the Ethical Committee (Ethics Committees of Canton Ticino; Dec 2020, CE TI 3775) and in accordance with local Federal rules, a retrospective analysis was conducted on consecutive patients with acute respiratory distress due to COVID-19 pneumonia, admitted to ICU during two pandemic waves (from March 2nd to April 10th, 2020 and from October 5th 2020 to January 15th, 2021). All critically ill COVID-19 patients` relevant data like demographics, severity score (NEMS - nine equivalents of nursing manpower use score -, SAPS - simplified acute physiology score), clinical information and laboratory/radiological results were obtained during patients` hospitalization, from electronic health records. Standard laboratory tests included complete blood count, CRP, ferritin, ASAT, ALAT, blood ionogram, creatinine, urea, D-dimer, Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), fibrinogen, blood gas analysis, SvO₂, NT-pro-BNP, blood and urines cultures and urine analysis for *Legionella Pneumophila* antigen. All patients underwent chest x-ray and transthoracic echocardiography, in order to assess the global cardiac function before any pronation cycle. Performing a chest CT scan was considered at ICU admission, if the examination had not been performed within the proceeding 24 hours.

After endotracheal intubation, a low PEEP strategy based on BMI was adopted: PEEP values of 10, 12 and 15 cmH₂O were implemented, respectively, for patients with BMI < 30, 30–50 and > 50 kg/m². Once PEEP adjustment was performed, according to *ARDSnet PEEP table* [17, 21] and PV-tools ventilatory measurements, FiO₂ was adapted to maintain a SpO₂ greater than 92% and a PaO₂ > 60 mmHg / 8 kPa. A protective ventilation strategy (TV 6–8 ml Kg⁻¹, P_{plat} < 30 cmH₂O) with permissive hypercapnia (pH > 7.20) was adopted [22], with pronation cycles of 16-hours beginning at the admission. A deep sedation

was maintained to pursue a Richmond Agitation and Sedation Scale (RASS) of -4 during the first 36 hours, combined with muscle relaxation in case of patient-ventilator asynchrony [23].

VTEs were considered *suspected* in case of an increase in serum D-dimer values over 1'500 ng/ml, while they were considered *confirmed* in case of lower legs venous ultrasound or pulmonary angio-CT-scan positive findings, according to current clinical standards [24]. Given the high risk of Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) in these patients [22], according to American Society of Hematology [25] daily monitoring by ultrasound Color-Doppler lower limbs was performed, in accordance to the American Society of Hematology's suggestions [25]. A VTE intermediate-prophylaxis was implemented since patients' ICU admission (Enoxaparine 60 mg bid SC if weight > 80 Kg, Enoxaparine 40 mg bid SC if weight < 80 Kg, Unfractionated Heparin in case of Acute Kidney Injury - AKI). In case of plasmatic D-dimer level greater than 1'500 ng ml⁻¹ or documented thrombosis, anticoagulation treatment was switched to a therapeutic dose (Enoxaparine 1 mg Kg⁻¹ bid SC – Unfractionated Heparin in case of AKI at 14 UI Kg⁻¹ for day in perfusion, according to anti-Xa values) [24]. All clinical and biological data were reported.

Primary outcome was to report the P/F ratio evolution during MV after application of low-PEEP according to BMI, during the first three days after oro-tracheal intubation (OTI). Secondary outcomes were to report clinical data about ICU LOS and duration of MV, the description of the demographic characteristics, the incidence of clinical complications (especially VTEs, AKIs and VAPs) and the critical care outcomes in critically ill COVID-19 patients.

Statistical analysis

Descriptive statistic was performed to summarize the clinical collected data. Gaussian distribution was verified by Kolmogorov-Smirnov 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. Significance level of p value was established to be < 0.01, with a confidence interval (CI) of 99%. Statistical data analysis was performed using the SPSS.26 package (SPSS Inc., Armonk, NY; USA).

Results

ICU patients' characteristics

During the first pandemic wave, 46 patients were admitted to the ICU, while during second wave 71 patients were furtherly admitted. Thirty-three patients did not receive invasive MV and were therefore excluded from the analysis; the seventy-nine patients who received invasive MV were instead included in the study (Fig. 1). Mean age was 67 ± 11 years; most patients were men (81%), often with one or more

chronic medical conditions, most commonly arterial hypertension (57%) and diabetes (35.7%) (Table 1). Almost all patients resulted hemodynamically stable (95%). A chest CT-scan was obtained in 64 (76.2%) patients, showing bilateral ground-glass opacities in all cases, as well as concomitant consolidations in 13 of them (15.5%). Demographic and clinical data were reported in Table 1.

Table 1
Baseline characteristics

	Unit	n.v.	Results
DEMOGRAPHIC DATA			
Patients on invasive MV	n		79
Age	years		67 ± 11 (29–86)
Male	n		68 (81%)
BMI	Kg m ⁻²		29 ± 5.1 (18.6–44.9)
SAPS			47 ± 17 (13–94)
NEMS			34 ± 9 (9–49)
COMORBIDITIES			
Arterial Hypertension	n		48 (57.1%)
Ischemic cardiopathy	n		19 (22.6%)
Diabetes	n		30 (35.7%)
Obstructive Sleep Apnea Syndrome	n		9 (10.7%)
COPD	n		12 (14.3%)
Mean duration of symptoms	days		5 (1–29)
AT ADMISSION			
HEMODYNAMICS			
Systolic arterial pressure	mmHg	110–140	129 (120–140)
Diastolic arterial pressure	mmHg	60–80	65 (60–75)
Heart Rate	bpm	60–100	85 (50–96)
Temperature	°C	36–38.3	37.0 (36.3–37.6)
Lactate	mmol L ⁻¹	< 2.0	1.2 (0.8–1.6)
LABORATORY			
ASAT	U L ⁻¹	10–50	47 (36–72)
ALAT	U L ⁻¹	10–50	33 (21–48)

Demographic characteristics and blood tests at ICU admission. Continuous measurements were presented as mean ± SD (min-max) otherwise as median (25th -75th) if they are not normally distributed. Categorical variables were reported as counts and percentages.

	Unit	n.v.	Results
Leucocyte	G L-1	4.0–10.0	6.8 (4.8–10)
Lymphocyte	G L-1	1.3–3.6	0.7 (0.5–1.0)
RADIOLOGY			
Chest-X-ray	n		61 (72.6%)
Chest-CT-scan			
- NO CT-scan	n		20 (23.8%)
- Ground Glass	n		51 (60.7%)
- Ground Glass & Consolidation	n		13 (15.5%)
Demographic characteristics and blood tests at ICU admission. Continuous measurements were presented as mean \pm SD (min-max) otherwise as median (25th -75th) if they are not normally distributed. Categorical variables were reported as counts and percentages.			

MV settings with low-PEEP

For patients with BMI < 30 Kg m⁻², mean titrated PEEP was 11 cmH₂O (SD 2.9), while for patients with BMI > 30 Kg m⁻² the mean PEEP was 16 cmH₂O (SD 3.18); no patients with BMI more than 50 Kg m⁻² were admitted. Upon ICU admission, early P/F ratio reported a median of 70 (54–101), with a median FiO₂ of 95% (80–100) with non-invasive medical oxygen supply. After the implementation of MV following OTI, the median FiO₂ resulted 70% (60–90), with a median first P/F ratio of 145 (111–206), significantly increased compared to the P/F ratio pre-OTI (-75, CI 99%, -97/-52, p < 0.001) (Fig. 2). Seventy-eight (92.8%) patients underwent pronation cycles, with a median of 4 cycles per patient (Table 2).

Table 2
MV setting and Clinical Outcomes

	Unit	n.v.	Results
BASAL RESPIRATORY DATA			
FiO ₂ at admission before OTI	%		95 (80–100)
P/F ratio at admission before OTI		> 300	70 (54–101)
FiO ₂ after OTI	%		70 (60–90)
P/F ratio after OTI		> 300	145 (111–206)
VENTILATORY STRATEGY			
PEEP-strategy			
- BMI < 30 Kg/m ²	cmH ₂ O		11 ± 2.9 (10–12)
- BMI 30–50 Kg/m ²	cmH ₂ O		16 ± 3.18 (12–18)
- BMI > 50 Kg/m ²	cmH ₂ O		NA
RESPIRATORY DATA EVOLUTION			
P/F ratio at first day		> 300	120 (94–174)
P/F ratio at second day		> 300	160 (120–220)
P/F ratio at third day		> 300	197 (140–235)
Pronation cycles	n		4 (2–5)
LABORATORY DATA (first 72 hours)			
C-Reactive-Protein max	mg L-1	< 5	185 (106–258)
Ferritin max	ng mL-1	30–500	1819 (878–3200)
Lactate De-Hydrogenase max	U L-1	135–225	530 (402–695)
Creatinine max	umol L-1	62–106	93 (72–129)
Troponin T hs max	ng L-1		14.8 (8.1–43.0)
Creatinine Kinase max	U L-1	39–308	235 (101–360)
Platelets min	G L-1	150–450	171 (133–236)

ICU respiratory data at admission, during treatment and PEEP strategy, with ICU MV and laboratory data. Continuous measurements were presented as mean ± SD (min-max) otherwise as median (25th -75th) if they are not normally distributed. Categorical variables were reported as counts and percentages.

	Unit	n.v.	Results
Bilirubin total max	umol L-1	< 21.0	8.3 (6.4–12.5)
CLINICAL OUTCOME			
Length of ICU stay	days		15 (10–28)
Length of MV	days		12 (8–26)
COMPLICATIONS			
Thromboembolism confirmed	n		19 (24.1%)
Massive hemorrhage	n		6 (7.6%)
Ventilator Associated Pneumonia (VAP)	n		37 (46.8%)
AKI needing RRT	n		10 (11.9%)
ICU respiratory data at admission, during treatment and PEEP strategy, with ICU MV and laboratory data. Continuous measurements were presented as mean \pm SD (min-max) otherwise as median (25th -75th) if they are not normally distributed. Categorical variables were reported as counts and percentages.			

The P/F ratio after low PEEP application (Table 2) progressively improved, with a median value of 120 (94–174) at day one (-44, CI 99%, -64/-24, $p < 0.001$), 160 (120–220) on the second day (-81, CI 99%, -103/-60, $p < 0.001$) and 197 (140–235) on the day three (-106, CI 99%, -133/-78, $p < 0.001$). This improvement resulted statistically significant both when comparing the P/F ratio between the first and second day (-36, CI 99%, -50/-22, $p < 0.001$) and between the second and third day (-23, CI 99%, -40/-6, $p < 0.001$) (Fig. 3).

ICU patient outcome

The median duration of ICU stay was 15 days (10–28); the median duration of MV was 12 days (8–26) (Table 2). At 28 days, 41 critically ill patients (48.8%) were discharged from ICU, 8 inpatients (9.5%) were still receiving MV (6 via endotracheal tube, 2 via tracheostomy) and 5 patients (4.8%) were transferred to another hospital. The ICU mortality rate was 31.6% (25 patients). No patient underwent reintubation within or after 72 hours from extubation. After the analysis of patients' survival, no specific variable was significantly associated with better survival, both at clinical level, like age (mean 72.2 vs 64.5 years, $p = 0.056$), and at biological level, like serum leucocyte (median 7 vs 8 G/L, $p = 0.09$), lymphocyte (median 0.6 vs 0.9 G/L, $p = 0.08$), and CK values (median 198 vs 232 U/L, $p = 0.91$).

Clinical Complications

Nineteen patients (24.1%) presented major VTE phenomena (16 EP, 3 veno-arterial thrombosis) and 8 patients (9.5%) presented DVTs. Fifteen (17.8%) patients received anticoagulation at a prophylactic dose, while 60 (71.4%) patients received a full therapeutic dosage. No patient presented any contraindication to parenteral anticoagulation; 6 (7.6%) patients presented bleeding complication, requiring anticoagulation

suspension and specialist treatment. Thirty-seven (46.8%) patients undergoing MV were diagnosed with VAPs and subsequently treated with antibiotic therapy in accordance with local clinical practice. Nineteen (24.1%) patients presented AKI, with 10 (11.9%) patients requiring renal replacement therapy (RRT) implementation.

Discussion

Acute respiratory distress induced by SARS-CoV-2 is a critical clinical condition associated with COVID-19 infection [26, 27]. In a multisystem disease such as COVID-19, a multidisciplinary approach is recommendable [3]; to minimize the high mortality rate potentially associated with COVID-19 pandemics, and to correctly manage this critical condition, adequate hospital resources, structured triage and appropriate clinical training are required. [3]. Clinical evidences led us to consider that, even if the classic criteria defining the ARDS were present in COVID-19 patients [28], atypical aspects were also evident, especially the lack of a reduced lung compliance with the consequent tendency to hypercapnia [29]. The lack of “baby-lung” pattern [30] and the ARDS-like pattern with low lung elastance [17, 19, 31], induced us to evaluate a more specific treatment [15].

According to *ARDSnet PEEP table* [17, 21], we preferred to ventilate patients with PEEP adapted to patients’ own BMI, carefully tailored to lungs physiology [28, 32]. This approach was consistent with Gattinoni et al [33] and Bendjelid et al [8], who both suggested the presence of two different ICU patient populations in COVID-19 pneumonia. The first population presents a high lung compliance due to a probable *alveolitis*, with a shunt effect due to loss of local hypoxic vasoconstriction; this population represented the great majority of our patients. The second population presents a low lung compliance and a pattern of “baby-lung” compatible with “classic ARDS” (only 2 patients in our cohort). Following the abovementioned indication, our mechanically ventilated patients were treated with a “low-PEEP approach”, representing thus a different strategy compared to the available literature [34]. More recently, Tsolaki et al [15] Barthélémy et al [16] and Mauri et al [13] suggested a low-PEEP strategy in the management of these “ARDS-like” lungs, on the basis of critically ill patients lung physiology. Agreeing with these evidences, after intubation we found patients easy to ventilate, with a compliance on average above 50 mL/cmH₂O higher than in “classic ARDS pattern” [33]. In comparison with other groups [24, 32, 35] our strategy led to less complications (like ICU paralysis, delayed awakening, agitation, etc.), an easier and faster extubation, quickly decreasing deep sedation as inflammation began to diminish, with no need for frequent tracheotomies. Higher PEEP could cause overdistension, resulting in an increased driving pressure, with a subsequent increased risk of lung damage [36–38]; moreover, PEEP levels greater than 10 cmH₂O can induce the reduction of venous return, with consequent worsening of the circulation status, as well as local biotrauma and a worsening of alveolar damage [16, 37, 38]. In comparison to Poston JT et al [34], and in agreement with Mauri T et al [13, 15] we applied lower PEEP levels; this approach resulted beneficial, with ventilator data such as P/F ratio showed a rapid improvement already in the first 3 days after OTI. Therefore, the physiology of these ARDS-like lungs, the so-called ARDS L-type [7, 14, 18, 19], appeared to respond appropriately to low PEEP values tailored to patients’ BMI.

Into the Shah et al's [39] case series, the daily lower limbs ultrasound in COVID-19 ICU patients identified a high prevalence rate of DVTs and PEs, even in patients undergoing prophylactic anticoagulation. In addition, many patients had a marked increase in D-dimers level, possibly linked to VTE in other anatomical districts potentially secondary to PE. In this context, an intermediate anticoagulation seems a reasonable approach, also consequently to recent evidence suggesting the role of endothelial inflammation as a cause of microthrombosis [39, 40]. However, other groups showed an increase in spontaneous bleeding in COVID-19 patients, especially in the retroperitoneal space [35]. In our series, 6 patient presented a major bleeding event; this data was in agreement with the literature [39], bringing forward the hypothesis that an intermediate [9] anticoagulation may counterbalance a phenomenon of prothrombotic diathesis without a relevant increase in hemorrhagic complications rate.

Our COVID-19 ICU patients management resulted in a reduction of the mortality rate (31.6%) when compared to other groups, which reported a 50% and a 61.5% of death rate [41]. We supposed that a relatively low-pressure ventilation could prevent the transition from an initial alveolitis to an iatrogenic ARDS, in which the ongoing inflammation is worsened, rather than treated, by high levels of PEEP, through a Ventilation-Induced-Lung Injury (VILI) mechanism. A median ICU LOS was reported to be equivalent to Bhatraju et al [41], even including patients who died in ICU. This data suggests that a low PEEP strategy with a protective MV approach can improve COVID-19 patients' in-hospital management, morbidity and mortality, although further studies are necessary to confirm this interesting hypothesis.

Our project was burdened by several limitations. Firstly, this study compared low PEEP in consecutive critically ill COVID-19 patients, and it was not possible to compare the data to a control group; all patients were treated according to emerging information regarding pathophysiological data about the disease [7, 8, 19] and for this reason this strategy was implemented in all critically ill patients admitted to ICU. Secondly, it was a monocentric observational retrospective study, with a relatively small series of patients. However, comparison with current literature was performed; even if patient populations differed, results can be assumed to be consistent, as the cohorts are comparable in terms of disease severity and biochemical markers. Moreover, the low PEEP-strategy was maintained in our Center during the two past waves, allowing us to obtain reproducible results.

Conclusion

A combination of low PEEP treatment and prophylactic anticoagulation in mechanically ventilated patients resulted in P/F ratio's rapid and progressive improvement during the first 72 hours after OTI. This approach was also associated with a rather small duration of MV and of ICU LOS, as well as with lower mortality rates when compared to the literature. As a consequence, this approach may eventually contribute to ameliorate critically ill COVID-19 patients' management.

Declarations

Ethics approval and consent to participate: Ethics Committees of Canton Ticino, CE TI 3775; all the patients signed a general informed consent form.

Consent for publication: All the patients signed the institutional informed consent form.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests and funding: The authors declare that they have no competing of interests and this study had no funding.

Authors' contributions: SC, MR, MB, AG, PU: project design and data analysis; AG, PAM: data collection; SC, AS, MB, AG, GB, AB, CG, RM: write the paper. All authors read and approved the final manuscript.

Acknowledgements: Not applicable

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Figures

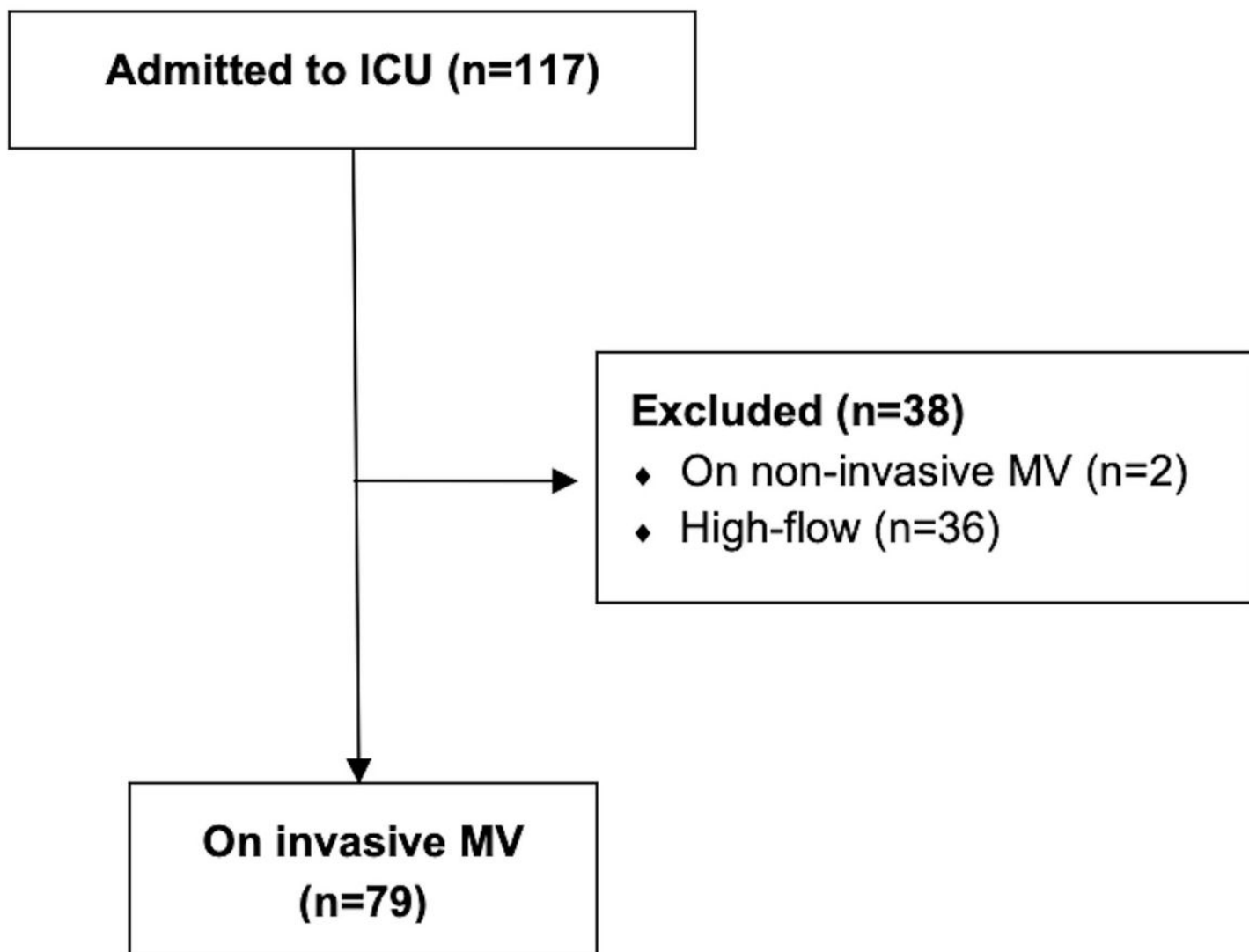


Figure 1

CLM COVID-19 patients Management of COVID-19 patients evaluated at our COVID-19 center during two pandemic waves (from March 2nd to April 10th 2020 and from October 5th 2020 to January 15th 2021). ICU admission was performed according to standard selection criteria (SpO₂ < 85% and/or dyspnea and/or signs of mental confusion). Patients not on invasive MV were excluded from the analysis.

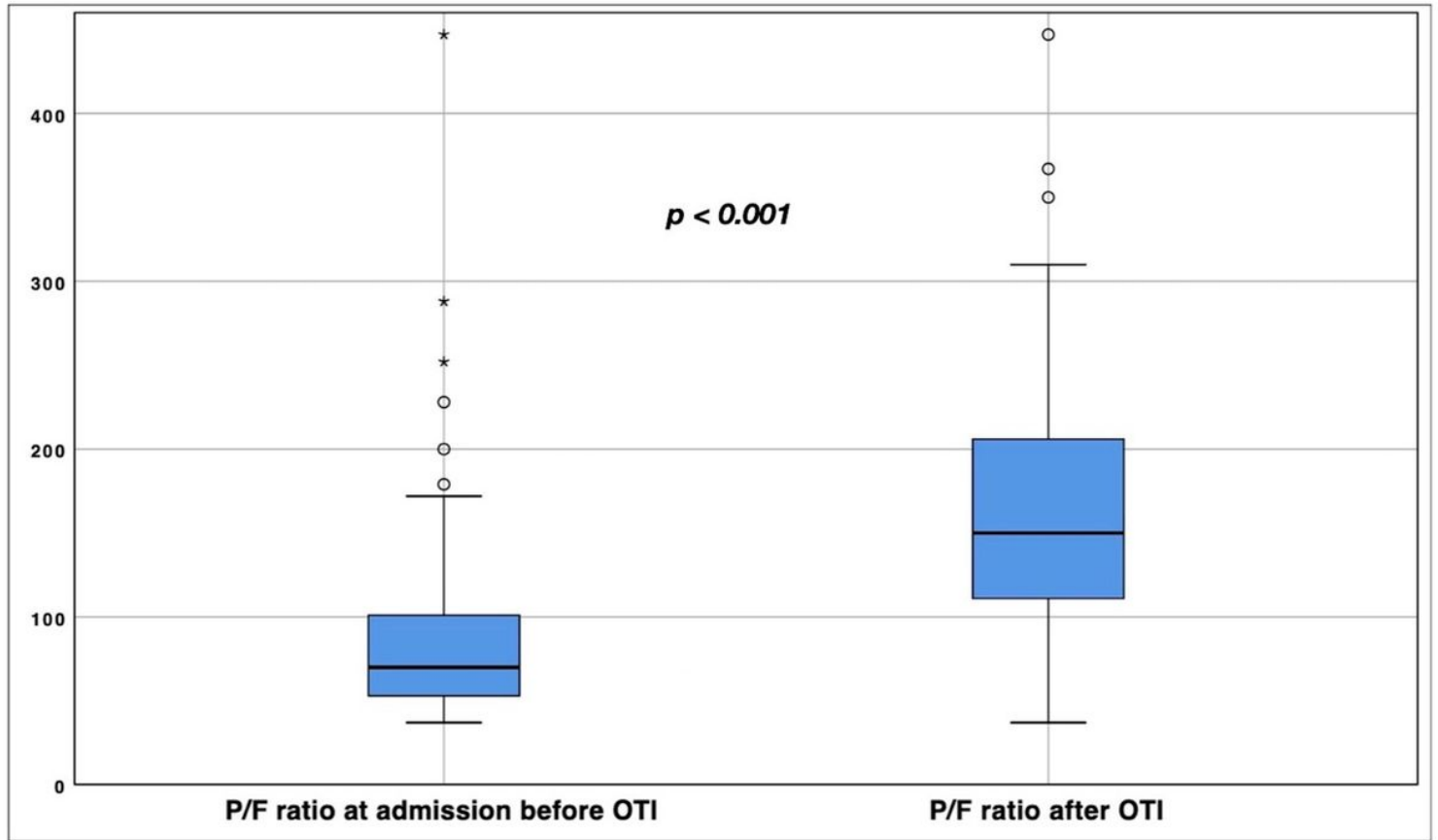


Figure 2

P/F ratio variation at OTI P/F ratio variation before/after OTI at ICU admission (-75, CI 99%, -98/-52, $p < 0.001$).

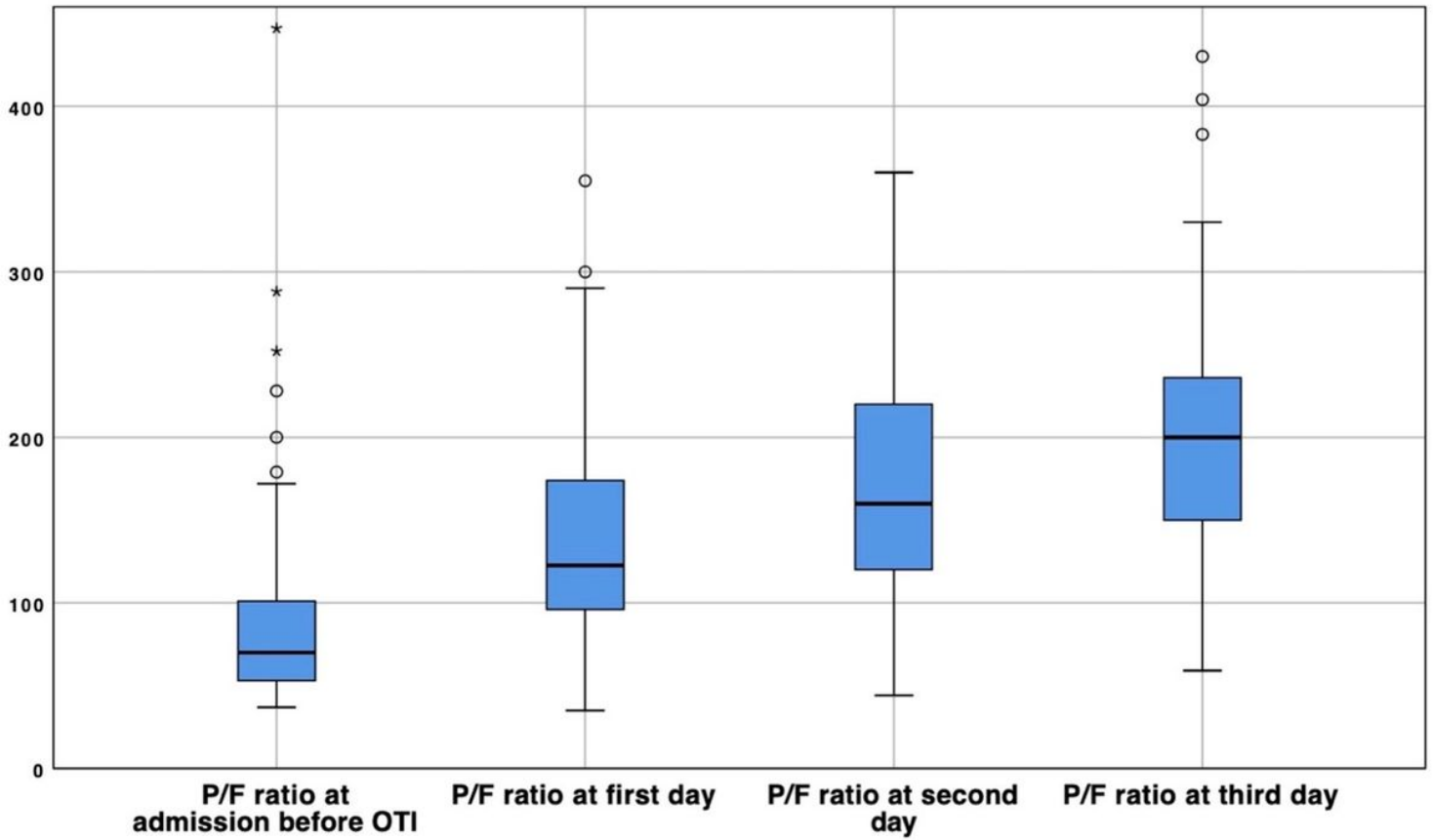


Figure 3

P/F ratio variation during MV P/F ratio variation at ICU admission compared to the first, second and third day of MV. All daily median PF-valued resulted significantly different compared to admission and compared to the day after, even with the use of low-PEEP setting on MV. All differences resulted statistically significant (CI 99%, $p < 0.001$).