studies[9,11] originated from Belgium, whereas the remaining two studies[8,10] originated from the UK and Sweden. All studies were of single-centre design: three studies[8,9,11] were retrospective whereas one study[10] was prospective. The meta-analysis of four studies[8–11] that represented data from 463 patients with COVID-19 revealed that per unit increase in frailty score as determined using Clinical Frailty Scale was associated with a significantly higher odds of mortality in patients with COVID-19 (Fig. 1a; pooled odds ratio=2.07; 95% confidence interval, 1.60–2.69).

Studies that were not included in meta-analyses also demonstrated a significant association between frailty status (regardless of degrees of frailty) and higher odds of mortality, and significant association between increasing level of frailty and a higher hazard of mortality. Our findings indicate that increased risk of mortality spanned the continuum of frailty in patients with COVID-19, and hence Clinical Frailty Scale or other validated frailty assessment tools can be useful in prioritising allocation of critical care resources for patients with COVID-19.

Declarations of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.12.002.

References

1. Darvall JN, Bellomo R, Bailey M, et al. Frailty and outcomes from pneumonia in critical illness: a population-based cohort study. *Br J Anaesth* 2020; **125**: 730–8
2. Owen RK, Conroy SP, Taub N, et al. Comparing associations between frailty and mortality in hospitalised older adults with or without COVID-19 infection: a retrospective observational study using electronic health records. *Age Ageing* July 17 2020. https://doi.org/10.1093/ageing/afaa167
3. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health* 2020; **5**: e444–51
4. Aw D, Woodrow L, Ogliari G, Harwood R. Association of frailty with mortality in older inpatients with Covid-19: a cohort study. *Age Ageing* 2020; **49**: 915–22
5. Apea VJ, Wan YI, Dhairyawan R, et al. Ethnicity and outcomes in patients hospitalised with COVID-19 infection in East London: an observational cohort study. *medRxiv* June 12 2020. https://doi.org/10.1101/2020.06.10.20127621
6. Osuafor CN, Davidson C, Mackett AJ, et al. Clinical features and inpatient trajectories of older inpatients with COVID-19: a retrospective observational study. *Res Square* August 26 2020. https://doi.org/10.21203/rs.3.rs-61056/v1
7. Hägg S, Jylhävä J, Wang Y, et al. Age, frailty, and comorbidity as prognostic factors for short-term outcomes in patients with coronavirus disease 2019 in geriatric care. *J Am Med Dir Assoc* 2020; **21**. 1555–1559.e2
8. Rawle MJ, Bertfield DL, Brill SE. Atypical presentations of COVID-19 in care home residents presenting to secondary care: a UK single centre study. *Aging Med* September 17 2020. https://doi.org/10.1002/agm2.12126
9. De Smet R, Mellaerts B, Vandewinckele H, et al. Frailty and mortality in hospitalized older adults with COVID-19: retrospective observational study. *J Am Med Dir Assoc* 2020; **21**. 928–932.e1
10. Tehrani S, Killander A, Åstrand P, Jakobsson J, Gille-Johnson P. Risk factors for mortality in adult COVID-19 patients; frailty predicts fatal outcome in older patients. *Int J Infect Dis* 2021; **102**: 415–21
11. Fagard K, Gielen E, Deschodt M, Devriendt E, Flamaing J. Risk factors for severe COVID-19 disease and death in patients aged 70 and over: a retrospective observational cohort study. *Res Square* November 3 2020. https://doi.org/10.21203/rs.3.rs-101387/v1

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Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients

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Editor—Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019. Although most patients have a favourable evolution, some patients have worse outcomes, progressing to acute respiratory distress syndrome (ARDS) and requiring treatment in an ICU.[1–4] Patients who survive may be susceptible to developing poor health-related quality of life (HRQoL) and persistent symptoms after ICU discharge; however, this has not been investigated. The present study aimed to determine the quality of life, functional status, and persistent symptoms of patients with COVID-19-induced ARDS at 6 months after requiring treatment in an ICU. The ethics committee of Galicia, Spain (code No. 2020-188), approved this study. Informed consent was obtained from all participants.

We prospectively evaluated all critically ill patients with COVID-19-induced ARDS admitted to the ICUs of seven hospitals located in northwestern Spain between March 15 and April 30, 2020. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase polymerase chain reaction (RT–PCR) test. The following information was collected during ICU admission: patient characteristics, coexisting disorders, treatments, complications, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, laboratory tests, need for mechanical ventilation, tracheotomy, renal replacement therapy, duration of mechanical ventilation, length of ICU stay, and ICU outcomes.

All patients who survived ICU admission were included to assess HRQoL, functional status, and persistent symptoms using a structured interview conducted by designated trained research coordinators at participating sites, 6 months after requiring ICU treatment. Patients were asked to recount their quality of life and functional status 3–6 months before COVID-19 at the time of the interview. HRQOoL was assessed using the EuroQol Group Association five-domain, three-level questionnaire (EQ-5D-3L), which consists of two sections: the descriptive system and the visual analogue scale. The descriptive system assesses five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three possible responses options: no problems, some problems, or extreme problems. The individual domains were converted to a utility score (EQ-5D index), a continuous range from −0.59 to 1.00, with 1.00 indicating 'full health' and 0 representing death. The visual analogue scale (EQ-VAS) represents 0 = worst imaginable health and 100 = best imaginable health.[5] Functional status was assessed according to the recently described Post-COVID-19 Functional Status scale (PCFS).[6] Persistent symptoms potentially correlated with COVID-19 were also obtained. All analyses were performed using R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS (version 26; SPSS, Inc, Chicago, IL, USA). The quantitative variables are expressed as median (inter-quartile range [IQR]) or median (standard deviation [SD]) and categorical variables as number (%).

During the study period, 120 critically ill COVID-19 ARDS patients were admitted to the ICUs. Among the 120 patients, 23 (19%) died during ICU admission, and 5 within the first 6 months after ICU discharge. Ninety-two patients were potentially eligible for the 6 month follow-up assessment. One patient declined to participate. Therefore, 91 patients were included. Supplementary Table S1 displays the patient characteristics and clinical course during ICU stay of the study population.

Of the 91 survivors at 6 month interview, a decrease in the quality of life was observed among 61 (67%) patients. The proportions of patients with moderate to extreme problems in the five dimensions studied with the EQ-5D-3L were mobility (56%), usual activities (37%), self-care (13%), pain/discomfort (48%), and anxiety/depression (46%) (Table 1).

At the 6 month interview, 57 (63%) patients reported decreased functional status. Thirty-five (38%) patients had lowered two grades in the PCFS, and 41 (45%) patients described persistent functional limitations (grades 2–4 in the PCFS) (Table 1).

Advanced age, male sex, need for mechanical ventilation during ICU stay, duration of mechanical ventilation, length of ICU stay, and length of hospital stay were associated with a decreased quality of life, decreased functional status at 6 months after ICU admission, or both (Supplementary Table S1).

Supplementary Table S2 shows persistent symptoms potentially correlated with COVID-19 observed in the 91 patients. At the 6 month evaluation, a high proportion of patients reported dyspnoea on exertion (57%), asthaenia (37%), myalgia (37%), and arthralgia (29%). Only 15 (16%) patients were completely free of persistent symptoms.

To our knowledge, this study represents the first description of the long-term health-related outcomes in survivors of COVID-19-associated ARDS. We found that at 6 months after requiring ICU admission, a large proportion of them had worsened quality of life, diminution of the functional status, and persistent symptoms compared with their pre-COVID-19 status. These data are consistent with prior studies that report poor long-term outcomes in critically ill survivors of ARDS not caused by COVID-19 and ICU survivors from other causes.[8–13] The term 'long covid' is being used to describe illness in people who have either recovered from COVID-19 but are still reporting long-term effects of the infection or have had the usual symptoms far longer than would be expected.[14] Follow-up clinics after hospital discharge are needed to characterise the sequelae of these patients, and to determine which interventions in the ICU, in the hospital after ICU discharge, and later in the community may mitigate or treat these sequelae. Research priorities include a better understanding of the pathophysiology, an evaluation of ICU and hospital treatments given, and impact of rehabilitation programmes on long-term outcomes after critical COVID-19. Early

Table 1 Quality of life and functional status of the study sample (n=91). Data are expressed as n (%) or mean (standard deviation). Quality of life was measured using the EuroQol, five-dimension, three-level questionnaire and the EQ-VAS (0–100). Functional status was measured using the Post-COVID-19 Functional Status scale. Means for continuous variables were compared using unpaired or paired t-tests when the data were normally distributed; otherwise, the Mann–Whitney U-test or Wilcoxon test was used. Proportions for categorical variables were compared using Pearson's χ^2 test or McNemar's test as appropriate. All tests were two-sided with a significance level of P<0.05. EQ-VAS, EuroQol visual analogue scale; EQ-5D-3L, EuroQol Group Association five-domain, three-level questionnaire.

		Before COVID-19	6 months after COVID-19	P value
Quality of life (EQ-5D-3L)				
Characteristics				
Mobility	No problems	85 (93.4)	40 (44.0)	<0.001
	Some problems	6 (6.6)	51 (56.0)	
	Unable to walk	0 (0.0)	0 (0.0)	
Self-care	No problems	91 (100.0)	79 (86.9)	<0.001
	Some problems	0 (0.0)	10 (11.0)	
	Unable to wash or dress myself	0 (0.0)	2 (2.2)	
Usual activities	No problems	90 (98.9)	57 (62.6)	<0.001
	Some problems	1 (1.1)	24 (26.4)	
	Unable to perform	0 (0.0)	10 (11.0)	
Pain or discomfort	No pain or discomfort	81 (89.0)	47 (51.6)	<0.001
	Some pain or discomfort	10 (11.0)	36 (39.6)	
	Extreme pain or discomfort	0 (0.0)	8 (8.8)	
Anxiety or depression	Not anxious or depressed	85 (93.4)	49 (53.8)	<0.001
	Moderately anxious or depressed	6 (6.6)	38 (41.8)	
	Extremely anxious or depressed	0 (0.0)	4 (4.4)	
EQ-5D index		0.9655 (0.0958)	0.7054 (0.2514)	<0.001
EQ-VAS (0–100)		87.58 (11.68)	66.36 (18.26)	<0.001
Post-COVID-19 Functional Status scale				
Grade				
0: No limitations in my everyday life.		77 (84.6)	28 (30.8)	<0.001
1: Negligible limitations, (still have persistent symptoms).		13 (14.3)	22 (24.2)	
2: Limitations in my everyday life, and occasionally need avoid or reduce usual activities.		1 (1.1)	20 (22.0)	
3. Limitations in my everyday life, and I am not able to perform all usual activities.		0 (0.0)	16 (17.6)	
4. Severe limitations. I am dependent on another person because of symptoms.		0 (0.0)	5 (5.5)	

rehabilitation[15] or ICU diaries to help reduce post-traumatic stress disorder[16] have been described to mitigate long-term sequalae.

A limitation of the present study is that it included only critically ill patients admitted to ICUs of hospitals located in northwestern Spain. Thus, the results may not reflect the experience and results of critically ill COVID-19 survivors of other ICUs in other regions. Another limitation is that the pre-COVID-19 assessment was based on patient recall of their quality of life and functional status, and these could be biased. Regardless, these preliminary results are shared to inform long-term health-related outcomes of critically COVID-19 patients who needed ICU admission. These findings may be important for health service planning and for planning the ongoing support and treatment of survivors of COVID-19 ARDS.

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Declarations of interest

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Appendix A. Supplementary data

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References

1. Grasselli G, Zangrillo A, Zanella A, et al. COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574–81
2. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; **323**: 2052–9
3. Auld SC, Caridi-Scheible M, Blum JM, et al. Emory COVID-19 Quality and Clinical Research Collaborative. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med* 2020; **48**: e799–804

4. Taboada M, Rama P, Pita-Romero R, et al. Critically ill COVID-19 patients attended by anesthesiologists in northwestern Spain: a multicenter prospective observational study. *Rev Esp Anestesiol Reanim* 2020 Sep 4; **68**: 10–20. https://doi.org/10.1016/j.redar.2020.08.004. Advance Access published on September 4, 2020
5. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208
6. Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J* 2020; **56**: 2001494
8. Herridge MS, Cheung AM, Tansey CM, et al. Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; **348**: 683–93
9. Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: different from general critical illness? *Curr Opin Crit Care* 2018; **24**: 35–40
10. Thompson K, Taylor C, Jan S, et al. Health-related outcomes of critically ill patients with and without sepsis. *Intensive Care Med* 2018; **44**: 1249–57
11. Biehl M, Kashyap R, Ahmed AH, et al. Six-month quality-of-life and functional status of acute respiratory distress syndrome survivors compared to patients at risk: a population-based study. *Crit Care* 2015; **19**: 356
12. Yende S, Austin S, Rhodes A, et al. Long-term quality of life among survivors of severe aepsis: analyses of two international trials. *Crit Care Med* 2016; **44**: 1461–7
13. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. Canadian Critical Care Trials Group. *N Engl J Med* 2011; **364**: 1293–304
14. Mahase E. Covid-19: what do we know about "long covid"? *BMJ* 2020; **370**: m2815
15. Mehlhorn J, Freytag A, Schmidt K, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. *Crit Care Med* 2014; **42**: 1263–71
16. McIlroy PA, King RS, Garrouste-Orgeas M, et al. The effect of ICU diaries on psychological outcomes and quality of life of survivors of critical illness and their relatives: a systematic review and meta-analysis. *Crit Care Med* 2019; **47**: 273–9

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Impending cognitive and functional decline in COVID-19 survivors. Comment on *Br J Anaesth* 2021; 126: 44–7

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Keywords: COVID-19; functional impairment; neurocognitive decline; neuroinflammation; neurotropic associations; viral pandemic

Editor—Baker and colleagues[1] predict a 'third wave' of neurocognitive decline in coronavirus disease 2019 (COVID-19) survivors.[1] Although their illustration of the wheel of factors surrounding post-COVID-19 cognitive and functional impairment is compelling, specific contextual literature, additional neurotropic associations, previous experiences with viral illnesses, and future perspective in this area demand further elucidation to complete the picture.

Appropriate to their discussion of the multisystemic role of COVID-19-associated inflammation in neurocognitive impairment, the findings of Zhou and colleagues[2] deserve mention. They studied the relationship between the inflammatory profile and post-COVID recovery cognitive function by online neuropsychological evaluation.[2] C-reactive protein levels positively correlated with the reaction time of the first and second parts of the continuous performance neuropsychological test. Although the clinical significance of these findings premised on multiple neuropsychological tests in a rather small cohort of COVID-19 survivors is open to debate, the possible links between COVID-19-related inflammation[2–4] and long-term functional impairment cannot be overlooked.

Alongside a multifaceted 'post-intensive care syndrome' aetiology for COVID-19-related neurocognitive decline detailed by Baker and colleagues,[1] there are additional

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