Similar pulmonary functional outcomes at 3 months in critical COVID-19 survivors hospitalized during the first, second, and third pandemic waves

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Research Article

Keywords: COVID-19, ARDS, Chest CT, pulmonary function test, intensive care unit, quality of life, pandemic, wave, mortality

Posted Date: February 25th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1384691/v1>

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Abstract

Introduction

Despite improvements in the management of COVID-19 patients, we still don't know whether pharmacological treatments and improvements in ventilatory support have changed outcomes for intensive care unit (ICU) survivors of the three consecutive waves (w) of the pandemic. The objective of this study was to assess pulmonary functional outcomes, radiologic pattern, and quality of life (QoL) in ICU COVID-19 survivors at 3 months, according to pandemic wave.

Methods

All patients admitted to the ICU for COVID-19 acute respiratory distress syndrome (ARDS) at two university hospitals were prospectively included and assessed 3 months post-ICU discharge by chest CT, pulmonary function test (PFT), 6-minute walking distance test (6MWD), respiratory muscle strength (RMS) test, and Short Form 36 (SF-36) questionnaire.

Results

Eighty-four ARDS COVID-19 survivors were included. Hospital length of stay was shorter during w3 vs w1 (23.4 ± 14.2 days vs 34.7 ± 20.8 days, $p = 0.03$). Fewer patients required mechanical ventilation (MV) during w2 vs w1 (33.3% vs 63.9%, $p = 0.0038$). Three months after ICU discharge, PFT, 6MWD, and RMS were similar, regardless of wave ($p > 0.05$). QoL (SF-36) was worse for patients in w1 vs w3 (64.7 ± 16.3 vs 49.2 ± 23.2 , $p = 0.0169$).

On linear/logistic regression analysis, MV was associated with decreased TLC, FEV1, DLCO, and RMS (w1,2,3, $p < 0.05$). Low SF-36 score was correlated with low 6MWD (w3, $p = 0.01$). The use of glucocorticoids was associated with better TLC, FEV1, DLCO, and number of affected segments on chest CT ($p = 0.0001$), and tocilizumab was associated with higher TLC ($p = 0.027$). Remdesivir improved MV duration in wave 2 ($p = 0.008$).

Conclusions

Despite better understanding and management of COVID-19, PFT, 6MWD, and RMS remained similar in ICU survivors, regardless of the pandemic wave in which they were hospitalized.

Introduction

Coronavirus disease 2019 (COVID-19) is the third and most important outbreak of coronavirus this century. This outbreak was recognized as a pandemic by the World Health Organization on the 11th of March, 2020. As of the 28th of January, 2022, among a total population of approximately 364 million inhabitants who have contracted SARS coronavirus-2 (SARS-CoV-2), more than 5.63 million people have died worldwide [1]. The number of patients affected by SARS-CoV-2 is still rising, with striking problems related to emerging variants of concern (VOC), despite vaccination rates of up to 84% in European countries [2].

The spectrum of disease is broad, with 5% of symptomatic COVID-19 patients suffering from severe respiratory failure, fulfilling the Berlin definition of acute respiratory distress syndrome (ARDS), requiring intensive care unit (ICU) admission [3, 4]. Despite the development of a panel of treatments that have shown efficacy for improving patient outcomes and reducing mortality (e.g. anti-coagulation, glucocorticoids (GC), anti-viral therapies, monoclonal antibodies, ventilatory support) [5, 6], we still face, in ICU-admitted patients, multiorgan acute complications related to SARS-CoV-2 infection (renal, hepatic, thromboembolic, neurologic, cardiac, muscular). These may be directly attributable to the virus, such as immune-mediated mechanisms or microangiopathy, or indirect challenges related to subsequent long hospital stays, bed rest, iatrogenic factors, or psychological disorders [7–9]. The 6-minute walking distance test (6MWD) is a good test to capture post COVID-19 disability, assessing both muscle dysfunction and ventilatory limitation. It has been shown to be reduced in 65% of ICU COVID-19 patients 3 months after discharge [10]. We do not know yet whether the present management of ICU COVID-19 patients has changed long-term outcomes compared to patients who were initially affected at the start of the pandemic.

The aim of the present study was to assess outcomes in ICU COVID-19 survivors 3 months after ICU discharge, according to the timing of hospitalization (1st, 2nd, and 3rd pandemic waves). The primary outcome was to assess the percentage of patients who exhibited an impaired walking distance, below 80%, during the 6-minute walking distance test (6MWD), 3 months after ICU discharge. Secondary outcomes included comparisons of pulmonary function tests, quality of life, and radiologic impairment 3 months after ICU discharge. Impact of COVID specific treatments was also assessed.

Methods

Design

This was a prospective observational and multicentric study. Patients admitted to intensive care or fulfilling the Berlin criteria for COVID-19 related ARDS at CHU Saint Pierre and CHU Brugmann (tertiary reference hospitals) were included in the study.

Patients

Adult patients were included at 3 months from ICU discharge and assessed by chest computed tomography (CT), lung function tests, and questionnaires. Exclusion criteria included language barrier, refusal, and psychiatric or mental disorders.

All included patients provided written informed consent to participate in the study. The study protocol was approved by the Saint-Pierre University Hospital ethics committee (AK/16-01-18/4613) and by the Brugmann University Hospital ethics committee (CE2020/141). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data collection

Baseline data

Data related to hospitalization were collected from the medical files of the patients, including demographics, APACHE II score, Sequential Organ Failure Assessment (SOFA) score at ICU admission, biological data, COVID-19 treatments, and complications.

The first COVID-19 pandemic wave (w1) refers to ICU admission between March 1, 2020 and October 9, 2020, the second wave (w2) was between October 10, 2020 and March 14, 2021, and the third wave (w3) was between March 15, 2021 and June 30, 2021.

3-month assessment

A comprehensive assessment of patients was performed 3 months after ICU discharge, according to a procedure previously described in Truffaut et al. [10]. Assessments included Chest CT, pulmonary function test (PFT), 6MWD with continuous SpO₂ monitoring, respiratory muscle strength (RMS) measurements, and three questionnaires: Quality of life (QoL) using the Short Form 36 (SF-36), Breathlessness using the modified Medical Research Council dyspnea scale (mMRC), and post-COVID disability using the post-COVID Functional Status (PCFS) test [11].

Statistical analysis

The statistical data treatment included descriptive statistics. Qualitative data are expressed as frequencies and percentages. For quantitative data, the mean and standard deviation were calculated.

The demographic, clinical characteristics and clinical outcomes were compared between the three waves (w1 vs. w2 vs. w3) for demographic and clinical characteristics. Normality and homoscedasticity were assessed with Shapiro's test and Levene's test, respectively, for quantitative variables. In case of data with a normal distribution, a one-way ANOVA was calculated. For pairwise comparisons, a Bonferroni post-hoc test was applied. In cases where the data were not normally distributed, the non-

parametric Kruskal Wallis test was used with a Dunn post-hoc test. The comparison between the three waves for qualitative data was tested with the Marascuilo procedure. The Marascuilo procedure was used to compare proportions when there were more than two groups with binary outcomes (yes/no). This is initially used to perform a test of overall homogeneity for a large contingency table, using the standard Chi Square Test. This is followed by multiple post-hoc comparisons between pairs of groups in the data.

The evolution of the scanner results was compared between waves (w1 vs. w2 vs. w3). The delta (three-month value – baseline value) was calculated for each subject. Next, the delta values were compared between waves with the one-way ANOVA and Bonferroni post-hoc test.

To compare the patients with and without medication (Remdevisir or Tocilizumab) or thromboembolic events for demographic and clinical variables, the one-way ANOVA or Mann Whitney U tests were applied in accordance with the normality of the distribution.

For each wave, the predictive factors of the 3-month clinical outcomes were assessed. A multiple linear or logistic regression analysis (according to data type) was used to determine the variables that had the greatest influence.

A p-value below 0.05 was considered as statistically significant. All analyses were performed using python (version 3.8) with the statistics package statsmodels (version 0.11.1). The package is released under the open source modified BSD (3-clause) license.

Results

Eighty-four ARDS survivors of the first three COVID-19 pandemic waves were included in the study (Fig. 1). The ICU mortality rate was not different between w1 and w2 (29% and 36%, $p = 0.29$) but was significantly lower during w3 vs w1 (18% vs 29%, $p = 0.05$) and vs w2 (18% vs 36%, $p = 0.0002$). Demographics and clinical data for the 84 included patients are summarized in Table 1.

Table 1
Baseline characteristics of patients, according to wave of the pandemic

Variables (mean, SD or n (%))	Wave 1 n = 36	Wave 2 n = 27	Wave 3 n = 21	P value (Anova or Kruskal Wallis tests)	p value (wave 1 vs. wave 2)	p value (wave 1 vs. wave 3)	p value (wave 2 vs. wave 3)
Age	56.64 ± 10.33	59.48 ± 10.92	53.1 ± 13.06	0.1555	0.8868	0.7876	0.2146
Sex, female	8 (22.2%)	11 (14.7%)	12 (57.1%)	0.0274	0.2872	0.0246	0.5205
non obese	14 (38.9%)	13 (48.15%)	11 (52.38%)	0.5739	0.7630	0.6111	0.9585
active smokers	3 (8.33%)	20 (74.07%)	1 (4.76%)	0.6047	0.6814	0.9889	0.6679
Medical history	1 (2.78%)	1 (3.70%)	1 (2.78%)	0.9261	0.9795	0.9346	0.9840
cancer		15 (55.56%)	8 (38.10%)	0.4111	0.5451	0.9652	0.4732
diabetes	15 (41.67%)	17 (62.96%)	10 (47.62%)	0.5677	0.8377	0.8453	0.5634
hypertension	20 (55.56%)	0	0	N/A	0.1974	0.7258	0.7318
HIV	2 (5.56%)	1 (3.70%)	2 (9.52%)	0.2526			
	6 (16.67%)						
OSA							
Length of stay (days)	34.72 ± 20.76	27.81 ± 16.93	23.43 ± 14.25	0.6097	0.1573	0.0304	0.4205
Hospital ICU	20.5 ± 15.97	15.04 ± 14.03	16.95 ± 11.72	0.7744	0.0546	0.5661	0.2543
ICU severity scores	10.06 ± 4.05	9.04 ± 4.82	7.57 ± 5.02	0.3045	0.1587	0.0038	0.1347
APACHE	3.67 ± 2.29	3.11 ± 1.25	3.62 ± 1.69	0.1185	0.6651	0.5879	0.3734
SOFA							

ICU: intensive care unit, ECMO: extracorporeal membranous oxygenation ; OSA, obstructive sleep apnea

Variables (mean, SD or n (%))	Wave 1 n = 36	Wave 2 n = 27	Wave 3 n = 21	P value (Anova or Kruskal Wallis tests)	p value (wave 1 vs. wave 2)	p value (wave 1 vs. wave 3)	p value (wave 2 vs. wave 3)
respiratory support	23 (63.89%)	9 (33.33%)	10 (47.62%)	0.0543	0.0412	0.4849	0.6020
mech. ventilation	12.22 ± 13.44	4.67 ± 7.58	7.86 ± 9.82 9 (42.86%)	0.1099	0.0088	0.2146	0.2621
mean duration	21 (58.33%)	7 (25.93%)	8 (38.09%)	0.8117	0.8377	0.8946	0.9972
curare	16 (44.44%)	10 (37.04%)	1 (4.76%)	0.0900	0.9205	0.0621	0.0438
prone	9 (25.00%)	8 (29.63%)	4 (19.05%)	N/A	0.0186	0.0935	0.9388
high flow oxygen	9 (25.00%)	8 (29.63%)	6 (28.57%)	0.0137	0.7325	0.8003	0.4571
CPAP	0	0					
BIPAP	2 (5.56%)	9 (33.33%)					
ECMO	3 (8.33%)	1 (3.70%)					
			3 (14.29%)	0.4207			
Laboratory data	9137.57 ±	4436.48 ±	6993.19 ± 9353.9	0.1408	0.1439	1.0000	0.8471
D-dimer, mg/dL	244.52 ± 106.17	174.03 ± 95.62	165.0 ± 94.07	0.5058	0.0108	0.0088	0.8085
CRP, mg/dL							
Treatments	21 (58.33%)	27 (100%)	21 (100%)	N/A	0.9908	< 0.0001	< 0.0001
glucocorticoids	3 (8.33%)	0	0	N/A	0.1126	0.0237	0.0387
antiviral	3 (8.33%)	0	0	N/A	0.9947		
remdesevir	3 (8.33%)	2 (7.41%)	0	N/A			
monoclonal antibody	1 (2.78%)	0	15 (71.43%)	< 0.0001			
tocilizumab	7 (19.44%)	1 (3.70%)	11 (52.38%)	0.0067			
broad spectrum antibiotics	31 (86.11%)	23 (85.19%)					
Complications	12 (33.33%)	5 (18.52%)	3 (14.29%)	0.1953	0.3934	0.2206	0.9246
thromboembolic event							
ICU: intensive care unit, ECMO: extracorporeal membranous oxygenation ; OSA, obstructive sleep apnea							

Mean hospital length of stay was shorter during w3 vs w1 (23.4 ± 14.2 days vs 34.7 ± 20.8 days, p = 0.03). Fewer patients required mechanical ventilation (MV) during w2 vs w1 (33.3% vs 63.9%, p = 0.0038), such that the use of curare was also reduced (p = 0.0227). The use of tocilizumab increased significantly during w3 (71.4% vs 19.4% for w1, p < 0.0001 and vs 3.7% for w2, p < 0.0001) while broad-spectrum antibiotic use decreased.

Three months after ICU discharge, no differences in the number of patients exhibiting impairment in the 6MWDt (< 80%) were observed between waves. The results of PFTs, RMS tests, and 6MWDt were similar overall, regardless of the wave. Quality of life, assessed by the SF-36, was worse in the vitality and mental health items for patients from w1 vs w3 (total scores 64.7 ± 16.3 vs 49.2 ± 23.2 , $p = 0.0169$). These results are summarized in Table 2.

Table 2
Comparisons of clinical outcomes between waves

Variables (mean, SD or %)	Wave 1	Wave 2	Wave 3	P value (Anova or K.Wallis)	p (w1 vs. w2)	p (w1 vs. w3)	p (w2 vs. w3)
PFT	2.88 ± 0.72	2.47 ± 0.82	2.26 ± 0.74	0.0096	0.1230	0.0094	1.0
FEV1 (L)		79.81 ± 21.06	79.19 ± 17.67	0.1056	0.2315	0.1489	1.0
FEV1 (%)	87.92 ± 14.71	2.95 ± 0.96		0.0322	0.1466	0.0443	1.0
FVC (L)	3.41 ± 0.83	74.52 ± 19.58	2.8 ± 0.94	0.2299	0.2585	1.0	1.0
FVC (%)			78.33 ± 18.25	0.2218	0.8973	0.9969	0.9130
FEV1/FVC	82.28 ± 15.73	0.83 ± 0.08	0.82 ± 0.1	0.6118	1.0	0.9340	1.0
DLCO (%)	0.83 ± 0.07	78.24 ± 22.23	75.35 ± 22.34				
	81.12 ± 18.32						
6MWDt	500.18 ± 89.07	417.71 ± 132.89	434.1 ± 109.0	0.0250	0.0533	0.0596	1.0
distance (m)				0.1831	0.2060	0.5454	1.0
distance (%)	73.05 ± 11.36	83.67 ± 91.36	67.88 ± 16.45	0.7904	0.8134	1.0000	0.8564
distance < 80%	n = 24 (66.67%)	n = 19 (70.37%)	n = 14 (66.67%)	0.7411	0.7331	0.9683	0.9038
oxygen desaturation	n = 11 (33.33%)	n = 6 (24.00%)	n = 6 (30.00%)				
RMS	89.03 ± 28.06	70.98 ± 34.01	77.81 ± 35.9	0.0931	0.0802	0.6038	1.0
IP max (cm H2O)				0.0637	0.1612	0.1040	1.0
EP max (cm H2O)	105.95 ± 32.06	87.71 ± 39.09	85.57 ± 36.07				
mMRC	0.74 ± 0.96	1.26 ± 1.1	1.33 ± 1.2	0.0722	0.1551	0.1399	1.0000
PCFS	1.31 ± 1.18	1.56 ± 1.19	1.67 ± 1.43	0.7272	1.0	1.0	1.0
SF36	64.71 ± 16.26	57.23 ± 21.46	49.19 ± 23.24	0.0241	0.4004	0.0169	0.6743
PFT: pulmonary function test, FEV: forced expiratory volume; FVC: forced vital capacity; DLCO: diffusing capacity of the lungs for carbon monoxide; 6MWT: 6-minute walking distance test, RMS: respiratory muscle strength, SF36: Short Form 36, PCFS: post-COVID Functional Status, mMRC: modified Medical Research Council dyspnea scale, IP: inspiratory pressure, EP: expiratory pressure							

No differences in affected segments were observed at baseline and 3-month chest CT, but at 3 months, more patients from w2 vs w1 exhibited ground glass opacities (41% vs 3%, $p = 0.0006$) and fibrosis was much more frequent in w1 vs w2 (94% vs 67%, $p = 0.0186$).

The multiple linear or logistic regression analysis highlighted that for w1 patients, total lung capacity (TLC), forced expiratory volume 1 (FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), maximum inspiratory pressure (PI Max), and

6MWDt at 3 months were correlated with mechanical ventilation (MV) and high APACHE II score (all $p < 0.05$ and $p \leq 0.01$, respectively), as well as SF-36 ($p = 0.006$). The number of affected segments on 3-month CT correlated with the initial number of affected segments on chest CT scan ($p = 0.04$) and with high APACHE II score ($p = 0.04$).

For w2 patients, TLC, FEV1, DLCO, and PI Max at 3 months were correlated with MV and high SOFA score (all $p \leq 0.02$ and $p \leq 0.03$, respectively). SF-36 correlated with SOFA ($p = 0.02$), and PCFS with extracorporeal membrane oxygenation (ECMO) duration ($p = 0.03$).

For w3 patients, TLC, FEV1, DLCO, and 6MWDt were correlated with MV ($p \leq 0.01$) as was SF-36 ($p = 0.03$). Low SF-36 and high PCFS scores were correlated with low 6MWDt ($p = 0.01$ and 0.03).

The use of glucocorticoids was associated with better TLC, FEV1, DLCO, and number of affected segments on 3-month CT (all $p < 0.0001$), and tocilizumab was associated with higher TLC ($p = 0.027$) (w1), and with a reduction in affected segments on 3-month CT ($p = 0.0065$) (w2). Remdesivir improved MV duration in w2 ($p = 0.0083$).

Patients in w3 suffering from acute thromboembolic events exhibited a decreased 6MWDt ($p = 0.035$) and a higher number of affected segments on 3-month CT ($p = 0.0293$).

Discussion

This study shows that, despite progressive better understanding and management of COVID-19 patients, pulmonary functional outcomes (PFT, 6MWDt, RMS) remained similar in each pandemic wave. Disappointingly, in survivors, long-term outcomes of ICU COVID-19 did not improve during the second and third waves. However, patients from w1 exhibited more fibrosis on chest CT compared with patients from w2, a result that can be explained by a lower use of GC in w1. W1 patients also reported worse QoL in vitality and mental health items versus those in w3, a result that is probably related to supplemental factors that affected emotional well-being in w1, such as reduced access to family members during ICU stay, isolation, and fear of spreading the virus to others [12].

On multivariate analysis, the main factors explaining pulmonary functional outcomes were MV and ICU severity score at admission that reflect more severe illness. Several studies have focused on ICU mortality rate and management differences between waves. Carbonell et al. reported, as in the present series, an increased use of GC in w2/3 vs w1 [13]. The need for MV remained high in the three waves but an increased use of high-flow nasal oxygen (HFNO) was described that was not observed in our survivors. In their study, mortality was similar during the first three consecutive waves, whereas it decreased significantly in our series. In a Swiss study comparing short-term outcomes of hospitalized patients during the first and second waves, mortality was also similar despite the use of GC in 76% vs 0% [14]. Length of stay was shorter by 2.5 days in w2, as observed in our series for w3 vs w1 (-11 days).

Our study particularly focused only on long-term outcomes in ICU COVID-19 survivors and not on the characteristics of survivors versus non-survivors. Outcomes in hospitalized, including ICU, patient cohorts from w1 at 3 months and 4 months are now well documented [10, 15–17], showing alterations in PFT (restrictive +/- decreased DLCO) and 6MWDt in about half of the patients, radiologic impairment in more than 70% of patients, and dyspnea in one-third. Radiologic abnormalities have been correlated with length of MV [15], length of ICU stay [16], initial radiologic extension [10], ICU admission and MV [17]. However, no studies have compared the outcomes of hospitalized patients according to successive pandemic waves.

It is surprising and disappointing that increased experience and use of effective medications in critically-ill patients since the mid-first wave did not change outcomes in survivors, despite a proven impact on 28-day mortality for GC [5], tocilizumab, and remdesivir, when given at the right time in the right patient [18, 19].

Mechanical ventilation is still a factor related to poor outcome 3 months after discharge, regardless of pandemic wave. MV has been reported as a major risk factor for death in COVID in two European studies [13, 20], but when they survive, patients are also more disabled after MV. Impaired DLCO and 6MWDt have been shown to be related to MV in a Spanish series of 78

COVID-19 ICU patients [21]. Noel-Savina et al., in a French cohort of 72 patients that included 75% ICU COVID-19 patients, also showed that COVID-19 patients who required MV exhibited more frequently impaired DLCO, gas exchange abnormalities, and interstitial lung disease on chest CT scan 4 months after discharge [17].

Limitations

Despite the relatively small sample size of our study, our results appear to correctly reflect the outcomes of the critically-ill COVID-19 population, as patient characteristics and management in this study were similar to other larger series [13, 14, 17].

Conclusions

The present study shows, for the first time, a comparison of pulmonary functional outcomes, radiologic impairment, and quality of life 3 months after ICU discharge in critically-ill COVID-19 patients in the three waves of the COVID-19 pandemic. Disappointingly, despite increased experience and the use of more effective medications since the mid-first wave of COVID-19, PFT, 6MWD, RMS, and chest CT alterations remained similar in ICU survivors, regardless of the wave of the pandemic in which they were hospitalized. QoL was decreased in w1 vs w3, probably related to the extreme fear observed at the beginning of the pandemic.

Declarations

Acknowledgements: The authors acknowledge the contribution of a medical writer, Sandy Field, PhD, for English language editing and formatting of the manuscript.

Author contributions: CD, JS, SA, MB, MC, AR, AC, DDB, NDV collected the data; SA, CD, AVB, OM, SAI, MB, DDB, NDV performed data analyses and prepared the manuscript. SA, AC, JS, CD, AVB, OM, SAI, MB, DDB, NDV, MC, AR have approved the final version of the manuscript.

Funding: No funding was received to perform this study.

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

Ethics approval and consent to participate: All included patients provided written informed consent to participate in the study. The study protocol was approved by the Saint-Pierre University Hospital ethics committee (AK/16-01-18/4613) and by the Brugmann University Hospital ethics committee (CE2020/141).

Consent for publication: Not applicable

Competing interests: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Figures

Figure 1

Flow chart of patients included in the study