Neurologic Outcomes of Survivors of COVID-19–Associated Acute Respiratory Distress Syndrome Requiring Intubation

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OBJECTIVES: To describe 3–6-month neurologic outcomes of survivors of COVID-19–associated acute respiratory distress syndrome, invasively ventilated in the ICU.

DESIGN: A bicentric prospective study during the two first waves of the pandemic (March to May and September to December, 2020).

SETTING: Two academic hospital ICUs, Paris, France.

PATIENTS: Adult COVID-19–associated acute respiratory distress syndrome survivors, invasively ventilated in the ICU, were eligible for a neurologic consultation between 3 and 6 months post ICU discharge.

INTERVENTIONS: Follow-up by face-to-face neurologic consultation.

MEASURES AND MAIN RESULTS: The primary endpoint was favorable functional outcome defined by a modified Rankin scale score less than 2, indicating survival with no significant disability. Secondary endpoints included mild cognitive impairment (Montreal Cognitive Assessment score < 26), ICU-acquired weakness (Medical Research Council score < 48), anxiety and depression (Hospital Anxiety and Depression score > 7), and posttraumatic stress disorder (posttraumatic stress disorder checklist for *Diagnostic and Statistical Manual of Mental Disorders* 5 score > 30). Of 54 eligible survivors, four non-French-speaking patients were excluded, eight patients were lost-to-follow-up, and one died during follow-up. Forty-one patients were included. Time between ICU discharge and neurologic consultation was 3.8 months (3.6–5.9 mo). A favorable functional outcome was observed in 16 patients (39%) and mild cognitive impairment in 17 of 33 patients tested (52%). ICU-acquired weakness, depression or anxiety, and posttraumatic stress disorder were reported in six of 37 cases (16%), eight of 31 cases (26%), and two of 27 cases (7%), respectively. Twenty-nine patients (74%) required rehabilitation (motor, cognitive, or psychologic). ICU and hospital lengths of stay, tracheostomy, and corticosteroids were negatively associated with favorable outcome. By contrast, use of alpha-2 agonists during ICU stay was associated with favorable outcome.

CONCLUSIONS: COVID-19–associated acute respiratory distress syndrome requiring intubation led to slight-to-severe functional disability in about 60% of survivors 4 months after ICU discharge. Cognitive impairment, muscle weakness, and psychologic symptoms were frequent. A large multicenter study is warranted to allow identification of modifiable factors for improving long-term outcome.

KEY WORDS: acute respiratory distress syndrome; cognitive dysfunction; COVID-19; disability evaluation; patient outcome assessment

COVID-19 ranges from an asymptomatic infection to severe respiratory failure and associated nonrespiratory complications and multiple organ failure (1). Patients with severe COVID-19 may require ICU admission

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for acute respiratory distress syndrome (ARDS) (2). ARDS survivors may present with severe sequelae that affect nerves, muscles, and the CNS, leading to long-term functional and cognitive impairment (3).

There is growing recognition that COVID-19 can lead to both acute and long-term neurologic sequelae. Proposed mechanisms of severe acute respiratory syndrome coronavirus 2–associated neurologic complications include direct neuroinvasion and indirect mechanisms of vascular and inflammatory/autoimmune origin (4). Underrecognition of neurologic manifestations may contribute to an increase in long-term complications and poor outcomes (5). In addition, there is a high burden of general critical care complications, which can make specific attribution to COVID-19 difficult.

As the pandemic is still ongoing, there is increasing concern about long-term disability in survivors of COVID-19–associated ARDS (6). The long-term functional consequences of the most severe forms of COVID-19 have been little studied. Of note, most studies conducted to date were monocentric or used telephone interviews (7–9).

The aim of this study was to describe 3–6-month functional and neuropsychologic outcomes of survivors of COVID-19–associated ARDS requiring invasive mechanical ventilation, during the two first waves of the COVID-19 pandemic.

MATERIALS AND METHODS

Study Design and Participants

The study was conducted in the ICUs of Bichat-Claude Bernard and Saint Anne hospitals, in the Paris area, during the first two waves (W) of the COVID-19 pandemic: from March to May 2020 (W1) and from September to December 2020 (W2). Patients included in the present study were consecutive ICU survivors of COVID-19–associated ARDS (confirmed by polymerase chain reaction), who had been treated with invasive mechanical ventilation. Non-French-speaking patients and patients who died during follow-up were excluded. Informed consent was obtained during the follow-up neurologic consultation for all patients. The study protocol was approved by the ethical committee of the French Society of Intensive Care Medicine, CE SRLF 21-40.

Neurologic Consultation

Included patients were invited to attend a dedicated face-to-face neurologic consultation, 3–6 months after their ICU discharge. During this consultation, a detailed interview, a physical examination, and a functional, cognitive and psychologic assessment were conducted by two neurointensivists (P.J., C.L.).

Data Collection

Patient medical history, Simplified Acute Physiology Score (SAPS) 2 score (10), modified Rankin scale (mRS) prior to hospitalization (11), ARDS severity at ICU admission (categorized according to the Berlin definition: mild [Pao_2/Fio_2 ratio = 201–300], moderate [Pao_2/Fio_2 ratio = 101–200], or severe [Pao_2/Fio_2 ratio ≤ 100]), the Glasgow Coma Scale score prior to intubation, and body temperature at admission were collected retrospectively. Treatments (sedation, neuromuscular blockade, norepinephrine, corticosteroids) during ICU stay, hospital and ICU lengths of stay, and mortality were collected retrospectively from medical records.

Outcome Measures

Two neurointensivists assessed outcomes using standardized scales. Functional outcome was assessed using the mRS and the instrumental activity of daily living (IADL) scale (11, 12). Muscle strength was assessed using the Medical Research Council (MRC) scale (13). ICU-acquired weakness was defined by a generalized and an MRC score less than 48. Global cognitive status was assessed using the Montreal Cognitive Assessment (MOCA) scale (14). Mild cognitive impairment was defined by a MOCA score less than 26. Anxiety and depression were assessed using the Hospital Anxiety and Depression (HAD) scale (15). Mild and moderate anxiety or depression disorders were defined by a score greater than 7 and greater than 11, respectively. The item "suicidal ideation" of the Quick Inventory of the Depressive Symptomatology 16-Item (QIDS-SR16) scale was used to describe the severity of depression (16). Suicidal ideation is a scale ranging between 0 and 3. 0—"I do not think of suicide or death". 1—"I feel that life is empty or wonder if it's worth living." 2—"I think of suicide or death several times a week for several minutes." 3—"I think of suicide or death several times a day in some detail, or I have made specific

plans for suicide or have actually tried to take my life." Insomnia-related symptoms were identified if the insomnia severity index (ISI) score was above 7, and a moderate insomnia if the score was above 14 (17). Posttraumatic stress disorder (PTSD) was assessed using the PTSD checklist for *Diagnostic and Statistical Manual of Mental Disorders* 5 (PCL 5) (18). PTSD was defined by a score of greater than 30. Functional complaints and rehabilitation needs were also recorded.

Statistical Analysis

Data are expressed as numbers (%) for categorical variables and medians (interquartile range [IQR]) for continuous variables. The primary endpoint was favorable functional outcome, defined by an mRS score less than 2, indicating survival with no significant functional disability. Comparisons relied on Fisher exact test for categorical data, and the Wilcoxon test for continuous data. Factors associated with a favorable outcome were identified by univariate analyses, and odds ratios (with their 95% CIs), adjusted for SAPS2 score, were computed. Secondary endpoints included mild cognitive impairment, ICU-acquired weakness, and mild anxiety or depression (HAD score > 7). All analyses were performed using JMP software, Version 16 (SAS Institute, Cary, NC). A p value of less than 0.05 was considered statistically significant.

RESULTS

Flowchart

Among the 280 patients hospitalized in the ICU for COVID-19–associated ARDS from March to May 2020 and from September to December 2020, 134 patients (48%) required invasive mechanical ventilation in the ICU (97 during W1, 37 during W2). Eighty patients died during their ICU stay, and 54 patients were discharged. Four patients were excluded because they did not speak French, and one died after ICU discharge. Eight patients (16%) were lost to follow-up. Forty-one invasive mechanical ventilation survivors were included in this study (**Supplemental Digital Content 1**, http://links.lww.com/CCM/H13).

Patients

Characteristics of the participants are presented in **Table 1**. Patients were 56 years (46–61 yr) old, and 31 (76%) of them were male. The most common comorbidities were obesity 19 (n = 19, 46%), hypertension (n = 14; 34%), diabetes (n = 6; 14%), and a history of cardiovascular disease (n = 6; 14%). Three patients (7%) had a history of anxiety or depression. One patient was disabled prior to hospitalization because of a stroke (mRS score of 5).

The SAPS2 score was 30 (25–36), and the initial Pao_2/Fio_2 ratio after invasive mechanical ventilation initiation was 131 (84–196). At admission, 10 patients (24%) had mild ARDS, 17 (41%) had moderate, and 14 (34%), severe ARDS.

During ICU stay, patients were sedated with propofol/midazolam and opioids (morphine, sufentanil) according to local protocols. Thirty patients (83%) required neuromuscular blockade, 26 (63%) required prone positioning, and four (10%) required venovenous extra corporeal membrane oxygenation. The minimal Pao_2/Fio_2 ratio was 81 (65–100). The duration of mechanical ventilation was 25 days (18–50 d). Twenty-eight patients (68%) required norepinephrine, and 11 (27%) required renal replacement therapy. Thirty patients (73%) received corticosteroids (dexamethasone), and 13 (32%) underwent tracheostomy to facilitate weaning from mechanical ventilation. Lengths of stay in the ICU and in hospital were 16 days (10–35 d) and 36 days (23–57 d), respectively.

Outcomes

Characteristics of neurologic outcomes are described in **Figure 1** and **Table 2**.

Functional Status. Median mRS score was 2 (1–2), with three patients (7%) reporting no symptoms at all, and 16 (39%) patients reporting a favorable functional outcome. IADL was 5 (5–5) in men, and 7 (3–8) in women.

Motor Status. Thirty-seven patients (90%) underwent a full assessment. MRC score was 57 (53–60), and ICU-acquired weakness was diagnosed in six patients (16%).

Cognitive Status. Thirty-three patients (80%) underwent a full assessment. MOCA was 26 (23–28.5), and cognitive impairment was reported in 17 patients (52%). Distribution of cognitive impairment is presented in **Figure 2**. The most affected domain was delayed recall with a score of 4 (2–4) in a scale of 0–5.

TABLE 1.
Baseline and ICU Stay Characteristics

Characteristics	All ($N = 41$)
Age, yr	56 (46–61)
Female gender	10 (24)
Body mass index, kg/m^2	29 (26–33)
Diabetes	6 (14)
Hypertension	14 (34)
Simplified Acute Physiology Score 2	30 (25–36)
Initial Pao_2/Fio_2 ratio	131 (84–196)
Body temperature, T°C	38.4 (37.9–39.0)
Glasgow Coma Scale	15 (14–15)
Minimal Pao_2/Fio_2 ratio	81 (65–100)
Neuromuscular blockade	30 (83)
Prone positioning	26 (63)
Venovenous extracorporeal membrane oxygenation	4 (10)
Duration of mechanical ventilation	25 (18–50)
Renal replacement therapy	11 (27)
Norepinephrine	27 (68)
Tracheostomy	11 (30)
Corticosteroids	30 (73)
ICU length of stay, d	16 (10–35)
Hospital length of stay, d	36 (23–57)

Results are expressed as medians (quartiles) for continuous variables and *n* (%) for qualitative variables.

Psychologic Status. Thirty-one patients (76%) underwent a full assessment of their psychologic status. Scores on the HAD Anxiety scale and HAD Depression scale were 4 (3–7) and 3 (1–7), respectively. Eight patients (26%) reported mild/moderate depression or anxiety or both (seven patients [23%] and six patients [19%] reported mild/moderate depression or anxiety, respectively). The item "suicidal ideation" of the QIDS-SR16 was equal to 0 for 28 patients (90%) ("I do not think of suicide or death"). One patient (3%) reported a QIDS-SR16 equal to 1 ("I feel that life is empty or wonder if it's worth living "). Two patients (6%) reported a QIDS-SR16 equal to 2 ("I think of suicide or death several times a week for several minutes"). The ISI was 4 (0.5–11), 14 (45%) had insomnia-related symptoms, and four (13%) had insomnia of moderate severity. Twenty-seven patients underwent a full assessment of PTSD using the PCL 5. PCL 5 was 8.5 (5.25–21), and two patients (7%) had PTSD.

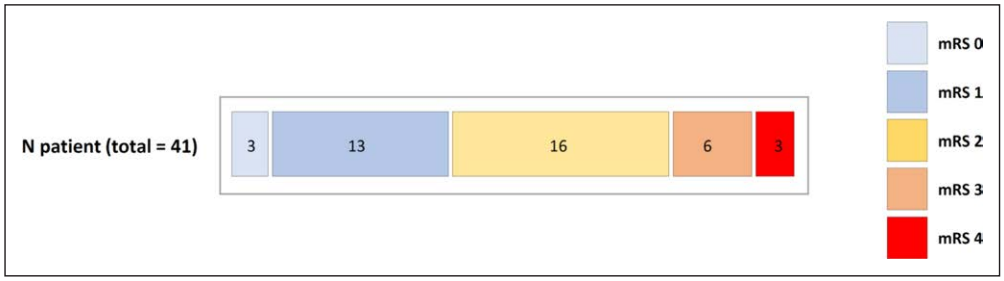

Figure 1. Functional outcome defined by the modified Rankin Scale (mRS) score at 4 mo after ICU discharge. Data from 41 survivors of COVID-19–associated acute respiratory distress syndrome requiring invasive mechanical ventilation. Distribution of patients depending on their outcome on the mRS scale. 0–1 = asymptomatic or symptomatic without disability. 2–4 = slight to severe disability.

Rehabilitation Needs. Thirty-nine patients (95%) underwent an evaluation

TABLE 2.
Outcomes Reported by COVID-19–Associated Acute Respiratory Distress Syndrome Survivors During Neurologic Consultation

Outcomes	Full Sample		Impairment	
	N	Median (IQR)	*n*	%
Median time between ICU discharge and consultation, **mo**	41	3.8 (3.6–5.9)		
Modified Rankin Scale score, mild to severe disability	41	2 (1–2)	25	61
Medical Research Council score, ICU-acquired weakness	37	57 (53–60)	6	16
M ody mass index, OCA, mild cognitive impairment (MOCA < 26)	33	26 (23–29)	17	52
HAD anxiety scale, anxiety (HAD > 7)	31	4 (3–7)	6	19
HAD depression scale, depression (HAD > 7)	31	3 (1–7)	7	23
Quick Inventory of Depressive Symptomatology 16-Item (sad mood item), any idea of suicide or death	31	0 (0–0)	3	10
Insomnia Score Index, insomnia-related symptoms	31	4 (0.5–11)	14	45
PCL 5 score, posttraumatic stress disorder symptoms (PCL 5 > 30)	27	8.5 (5.25–21)	2	7
Functional complaints	33		39	85
Follow-up interventions				
Any intervention	39		29	74
Physiotherapy management	39		23	59
Neuropsychologic therapy	39		12	31
Psychologic therapy	39		12	31

HAD = Hospital Anxiety Depression, IQR = interquartile range, MOCA = Montreal Cognitive Assessment, PCL = Posttraumatic Stress Disorder Checklist for *Diagnostic and Statistical Manual of Mental Disorders* 5.
Results are expressed as medians (quartiles) for continuous variables and *n* (%) for qualitative variables.

of their rehabilitation needs, and 33 of 39 patients (85%) reported functional complaints. Twenty-nine (74%) required rehabilitation (motor, cognitive, or psychologic). Physiotherapy was the most important need (59% of patients), followed by cognitive or psychologic complaints (31% of patients).

Factors Associated With Favorable Outcome

None of the demographic characteristics were associated with favorable outcome. Lengths of stay in the ICU and in hospital, tracheostomy, and corticosteroid administration were negatively associated with favorable outcome. By contrast, the use of alpha-2 agonists was associated with favorable outcome. Minimal Pao_2/Fio_2 ratio, venovenous extracorporeal membrane oxygenation, norepinephrine, and renal replacement therapy requirement were not associated with outcome. These are described in **Supplemental Digital Content 2** (http://links.lww.com/CCM/H14). The above associations remained similar after adjustment for SAPS2 scores. We found no association between initial Pao_2/Fio_2 ratio or minimum Pao_2/Fio_2 ratio and good functional outcome ($p = 0.9$ and $p = 0.65$, respectively).

Compared to patients with unfavorable functional outcomes, patients with favorable functional outcomes had similar cognitive and anxiety/depression scores and lower MRC scores.

DISCUSSION

In this cohort study of 41 survivors of COVID-19–associated ARDS who underwent a neurologic consultation 4 months after ICU discharge, only 39% patients reported a favorable functional outcome, with no functional disability. The most common complaints at the time of consultation were muscle weakness (59%), followed by cognitive (31%) and psychologic (31%) complaints.

Persistent functional disability was previously reported in patients at 1 year and 5 years following ARDS (3, 19). Although the different functional assessment tools used in our study preclude any strict comparison with studies conducted in non–COVID-19 patients, the

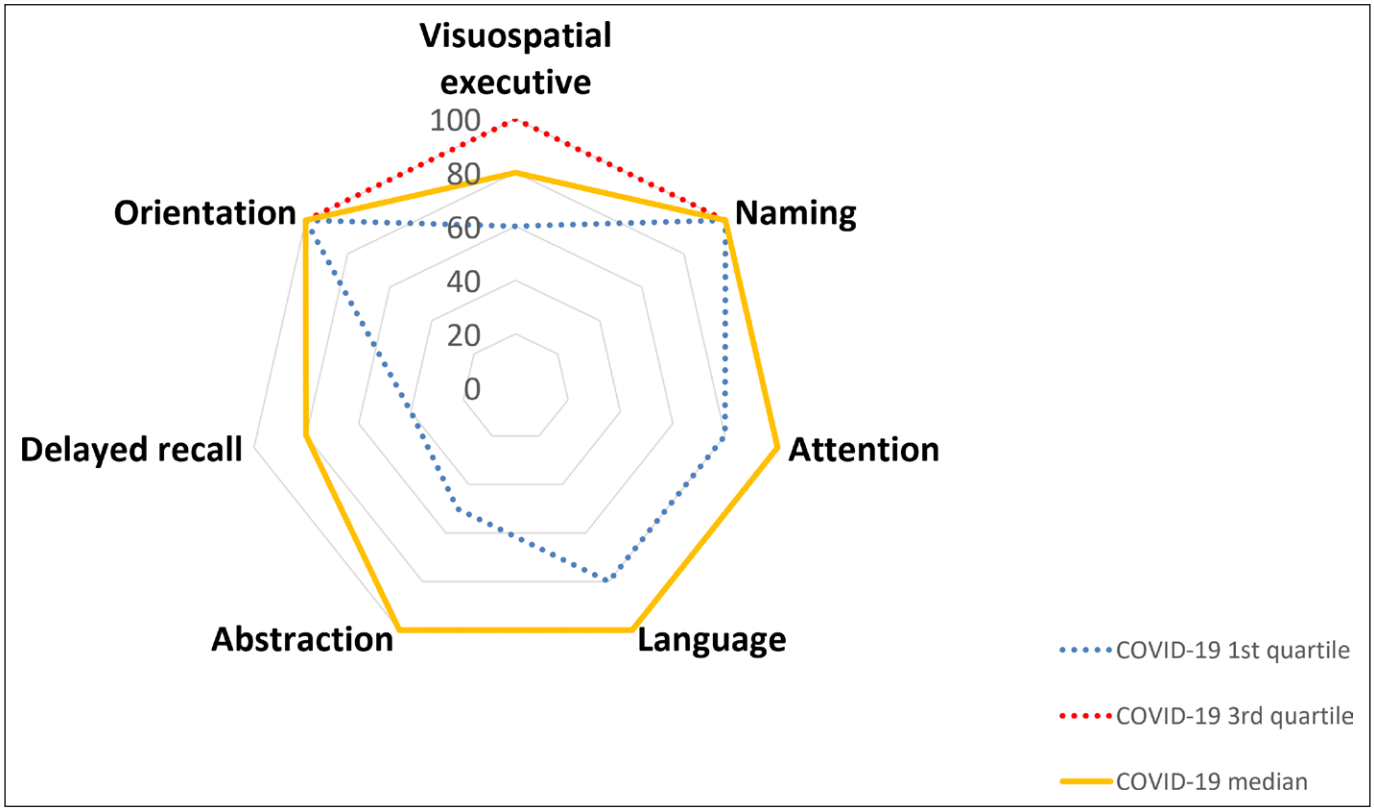

Figure 2. Distribution of cognitive deficits using the Montreal cognitive assessment. Data from 33 survivors of COVID-19–associated acute respiratory distress syndrome requiring invasive mechanical ventilation in an ICU. Delayed recall was the most affected domain.

burden of neurologic sequelae appears to be high and largely similar. Our study confirms preliminary data from a single-center study conducted in COVID-19–associated ARDS survivors (7). In this study, functional status was assessed during a telephone interview (an assessment with good correlation with mRS [20]) and was altered in 58% cases.

Previous multicenter studies conducted in adult patients with severe COVID-19 described baseline factors associated with ICU mortality, including greater age, male sex, current smoking status, and pre-existing chronic kidney, respiratory, and/or cardiovascular disease (21, 22). By contrast, our study investigated several ICU-related variables potentially associated with impaired functional recovery. We found no association between baseline characteristics (i.e., SAPS2 or initial Pao_2/Fio_2 ratio) and functional outcome. We identified a significant association between the use of α-2 adrenergic receptor agonists and favorable outcome. Although this remains largely speculative, these findings may reflect a potential neuroprotective effect of α-2 adrenergic receptor agonists. It is more likely that it may only identify patients for whom early discontinuation of IV gamma-aminobutyric acid-agonists (i.e., propofol, midazolam) was feasible and successful, allowing a faster recovery from coma and ventilator weaning and early rehabilitation (23). These findings are in line with previous data published in a large multicenter cohort study, suggesting that sedation strategies may impact neurologic outcomes of COVID-19 ARDS patients (24). In our study, post hoc analyses adjusted for SAPS2 at admission, revealed similar associations. Corticosteroids were also associated with poorer functional outcomes, likely reflecting a more severe illness at admission, although a deleterious effect of steroids on muscle function recovery cannot be excluded. This association may also simply be skewed by the design of our study, which excluded ICU non-survivors.

ICU-acquired weakness was diagnosed in 16% of the survivors, which is in line with previous cohort studies conducted in the non–COVID-19 population, with published rates of 22% at 3 months and 8–15% at 6 months after ICU discharge (19, 25). Of note, the impact of unilateral brachial plexopathy after prone positioning may lead to disability, and this may persist over time (3, 19). Although physiotherapy was implemented

in many cases (60% of patients), it is important to note that during the pandemic, many patients could not receive the necessary physiotherapy because of healthcare worker shortage.

Mild cognitive impairment was frequent but did not impact the functional outcome in our study, probably because of the small population size. Indeed, it was demonstrated in other studies in the non–COVID-19 population that mild cognitive impairment impacts daily living activities and might have an effect on functional outcome (26). In our study, the profile of cognitive assessments revealed that delayed recall was the most affected domain, in agreement with previous studies describing cognitive deficits in COVID-19 and non-COVID-19–associated ARDS patients (27–29).

Psychologic sequelae were reported by the HAD score in 26% of patients of this cohort, and 39% had insomnia-related symptoms at the time of the neurologic consultation. This is also in agreement with a previous study of non-COVID-19–associated ARDS survivors (24–28% for anxiety and depression [3, 30]) and COVID-19–associated ARDS survivors (8). In contrast with previous reports on non-COVID-19–associated ARDS, the rate of PTSD was lower in this cohort (7% vs 21–35% [31, 32]). This result is in accordance with two other studies showing 10% and 18% of PTSD in COVID-19-associated ARDS survivors (7, 8). Psychologic assessment following ICU stay appears crucial during the pandemic, as limited visits and social distancing may have major consequences on mental health (33).

There was a high prevalence of functional complaints and rehabilitation needs (74%) in this population four months after ICU discharge, highlighting the importance of a neurologic follow-up for survivors of severe COVID-19. Critical care recovery clinics providing follow-up consultations with multidisciplinary services to address the medical and rehabilitation needs of COVID-19 survivors may improve the patient's care pathway (34).

Our study has several strengths. We assessed neurologic outcomes via face-to-face consultations, which were conducted by neurointensivists in two academic centers. Other studies were monocentric and used telephone interviews instead of face-to-face consultation (7, 8). Our study represents a necessary preliminary step before conducting a larger multicenter study, which will assess long-term follow-up of COVID-19 patients recruited in the French multicenter Dexamethasone and Oxygen Support Strategies in ICU Patients With Covid-19 Pneumonia (COVIDICUS) randomized clinical trial (clinical trial NCT04344730).

Our study has limitations, including a small sample size precluding identification of independent factors associated with functional disability. We only included patients in the Paris area, and our findings cannot necessarily be extrapolated to other geographic regions. The lack of a historical or concurrent control group of non–COVID-19 ARDS patients is another limitation. Although COVID-19 patients were managed in both ICUs according to current guidelines, the difference in the number of patients recruited in the two ICUs over the two waves may reflect a change in patient management. Repeated follow-up evaluations would have been of interest to understand time-dependent changes in outcomes, but they were not easily feasible during lockdown periods in France.

The rate of patients with poor outcomes reported in our study might have been underestimated by decisions of withdrawal of life-sustaining therapy for perceived poor neurologic prognosis during ICU stay. However, such decisions were rarely observed (2/134 patients of our cohort), as the study population consisted of ARDS patients without primary brain injury. Medical management of patients was heterogeneous, as recommendations regarding the care of COVID-19–associated ARDS evolved rapidly during the course of the pandemic. Intubation was delayed during the second wave because of the more frequent use of high-flow nasal cannulae and noninvasive mechanical ventilation. Of note, W2 patients requiring invasive mechanical ventilation had a higher mortality rate than W1 patients (n = 30/37; 81% vs n = 50/97; 52%).

CONCLUSIONS

COVID-19–associated ARDS led to slight-to-severe functional disability in about 60% of patients 4 months after ICU discharge. Cognitive impairment, muscle weakness, and psychologic symptoms were frequent. Organization of postintensive care follow-up consultations during the pandemic was feasible. A large multicenter study is warranted to allow identification of modifiable factors for improving long-term outcome.

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