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ORIGINAL



# Influence of socio-economic status on functional recovery after ARDS caused by SARS-CoV-2: the multicentre, observational RECOVIDS study

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## Abstract

**Purpose:** Survivors after acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) are at high risk of developing respiratory sequelae and functional impairment. The healthcare crisis caused by the pandemic hit socially disadvantaged populations. We aimed to evaluate the influence of socio-economic status on respiratory sequelae after COVID-19 ARDS.

**Methods:** We carried out a prospective multicenter study in 30 French intensive care units (ICUs), where ARDS survivors were pre-enrolled if they fulfilled the Berlin ARDS criteria. For patients receiving high flow oxygen therapy, a flow  $\geq 50$  l/min and an  $\text{FiO}_2 \geq 50\%$  were required for enrollment. Socio-economic deprivation was defined by an EPICES (Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé - Evaluation of Deprivation and Inequalities in Health Examination Centres) score  $\geq 30.17$  and patients were included if they performed the 6-month evaluation. The primary outcome was respiratory sequelae 6 months after ICU discharge, defined by at

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least one of the following criteria: forced vital capacity < 80% of theoretical value, diffusing capacity of the lung for carbon monoxide < 80% of theoretical value, oxygen desaturation during a 6-min walk test and fibrotic-like findings on chest computed tomography.

**Results:** Among 401 analyzable patients, 160 (40%) were socio-economically deprived and 241 (60%) non-deprived; 319 (80%) patients had respiratory sequelae 6 months after ICU discharge (81% vs 78%, deprived vs non-deprived, respectively). No significant effect of socio-economic status was identified on lung sequelae (odds ratio (OR), 1.19 [95% confidence interval (CI), 0.72–1.97]), even after adjustment for age, sex, most invasive respiratory support, obesity, most severe P/F ratio (adjusted OR, 1.02 [95% CI 0.57–1.83]).

**Conclusions:** In COVID-19 ARDS survivors, socio-economic status had no significant influence on respiratory sequelae 6 months after ICU discharge.

**Keywords:** ARDS, COVID-19, Socio-economic, Deprivation, Respiratory sequelae

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes severe cases of hypoxemic pneumonia. During the first months of the coronavirus disease 2019 (COVID-19) crisis, around 5% of symptomatic patients required admission to the intensive care unit (ICU) and 50–70% of those needed mechanical ventilation, due to progression to acute respiratory distress syndrome (ARDS) [1–3]. COVID-19 ARDS survivors are at high risk of developing functional impairment and new disabilities, not only due to the severity of the pulmonary infection, but also because of potential multi-organ dysfunction and long ICU stay, as previously reported in non-COVID-19 ARDS [4]. Many COVID-19 cohort studies involved non-ARDS patients, and little is known about the respiratory sequelae late after ICU discharge in patients who survive ARDS [5–7]. A recent meta-analysis of 23 observational cohort studies showed in pooled analysis that lower socio-economic status was associated with higher mortality up to 30 days after admission to critical care, and may also be associated with functional status and discharge destination after ICU admission [8]. The healthcare crisis caused by the COVID-19 pandemic hit socially disadvantaged populations particularly hard [9–11], and may have exacerbated these social disparities in health [12]. In a study using surveillance data reported to the Swiss Federal Office of Public Health from March 1, 2020, to April 16, 2021, Riou et al. reported that during the COVID-19 pandemic in Switzerland, people living in neighbourhoods of low socio-economic position were less likely to be tested but more likely to test positive, be admitted to hospital, or die, compared with those living in areas of high socio-economic position [13]. A life-course trajectory of disadvantaged socio-economic status has been shown to be an important predictor of lower lung function during adulthood [14].

## Take-home message

In this prospective multicenter cohort of 401 patients who survived acute respiratory distress syndrome due to coronavirus disease 2019, socio-economic status defined by EPICES score was not significantly associated with respiratory sequelae 6 months after intensive care unit (ICU) discharge in French healthcare settings.

The frequency of respiratory sequelae defined by the presence of at least one of the following elements: forced vital capacity < 80%, diffusing capacity of the lungs for carbon monoxide < 80%, oxygen desaturation during a 6-min walk test and fibrotic-like findings at chest computed tomography, was still high (80%) at 6 months after ICU discharge.

Thereby, socio-economic status may hamper recovery from long-term COVID-19 ARDS consequences. In this context, we conducted the prospective, multicentre RECOVIDS study, to assess the influence of socio-economic status on respiratory recovery in COVID-19 ARDS patients.

## Methods

### Study design

Details of the study design have previously been published [15]. Briefly, the RECOVIDS study is an observational, multicentre cohort study performed in 30 French centres during routine care for post-ICU functional recovery. The main objective was to evaluate respiratory recovery after COVID-19-related ARDS at 6 months after ICU discharge, according to patients' socio-economic deprivation status. The study was approved by the ethics committee "Comité de Protection des Personnes Sud Méditerranée II" on 10/07/2020 under the number 2020-A02014-35. In line with French legislation, oral informed consent was obtained from all patients.

## Patients

All adult patients admitted to an ICU for SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR), in any of the 30 participating centres were eligible. To be included, patients had to have undergone chest computed tomography (CT) scan at the initial phase of management; have ARDS diagnosed according to the Berlin 2012 definition [16] or received high flow nasal oxygen with a flow of at least 50L/minute with  $\text{FiO}_2 > 50\%$  and a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 200$ . The main exclusion criteria included a walking perimeter  $< 50$  m or World Health Organization (WHO) performance status 3 or 4; chronic respiratory insufficiency; patients not affiliated to the national health insurance and patients under legal protection (details in Supplemental eMethods 1). Moreover, patients who subsequently failed to attend the first evaluation at 6 months after ICU discharge or who did not have the required tests to enable evaluation of the primary endpoint were excluded from statistical analysis.

## Procedures

As previously described [15], patients were screened at ICU discharge and during hospitalization in post-ICU units. If patients fulfilled the inclusion and exclusion criteria, they were pre-included. The scheduled follow-up was performed at  $6 \pm 1$  months after ICU discharge and included a clinical exam with evaluation of dyspnea by the modified Medical Research Council dyspnea scale (mMRC) [17], a 6-min walk test (6MWT) performed according to the guidelines from the European Respiratory Society (ERS) and the American Thoracic Society (ATS) [18], pulmonary function tests (PFT) including spirometry, plethysmography and measurement of diffusing capacity of the lungs for carbon monoxide ( $\text{DL}_{\text{CO}}$ ) according to the ATS/ERS guidelines [19, 20], and chest CT without contrast. Dependency was evaluated using the activities of daily living (ADL) [21] and lower limb weakness using the Borg scale before and after the 6MWT. Respiratory quality of life was evaluated focusing on potential effects of respiratory status using the Visual Simplified Respiratory Questionnaire (VSRQ) [22] (Supplemental eFigure 1).

Social deprivation was assessed at the individual level using the EPICES (Evaluation of Deprivation and Inequalities in Health Examination Centers) score [23]. The EPICES score measures social and material deprivation using 11 items relating to social conditions, leisure activities and family/social support [24, 25] (Supplemental eFigure 2). Patients with an EPICES score  $\geq 30.17$  (corresponding to the lower boundary of the fourth quintile in the validation study of this score) were considered as socially deprived [25]. Ecological deprivation was also assessed at the level of the IRIS (aggregated units

for statistical information) using the French European Deprivation Index (FEDI) based on a combination of 10 weighted census-derived variables [26].

Data related to socio-demographic characteristics and the ICU stay until hospital discharge are detailed in the Supplemental eMethods 2.

## Outcomes

The primary outcome was the presence of lung sequelae at 6 months after ICU discharge, defined as the presence of any one or more of the following criteria:

1. Alterations on PFTs:
  - (a)  $\text{DL}_{\text{CO}} < 80\%$  of the theoretical value
  - (b) And/or forced vital capacity (FVC)  $< 80\%$  of the theoretical value
2. Oxygen desaturation during a standardized 6MWT:
  - (a)  $\Delta \text{SpO}_2$  ( $\text{SpO}_2$  pre walk- $\text{SpO}_2$  post walk)  $\geq 4\%$  and  $\text{SpO}_2$  post walk  $< 90\%$
3. Fibrotic-like pulmonary findings on thin-slice non-enhanced chest CT:
  - (a) traction bronchiectasis
  - (b) lung architectural distortion
  - (c) loss of lung volume with reticular and/or ground glass opacities
  - (d) honeycombing

Chest CT interpretation were centralized and performed independently by two experienced chest radiologists blinded to clinical information. In case of disagreement, a final decision was reached by consensus. The fibrotic-like findings were qualitatively measured and corresponded to the terms used to describe pulmonary fibrosis in the Glossary of Terms for Thoracic Imaging of the Fleischner Society [27].

The main secondary outcomes included the persistence of dyspnea, PFT results and muscular dependency, 6 months after ICU discharge (details in Supplemental eMethods 3).

## Sample size calculation

Given the lack of specific COVID-19 data at the time the study was designed, the sample size was based on the expected number of admissions in the participating centers as estimated from the number of patients admitted to ICU during the first wave in Spring 2020. Accordingly, 500 patients were expected to be included, enabling detection of an odds ratio (OR) ranging from 1.664 to 2.924, at a two-sided significance level of 5%, power of 80%, with a social deprivation rate of 50% (based on the

IVOIRE cohort study [23]), and assuming a respiratory sequelae rate at 6 months ranging from 50% to 90% in patients surviving ARDS [28].

### Statistical analysis

Patient characteristics are described according to deprivation status as number and percentage for categorical variables, and mean  $\pm$  standard deviation (SD) (or median and (Q1–Q3) depending on the distribution) for continuous variables. Data were compared using the Chi-2 or Fisher's exact test for categorical variables, and the Student *t* or Wilcoxon tests for continuous variables, as appropriate.

The impact of social deprivation on the presence of lung sequelae at 6 months was analyzed using logistic regression. Analyses were adjusted for clinically relevant factors [age, gender, Simplified Acute Physiology Score II (SAPSI) and Sequential Organ Failure Assessment (SOFA) score at ICU admission, Charlson comorbidity score, body mass index (BMI) at ICU admission, most invasive respiratory support during ICU stay, most severe P/F ratio, hospital acquired pneumonia, length of ICU stay, corticosteroids, presence of rehabilitation between hospital discharge and 6-month evaluation, COVID-19 wave, and center characteristics (university vs non-university hospital)]. We also performed multilevel logistic regression using the FEDI: the first level was the FEDI, and the second was the patient, to take into account the deprivation effect at a contextual and individual level. The model was adjusted for the same factors as above. The main analysis was performed on complete cases. A sensitivity analysis was also performed on imputed data. Missing data were assumed to be missing at random. The chained equation method was used to impute missing data of any patients fulfilling the inclusion, non-inclusion and secondary exclusion criteria. Ten imputed data sets were generated and the modeling described above was applied to each. Finally, results of the 10 analyses were pooled to obtain OR and the associated 95% confidence interval (CI) for each parameter.

Collinearity between adjustment variables was verified by calculating the variance inflation factor (VIF); all values were  $< 5$ , indicating absence of multicollinearity.

All secondary outcomes are described in each group (deprived/non-deprived) and were compared between groups using the Chi-2, Student *t* or Wilcoxon test, as appropriate.

All analyses were performed using SAS Version 9.4 (SAS Institute Inc. Cary, NC, USA) with a bilateral significance threshold of  $p < 0.05$ .

## Results

### Study population

A total of 4529 adult patients with ARDS were discharged alive from 30 participating ICUs between September 2020 and June 2021. Among them, 742 (16%) were invited to participate, of whom 543 (73%) consented to participate. Finally, 401 patients were fully analyzable after verification of compliance with inclusion and non-inclusion criteria, and exclusion of patients who did not attend the 6-month evaluation, or for whom the primary endpoint or the EPICES score were not available (Fig. 1).

Imputed and analyzable patients were comparable regarding demographic and clinical characteristics at baseline (Supplemental eTable 1).

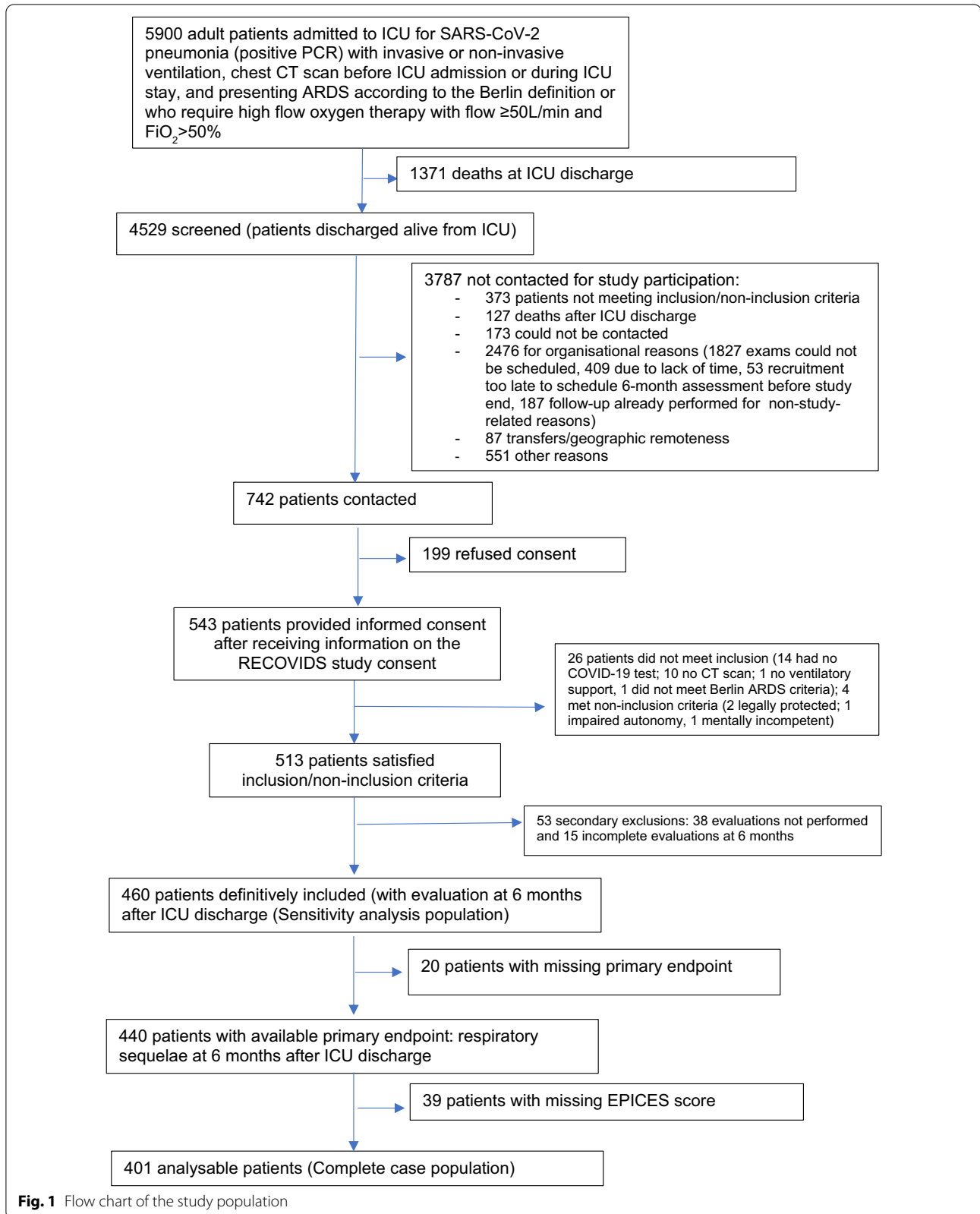
Among the 401 patients included in the final analysis, 160 (40%) were classed as deprived. Mean age ( $64 \pm 11$  years) did not differ significantly by deprivation status. Deprived patients were more frequently women (39% vs 28%;  $p = 0.02$ ), obese (49% vs 35%;  $p = 0.007$ ) and less often had a history of heart failure (1% vs 5%;  $p = 0.03$ ) compared with non-deprived patients. Regarding social inequalities, deprived patients more frequently lived alone (31% vs 9%;  $p < 0.0001$ ), were less often eligible to pay income tax (32% vs 62%;  $p < 0.001$ ), had a lower rate of graduation from high school (69% vs 55%;  $p = 0.007$ ) and were less often in employment before COVID (29% vs 37%;  $p = 0.001$ ) than non-deprived patients (Table 1).

The characteristics of ICU and post ICU stay and management did not significantly differ between the 2 groups (Table 2), except for respiratory assistance at ICU discharge, which was more frequent in non-deprived vs deprived patients (82% vs 72%;  $p = 0.024$ ) (Supplemental eTable 2). There were no significant differences between groups concerning ICU adverse events (Supplemental eTable 3).

The type of post-ICU rehabilitation was similar between deprived and non-deprived patients, as were the hospital discharge conditions (Supplemental eTable 4). In the overall cohort, 30% of patients were prescribed rehabilitation at hospital discharge, but half of the overall population (52%) actually performed rehabilitation once discharged, with no difference according to deprivation status.

### Primary outcome

In all, 319 patients (80%) had lung sequelae at 6 months after ICU discharge (81% in deprived patients vs 78% in non-deprived patients) (Supplemental eTable 5), with no significant impact of deprivation (crude OR = 1.19 [0.72; 1.97];  $p = 0.49$ ) even after adjustment for clinically relevant factors (adjusted OR = 1.02 [0.57–1.83];  $p = 0.95$ ). Complementary analysis (multilevel modelling



**Table 1 Comparison of patients at admission to the intensive care unit according to socio-economic status**

	No./total (%) All patients, N = 401	No./total (%) Non-deprived, N = 241	No./total (%) Deprived, N = 160	p value
<b>Sociodemographic characteristics</b>				
Age, mean (SD), years	64 (11)	64 (11)	62 (12)	0.14
Female	129 (32)	67 (28)	62 (39)	0.02
EPICES score, mean (SD)	27 (18)	15 (9)	44 (13)	
<b>Quintiles of EPICES score</b>				
1 [0; 7,10[	40 (10)	40 (17)	0 (0)	
2 [7,10; 16,56[	96 (24)	96 (40)	0 (0)	
3 [16,56; 30,17[	105 (26)	105 (44)	0 (0)	
4 [30,17; 48,52[	113 (28)	0 (0)	113 (71)	
5 [48,52; 100]	47 (12)	0 (0)	47 (29)	
Less than high school diploma	238/392 (61)	130/235 (55)	108/157 (69)	0.007
<b>Employment status</b>				
Employed	134/396 (34)	88/237(37)	46/159 (29)	0.001
Retired	229/396 (58)	139/237 (59)	90/159 (57)	
Not working	33/396 (8)	10/237 (4)	23/159 (14)	
<b>Socioeconomic category</b>				
Farmers	11/358 (3)	5/225 (2)	6/133 (4)	<.001
Self-employed/own business	39/358 (11)	31/225 (14)	8/133 (6)	
Upper management and liberal professions	70/358 (20)	57/225 (25)	13/133 (10)	
Intermediate professions	46/358 (13)	33/225 (15)	13/133 (10)	
Employees	105/358 (29)	47/225 (21)	58/133 (44)	
Labourers	87/358 (24)	52/225 (23)	35/133 (26)	
<b>Married or living maritally</b>				
Have children	308/396 (78)	211/238 (89)	97/158 (61)	<.001
Living alone	347/393 (88)	210/235 (89)	137/158 (87)	0.43
Urban dwelling	72/396 (18)	22/237 (9)	50/159 (31)	<.001
Eligible to pay income tax	188/393 (48)	106/236 (45)	82/157 (52)	0.16
Prefer not to say	201/394 (51)	150/235 (64)	51/159 (32)	<.001
Formal home help	38 (9)	25/235 (11)	13/159 (8)	
Katz ADL score, median (IQR) [no.]	42/395 (11)	21/236 (9)	21/158 (13)	0.17
	6 (6–6) [394]	6 (6–6) [238]	6 (6–6) [156]	
<b>Pre-existing conditions</b>				
Alcohol				0.009
None (never or former)	174/387 (45)	90/229 (39)	84/158 (53)	
At least one drink per day	213/387 (55)	139/229 (61)	74/158 (47)	
Tobacco				0.008
Never	191/400 (48)	106/240 (44)	85/160 (53)	
Current	11/400 (3)	3/240 (1)	8/160 (5)	
Former	198/400 (49)	131/240 (55)	67/160 (42)	
Charlson comorbidity index $\geq$ 1	183/400 (46)	104/240 (43)	79/160 (49)	0.23
Hypertension	196 (49)	114 (47)	82 (51)	0.44
Diabetes	110 (27)	60 (25)	50 (31)	0.16
Mild to severe chronic renal failure	7/398 (2)	2/239 (1)	5/159 (3)	0.12
Congestive heart failure	12 (3)	11 (5)	1 (1)	0.03
Chronic pulmonary disease	28/400 (7)	14/241 (6)	14/159 (9)	0.26
Solid tumor with or without metastases (< 5 years)	12 (3)	13 (5)	12 (8)	0.4
Hematological malignancy	12 (3)	8 (3)	4/160 (3)	0.77
<b>BMI</b>				
< 30	234/395 (59)	155/240 (65)	79/155 (51)	0.02
[30; 40[	131/395 (33)	67/240 (28)	64/155 (41)	

**Table 1 (continued)**

	No./total (%) All patients, N = 401	No./total (%) Non-deprived, N = 241	No./total (%) Deprived, N = 160	p value
≥ 40	30/395 (8)	18/240 (7)	12/155 (8)	
<b>COVID-19 epidemic wave</b>				0.75
First wave	141 (35)	88 (36)	53 (33)	
Second wave	209 (52)	122 (51)	87 (54)	
Third wave	51 (13)	31 (13)	20 (13)	
<b>Severity of illness</b>				
SOFA, median (IQR)	4 (3–6)	4 (3–6)	4 (3–6)	0.92
SAPS II, median (IQR) [no.]	34 (28–43) [399]	34 (28–44) [240]	35 (28–43) [159]	0.59

ADL activity daily living, BMI body mass index, COVID-19 coronavirus disease 2019, EPICES evaluation of deprivation and inequalities in health examination centres (translated from French), IQR interquartile range, SD standard deviation, SOFA sequential organ failure assessment, SAPS II, simplified acute physiology score II

and analysis of the imputed population) yielded similar results (Table 3).

### Secondary outcomes

Regarding respiratory evaluations (Table 4), deprived patients more often had dyspnea than non-deprived patients according to the mMRC scale (66% vs 50%;  $p=0.004$ ), with a lower walking distance on the 6MWT (411 m ± 131 vs 444 m ± 121;  $p=0.01$ ), slightly lower level of SpO<sub>2</sub> at the end of the 6MWT (95% [93–97] vs 94% [92–97];  $p=0.04$ ) and a slightly more altered functional respiratory profile. Absolute values of volumes and flows collected on PFT were significantly lower in deprived patients, but when using predicted values, only forced expiratory volume in 1 s (FEV1) and FVC were significantly lower in deprived compared to non-deprived patients. Quality of life (QoL) assessed by the VSRQ score was lower in deprived patients.

Fibrotic-like lesions on chest CT were found in 37%, with no significance difference between deprived and non-deprived patients (33% vs 41%;  $p=0.09$ ) (Table 4).

Concerning muscular dependency (Supplemental eTable 6), there was no difference between deprived and non-deprived patients.

### Discussion

This study accrued one of the largest multicentre cohorts to date of COVID-related ARDS survivors, with extensive evaluation of respiratory and physical status at 6 months after discharge from the ICU. A high proportion (80%) of patients had persistent respiratory defects at 6 months, although we did not observe any difference in respiratory recovery according to socio-economic status. This corroborates a previous report, which found no difference across patient groups in self-perceived recovery after COVID-19, according to the Index of Multiple Deprivation [29].

In our study, the absence of any effect of social deprivation status on respiratory recovery could be explained by several factors. First, there was no difference in terms of rehabilitation after hospital discharge between deprived and non-deprived patients. The impact of socio-economic status on health has long been established [30], and this overall effect is largely mediated by lifestyle [31, 32]. However, in practical terms, lifestyle choices are often constrained by the socio-economic environment and the individual's living conditions [33, 34], culminating in overall poorer health outcomes in individuals with higher levels of poverty or social deprivation [35, 36].

However, the majority of studies to date have mainly investigated the relation between socio-economic status and mortality, especially in the context of the COVID-19 pandemic [8, 13, 36–38]. There is no evidence that socio-economic status influences post ICU rehabilitation access or compliance, as has been described in patients with chronic obstructive pulmonary disease [39] or after surgery [40]. The long-term effects of rehabilitation after ICU in patients who received prolonged mechanical ventilation remain debated [41]. One study reported a positive effect of rehabilitation on physical function at 6 months after discharge [42]. It is thus possible that rehabilitation, including at the very least, regular physical activity, could help patients to limit the sequelae of COVID-19 and recommendations have been issued for the use of rehabilitation programs after COVID-19 [43–45]. Several studies have shown short-term benefits of early rehabilitation at ICU discharge, when performed in dedicated rehabilitation facilities, with effects observed in muscle strength, physical autonomy [46, 47] and respiratory function [46]. However, data are sparse regarding the value of pursuing rehabilitation after hospital discharge. One randomized, controlled trial showed that respiratory rehabilitation performed 6 months after COVID-19 in patients aged over 65 years



**Table 2 Patient management in ICU and post ICU ward until hospital discharge according to socio-economic status**

	No./total (%) All patients, N = 401	No./total (%) Non-deprived, N = 241	No./total (%) Deprived, N = 160
<b>Most invasive respiratory support</b>			
IMV	205 (51)	123 (51)	82 (51)
NIV $\geq$ 24 h then IMV	36 (9)	21 (9)	15 (9)
NIV ( $\pm$ HFOT)	36 (9)	20 (8)	16 (10)
HFOT	124 (31)	77 (32)	47 (29)
<b>Most severe P/F ratio</b>			
[200; 300[	19/395 (5)	15 (6)	4 (3)
[100; 200[	170/395 (43)	104 (43)	66 (41)
< 100	206/395 (52)	121 (50)	85 (53)
<b>Prone positioning</b>			
Number of prone sessions, median (IQR) [no.]	219 (55)	135 (56)	84 (53)
	3 (2–5) [211]	3 (2–5) [135]	3 (1–5) [84]
<b>Patients receiving IMV</b>			
Duration, median (IQR), d [no.]	241/401 (60)	144/240 (60)	97/160 (61)
	17 (9–8) [227]	16 (9–26) [135]	17 [9–28] [92]
PEEP max, mean (SD), cm of water [no.]	13 (2.9) [230]	13.2 (3.1) [138]	12.8 (2.7) [92]
Pplat max, mean (SD), cm of water [no.]	29.4 (5.6) [200]	29.1 (5.6) [124]	29.8 (5.5) [76]
Cst min, mean (SD), ml per cm of water [no.]	25.5 (12.7) [142]	26.3 (11.7) [89]	24 (14.2) [53]
Neuromuscular blockade	220 (91)	131 (91)	89 (92)
Neuromuscular blockade duration, median (IQR), days [no.]	5 (3–10) [215]	5 (3–10) [130]	4 (3–9) [85]
Inhaled nitric oxide	33/239 (14)	19/142 (13)	14/97 (14)
VV ECMO	14/240 (6)	10/143 (7)	4/97 (4)
VV ECMO duration, median (IQR), days [no.]	10.5 (6–15)	10.5 (7–12)	9 (2–16)
<b>IMV weaning</b>			
Tracheal re-intubation after weaning failure	26/241 (11)	13/144 (9)	13/97 (13)
Tracheotomy	52/241 (22)	32 (22)	20/97 (21)
IMV with tracheotomy duration, median (IQR), days [no.]	18 (14–31) [33]	16 (12–28) [19]	22.5 (14–35) [14]
<b>Patients receiving NIV during ICU stay</b>			
Maximum Pressure support, median (IQR), cm of water [no.]	133/401 (33)	83/240 (35)	50/160 (31)
	9 (7–12) [109]	10 (7–12) [70]	8 (6–11) [39]
PEEP max, median (IQR), cm of water [no.]	8 (6–10) [119]	7 (6–8) [74]	8 (6–10) [45]
FiO <sub>2</sub> max, median (IQR), % [no.]	60 (40–100) [129]	60 (40–100) [79]	60 (40–90) [50]
NIV duration, median (IQR), days [no.]	3 (2–6) [121]	3 (2–6) [77]	4 (2–6.5) [44]
<b>Patients receiving HFOT during ICU stay</b>			
Flow max, median (IQR), L/min [no.]	307/400 (77)	184/241 (76)	123/160 (77)
	50 (50–60) [291]	50 (50–60) [174]	50 (50–60) [117]
FiO <sub>2</sub> max, median (IQR), % [no.]	80 [60–100] [294]	80 (60–100) [175]	80 (60–100) [119]
HFOT duration, median (IQR), days [no.]	5 (3–8) [297]	5 (3–8) [178]	5 (3–8) [119]
<b>Other organ support</b>			
Vasopressors	191 (48)	118 (49)	73 (46)
Vasopressor duration, median (IQR), days [no.]	6 (3–12) [183]	6 (3–10) [116]	5 (3–15) [67]
Inotropic agent	10 (2)	7 (3)	3 (2)
Renal replacement therapy	19 (5)	9 (4)	10 (6)
VA ECMO	1 (0)	0 (0)	1 (1)
<b>SARS-CoV-2 infection treatment</b>			
Antiviral therapies	85/400 (21)	51/241 (21)	34/159 (21)
Corticosteroids therapies	223/400 (56)	133/241 (55)	90/159 (56)
Other Immunomodulatory therapies	23/400 (6)	12/241 (5)	11/159 (7)
Length of ICU stay, median (IQR), days	13 (7–28)	13 (7–27)	13 (7–30)
Length of hospital stay, median (IQR), days	23 (15–45)	22 (15–45)	25.5 (15–50)
Time from ICU discharge to hospital discharge, median (IQR), days	7 (4–14)	7 (4–14)	7.5 (5–16)
<b>Significant complications between ICU discharge and hospital discharge</b>			
ICU re-admission	11/399 (3)	5 (2)	6 (4)
Tracheal intubation for IMV	2/399 (1)	1 (1)	1 (1)

**Table 2 (continued)**

ICU intensive care unit, IMV invasive mechanical ventilation, NIV non-invasive mechanical ventilation, HFOT high flow oxygen therapy, P/F ratio partial pressure of arterial oxygen divided by fraction of inspired oxygen, PEEP max maximum of positive end-expiratory pressure, Pplat max maximum of plateau pressure, Cst min minimum of static compliance of the respiratory system, VV ECMO veno-venous extracorporeal membrane oxygenation, FIO<sub>2</sub> max maximum of fraction of inspired oxygen, AV ECMO arterio-venous extracorporeal membrane oxygenation, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

**Table 3 Results of primary analysis: effect of socio-economic status on lung sequelae 6 months after ICU discharge**

	Complete case analysis <sup>a</sup>		Multilevel analysis <sup>b</sup>		Imputed data sets <sup>c</sup>
	OR [95% CI]	p value	Adjusted <sup>d</sup> OR [95% CI]	p value	Adjusted <sup>d</sup> OR [95% CI]
EPICES		0.49		0.95	
Deprived	1.19 [0.72; 1.97]		1.02 [0.57; 1.83]		1.08 [0.62; 1.87]
Non-deprived	Reference		Reference		Reference

OR odds ratio, CI confidence interval, EPICES evaluation of deprivation and inequalities in health examination centres (translated from French), FEDI French European deprivation index, BMI body mass index, SOFA sequential organ failure assessment, SAPS II simplified acute physiology score II, P/F ratio partial pressure of arterial oxygen divided by fraction of inspired oxygen, ICU intensive care unit

<sup>a</sup> Number of analyzed patients: 378

<sup>b</sup> Analysis taking account of FEDI, number of analyzed patients: 366

<sup>c</sup> Sensitivity analysis, number of analyzed patients: 460

<sup>d</sup> Adjusted for: center characteristics (university vs non-university Hospital), sex, age, COVID-19 wave, BMI at inclusion, corticosteroids, SAPS II and SOFA at inclusion, most invasive respiratory support during ICU stay, most severe P/F ratio, hospital acquired pneumonia, length of ICU stay, rehabilitation between hospital discharge and 6 month visit, Charlson comorbidity index

yielded a significant improvement in lung function tests, and 6MWT distance [48]. In our cohort, 52% of the population were able to attend rehabilitation after hospital discharge, regardless of their level of social deprivation, even though only 30% of the population left the hospital with a prescription for rehabilitation. The dose of rehabilitation was similar in the 2 groups, although this finding should be taken with caution due to the few data available. The French health system provides access with full coverage for all citizens, likely indicating that there was equal access to rehabilitation services for all patients throughout the country. Together with the medical follow-up, this probably explains why there was no difference regarding rehabilitation.

A second potential explanation for our principal finding could be the choice of respiratory parameters to evaluate recovery. Indeed, the parameters chosen may not have been sensitive to the effects of social deprivation. We chose to evaluate residual pulmonary lesions [49], but not the clinical repercussions, apart from severe injury resulting in oxygen desaturation during exercise. The breathing difficulties that result from pulmonary lesions and/or from the deconditioning caused by a prolonged ICU stay are multifactorial in origin, and also depend on muscle strength, cardiac function, nutritional status and mental health [4].

Third, in our cohort, the proportion of socially deprived patients was lower (40%) than in the IVOIRE study (48%) [23]. Contrary to the IVOIRE study, we did not observe any difference at admission between deprived and

non-deprived patients in terms of comorbidities (Charlson index) or autonomy (ADLs). These differences suggest that the socio-economic status was dissociated from the baseline health state in our cohort. The relative similarity between groups in terms of health status at admission, and progression through ICU up to discharge, suggest that all patients may have been equally affected by respiratory lesions in the ICU, regardless of their socio-economic status. The effect of deprivation might be expected to be most marked after hospital discharge.

In our study, deprived patients had more impaired respiratory function, as shown by lower values for clinical and functional parameters, oxygenation and quality of life associated with respiratory status. Yet, despite these differences in functional parameters, the mean values all remained above pathological levels. FVC was lower in deprived patients, but nevertheless remained above the threshold of 80% that defines a pathological state [50]. There was a significantly higher proportion of women and patients with obesity among the deprived, and this may also explain why the distance walked was shorter, with lower absolute values for volumes and flows. Indeed, obese patients generally harbour mild restrictive ventilatory disorders [51]. The theoretical values for volumes and flow that were used as reference are lower in women than in men [52]. The respiratory quality of life appears to be more altered in deprived patients, possibly meaning that the clinical and functional profile are really relevant.

**Table 4 Respiratory outcomes 6 months after ICU discharge according to socio-economic status**

	No./total (%) All patients, N = 401	No./total (%) Non-deprived, N = 241	No./total (%) Deprived, N = 160	p value
Dyspnea, mMRC scale $\geq 1$ (n = 368)	207/368 (56)	112/223 (50)	95/145 (66)	0.004
<b>6-min walk test</b>				
Distance, mean (SD), m [no.]	431 (126) [390]	444 (121) [237]	411 (131) [153]	0.01
Distance, mean (SD), % predicted	86 (24) [329]	87 (25) [205]	83.1 (23) [124]	0.11
SpO <sub>2</sub> before test, median (IQR), % [no.]	97 (96–98) [387]	97 (96–98) [235]	97 (95–98) [152]	0.43
SpO <sub>2</sub> at end of the test, median (QR), % [no.]	95 (92–97) [385]	95 (93–97) [236]	94 (92–97) [149]	0.04
Delta SpO <sub>2</sub> , median (IQR), [no.]	− 2 (− 4–0) [383]	− 2 (− 4–0) [234]	− 2 (− 5–0) [149]	0.13
Dyspnea (Borg scale) before test, median (QR) [no.]	0 (0–1) [376]	0 (0–1) [232]	0 (0–1) [144]	0.73
Dyspnea (Borg scale) after test, median (QR) [no.]	2 (1–4) [377]	2 (1–4) [233]	3 (1.3–4.5) [144]	0.05
Delta dyspnea, median (IQR) [no.]	2 (0.5–3) [376]	2 (0–3) [232]	2 (1–3) [144]	0.07
<b>Pulmonary function tests</b>				
FEV <sub>1</sub> , mean (SD), ml [no.]	2769 (779) [394]	2852 (768) [235]	2647 (783) [159]	0.01
FEV <sub>1</sub> , mean (SD), % [no.]	99 (21) [395]	100 (20) [236]	96 (21) [159]	0.03
FVC, mean (SD), ml [no.]	3381 (955) [390]	3492 (941) [232]	3217 (956) [158]	0.005
FVC, mean (SD), % [no.]	95 (20) [392]	97 (20) [234]	93 (20) [158]	0.04
FEV <sub>1</sub> /FVC, mean (SD), [no.]	82 (8) [390]	82 (8) [232]	83 (9) [158]	0.50
FEV <sub>1</sub> /FVC < 70%, % [no.]	26 (7) [390]	14 (6) [232]	12 (8) [158]	0.55
VC, mean (SD), ml [no.]	3406 (1018) [344]	3529 (1043) [208]	3216 (952) [136]	0.005
VC, mean (SD), % [no.]	94 (20) [343]	96 (21) [207]	92 (18) [136]	0.12
FRC, mean (SD), ml [no.]	2901 (825) [377]	3019 (818) [227]	2723 (806) [150]	< 0.001
FRC, mean (SD), % [no.]	90 (21) [332]	92 (22) [199]	88 (21) [133]	0.09
TLC, mean (SD), ml [no.]	5375 (1221) [383]	5522 (1230) [231]	5153 (1178) [152]	0.004
TLC, mean (SD), % [no.]	88 (15) [387]	89 (16) [234]	86 (14) [153]	0.05
TLC < 80% predicted	107/387 (28)	61 (26) [234]	46 (29) [153]	0.40
DL <sub>CO</sub> , mean (SD), % [no.]	73 (19) [380]	74 (17) [229]	71 (22) [151]	0.18
K <sub>CO</sub> , mean (SD), % [no.]	90 (18) [343]	91 (16) [212]	89 (21) [131]	0.43
VSRQ scale, median (IQR), [no.]	56 (41–69) [391]	59 (45–71) [235]	50 (38–63.5) [156]	< 0.001
<b>Chest CT</b>				
No lesions	50/386 (13)	35/233 (15)	15/153 (10)	0.13
Fibrotic-like lesion(s) <sup>a</sup>	148/389 (38)	97/234 (41)	51/155 (33)	0.09
Residual lesions <sup>b</sup>	336/386 (87)	198/233 (85)	138/153 (90)	0.13

mMRC the modified Medical Research Council dyspnea scale, SpO<sub>2</sub> peripheral capillary oxygen saturation, FEV<sub>1</sub> forced expiratory volume in 1 s, FVC forced vital capacity, VC vital capacity, FRC functional residual capacity, TLC total lung capacity, DL<sub>CO</sub> diffusion capacity of the lung for carbon monoxide, K<sub>CO</sub> carbon monoxide transfer coefficient, VSRQ Visual Simplified Respiratory Questionnaire, CT computed tomography

<sup>a</sup> Fibrotic-like lesions: traction bronchiectasis, lung architectural distortion, loss of lung volume with reticular and/or ground glass opacities, honeycombing

<sup>b</sup> Residual lesions: ground-glass opacities, reticulations or parenchymal bands

The proportion of patients with respiratory sequelae at 6 months after COVID-19 was 80% in our study, which is higher than rates reported to date. This is likely related to the ICU stay and the severity of the initial pulmonary injury, with our patients classed among the most severe [53]. Of note, only 4% of patients still had respiratory support for prolonged respiratory insufficiency at 6 months. It has been shown that DL<sub>CO</sub> was significantly associated with the severity of the initial pneumonia [6, 7]. Here, 64% of patients had DL<sub>CO</sub> < 80% at 6 months after discharge from ICU, which is also higher than previously reported.

Fibrotic-like pulmonary lesions have also been reported in the most severely ill COVID-19 patients [5, 54].

Our study has several limitations. First, a significant proportion of patients (84%) who were discharged alive from the ICU could not be included, although mainly related to organizational difficulties (65% of the mentioned reasons) due to the ongoing pandemic. Indeed, substantial resources were redirected to COVID-19 care, with a resultant shortage of personnel dedicated to other tasks, including research, and many complementary examinations were not available.

Secondly, we cannot rule out the potential for selection bias, as around 30% of patients contacted at ICU discharge refused to participate in the study. These patients might be more frequently socially deprived than patients who consent to participate. Furthermore, patients who were not affiliated to any national health insurance system were excluded in accordance with French legislation. Third, certain patients could not be included in the final analysis, because either the EPICES score or 6-month outcome was missing. However, imputation of missing data analysis led to consistent results. Fourthly, the EPICES score has only been validated in France, and is more the reflection of overall vulnerability, rather than a purely social measure of deprivation [23]. Several studies performed outside of France have shown an association between socio-economic status and the severity of COVID-19, with an increased risk of hospitalization in ICU and death in socially disadvantaged patients [8, 13, 55, 56]. Therefore, it is possible that we evaluated a direct influence of social deprivation. In addition, the socio-economic deprivation measured at the time of recruitment into the study corresponds to the state prior to admission to ICU. We cannot exclude the possibility that it may have evolved over the course of the study period, up to the evaluation of the functional recovery at 6 months. Finally, the French health insurance system is quite specific in that it provides 100% coverage for the most disadvantaged citizens. Therefore, results cannot be extrapolated to other countries, where health systems likely differ. In particular, in this cohort, access to rehabilitation and physiotherapy during and after hospitalization was equitable thanks to public access to these services. Our results may not be generalizable to healthcare systems, where rehabilitation and physiotherapy services are not delivered through the public healthcare system.

## Conclusion

In patients discharged alive after ARDS due to COVID-19, there was no significant difference in terms of respiratory sequelae at 6 months between patients who were socially deprived and those who were not.

## Supplementary Information

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#### Author contributions

PLD and JPQ had full access to all study data and take responsibility for the integrity of the data analysis. PLD, IF, EK, MD, JPQ, conceptualized and designed the study. All authors contributed to the analysis and/or interpretation of the data. PLD, IF, EK, JPQ drafted the original manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript for submission.

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#### Data availability

The data that support the findings of this trial are available from the corresponding author (JPQ) upon reasonable request.

#### Declarations

#### Conflicts of interest

The authors declare no financial or non-financial interests directly or indirectly related to this work.

#### Ethics approval and consent to participate

The study was approved by the ethics committee "Comité de Protection des Personnes Sud Méditerranée II" on 10/07/2020 under the number 2020-A02014-35. In line with French legislation, oral informed consent was obtained from all patients.

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