Acta Anaesth. Bel., 2024, 75 (1): *33-40*

Original Study

Long-term cognitive dysfunction after COVID ARDS

L. Vanginderhuysen[1,*], B. Janssen[2,*], G. Vingerhoets[2], X. Willaert[1], A. Creemers[1], D. Mesotten[1,3,*], S. Thiessen[1,4,*]

[1]Dept Anaesthesiology & Intensive Care Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium; [2]Dept Psychology, Ghent University, Sint-Pietersnieuwstraat 33, Gent, Belgium; [3]UHasselt, Faculty of Medicine and Life Sciences, Diepenbeek, Belgium; [4]Department of Anaesthesiology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium. [*]Equal contribution.

Corresponding author: Steven Thiessen, Dept Anaesthesiology & Intensive Care Medicine, Ziekenhuis Oost-Limburg, Synaps Park 1, B-3600 Genk, Belgium. Tel. +32/89/325315. E-mail: steven.thiessen@zol.be

Abstract

Background: **COVID-19 acute respiratory distress syndrome (C-ARDS) survivors suffer from long-term physical complications. However, at the time of this study limited data are available on possible long-term cognitive impairment.**
Objectives: **We hypothesized that COVID-19 ICU patients perform worse on cognitive tasks 6 months after admission, in comparison to reference values of a healthy population.**
Design: **Two-center cohort study with a six months' time horizon.**
Patients: Patients admitted to the ICU for COVID-19 associated respiratory failure between March and June 2020.
Setting: **Post-ICU follow up.**
Methods and main outcome measures: **The primary measure was the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score (with lower values indicating worse global cognition). The secondary outcome measure was the Trail Making Test (TMT) Part B (population age-, sex-, and education-adjusted mean score, 50±10, with lower scores indicating worse executive functions). The Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, on a scale from 1.0 to 5.0, with 5.0 indicating severe cognitive impairment) was taken for not patients not fluent in Dutch.**
Results: **117 COVID-19 patients were admitted to the ICU, of whom 32 patients (27%) died within 6 months. 67/85 (79%) patients participated in the cohort study. COVID-19 survivors had lower total RBANS cognition scores than the age-adjusted population norms (n=45). Fifteen (33%) patients had a global cognition score 1.5 SD below the population means. RBANS-subscale performance showed that both memory (immediate and delayed recall) and attention were at minus 1 SD below normative means, while language and visuospatial cognition were unaffected. Median TMT B score was 40 (IQR 10-65) (n=45). There were elevated scores of the short form IQCODE (mean 3.4 (SD 0.4).**
Conclusions: **Our results suggests that COVID-19 ARDS negatively affects long-term cognitive function.**
Trial registration: **ClinicalTrials.gov NCT04593069.**

Keywords: **COVID-19, Post-acute COVID-19 syndrome, Cognition disorders, Executive function, Neuropsychological tests.**

Approvals by the ethics committee: The cohort study was approved by the independent ethics committee of both hospitals, chairman Dr. Patrick Noyens (ZOL, 20/0075U and ZMK 2020-004, Eudract/B-nr: B3712020000016) and registered on ClinicalTrials.gov (NCT04593069). The COGCOV study was approved by the Ethics committee on 30 September 2020. Patient inclusion happened between March and June 2020.

Introduction

Since the outbreak of COVID-19, the main talking point of this new disease was its induction of acute respiratory distress syndrome (ARDS) and its associated mortality[1].

Ever since this global pandemic and its initial respiratory impact has subsided, the focus shifted to the long term neurologic and cognitive sequalae after infection, commonly referred to as "Long COVID"[2]. Interestingly, it appears that COVID-19 infection may be associated with more than 200 different symptoms, with shortness of breath, fatigue, impaired taste and smell, sleep and mood disturbances, depression, anxiety, as well as post-traumatic stress disorder being the most well known[3,4].

The World Health Organization (WHO) acknowledged "Long COVID" as a disease at the end of 20225. It has been defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation[5]. This cognitive dysfunction (sometimes referred to as brain fog) occurring in long COVID patients has been attracting more attention[6]. By now we know that COVID is associated with cognitive dysfunction with most impact on attention, memory and executive functioning[7,8].

Cognition and cognitive (dys)functioning transcend general intelligence as it also affects executive functions. The latter refer to a family of top-down mental processes needed to concentrate and pay attention[9]. There are three core executive functions: inhibition, working memory and cognitive flexibility. These are the essentials parts of the higher-order executive functions such as reasoning, problem solving and planning, which is needed for participation in everyday life[9]. Executive functions develop during childhood and adolescence. It has been recently shown that critical illness impairs executive functions in children post ICU, compared with population means and healthy controls[10,11]. These executive functions can remain impaired over a period of years after pediatric critical illness[12]. Critical illness, such as due to ARDS, is also known to affect cognition and executive functions in adults[13–17]. Since cognitive dysfunction has an impact on quality of life, the awareness of the potential impact of COVID on cognition was deemed important to be studied at the time of this study[18].

Whether C-ARDS would impair cognitive function to a similar extend had not been well described at the start of this study. Therefore, we conducted a prospective study to analyze the long-term impact of C-ARDS on general cognition and executive functions, and which factors could affect it. Our objective was to evaluate cognitive function in C-ARDS survivors, focusing on global and more specifically executive neurological functioning.

Methods

Patient selection

All patients who had been admitted for COVID-19 pneumonia to the ICUs of two Belgian hospitals (Ziekenhuis Oost-Limburg and Ziekenhuis Maas & Kempen) during the first COVID-19 pandemic wave were screened 4-5 months after ICU admission for eligibility.

Neurocognition testing

Dutch speaking C-ARDS survivors, who consented for participation were tested with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the Trail Making Test (TMT), similar to the BRAIN-ICU study[14].
The RBANS is a comprehensive and validated neuropsychometric battery for the evaluation of global cognition, including individual domains of immediate and delayed memory, attention, visuospatial construction, and language. Executive function (specifically, cognitive flexibility and set shifting) was assessed with the use of the TMT, Part B.

For both tests, lower scores indicate worse global cognition and executive function, respectively.

The Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (short IQCODE) was used in this study to evaluate cognitive impairment in patients not able to perform the RBANS and TMT[19]. In the BRAIN-ICU study, the IQCODE was used to detect pre-existing cognitive impairment on the basis of a score of 3.3 or more, on a scale from 1.0 to 5.0, with 5.0 indicating severe cognitive impairment[14].

To optimize its reliability, neurocognitive testing was done by one trained psychologist (BJ), who performed the tests in the environment preferred by the patient (at home, in hospital).

Outcome measures

The primary outcome measure was the RBANS score 6 months after ICU admission for C-ARDS to assess global cognitive function. The population age-adjusted mean value of RBANS is 100 (μ0) with a standard deviation of 15[20]. The scale ranges from 40 to 160. For the total score of RBANS, the Minimal Clinically Important Difference (MCID) is estimated at 8[21].

However, in the BRAIN-ICU study a mean difference of 20 points was found between healthy controls and critically ill patients[14].

In the a priori power analysis, we calculated the sample size based on a one-sided difference of 10, ($\mu 1 = 90$). With a sigma (SD) of 25 in the study cohort and an $\alpha = 0.05$ (one-sided), we needed to test 39 patients to reach a power of 0.80 and 54 patients for a power of 0.90. To assess the global cognitive function in all patients, regardless of their Dutch proficiency, the IQCODE was used. A short form IQCODE score of 3.3 or higher suggests clinically significant cognitive dysfunction[14].

The secondary endpoint was the executive function of the C-ARDS survivors through the Trail Making Test, Part B (TMT). The TMT has a population age-, sex-, and education-adjusted mean score of 50±10[22]. The IQCODE is 5-point Likert scale, with higher scores indicating cognitive decline[14].

Tertiary outcome measurement was the EuroQoL EQ5D-5L utility index and its Visual Analogue Scale score.

Covariates

Due to the anticipated small total number of participants, a limited baseline characteristics' set to be used as covariates was chosen a priori. This included commonly used baseline characteristics for outcome benchmarking: severity of critical illness (APACHE IV score, ranging from 0 to 286, with higher scores indicating more severe critical illness); the comorbidities (Charlson comorbidity index (CCI), ranging from 0 to 33, with higher scores indicating a greater burden of coexisting conditions) and clinical frailty (Rockwood clinical frailty index, ranging from 1 to 9, with higher scores indicating more frailty).

The level of education was also taken as a covariate for neurocognitive outcome. Therefore, the International Standard Classification of Education (ISCED) was used, a scale ranging from 0 to 8, with higher scores indicating higher education. To avoid collinearity, age was not used as a separate covariate as it is an input variable of both the APACHE IV score and the CCI.

Post ICU admission variables to be taken into account were total number of days in ICU, days of deep sedation and days of delirium/agitation[23]. Deep sedation was defined as a score below minus 3 on the Richmond Agitation–Sedation Scale (RASS). RASS scores range from −5 to 4, with lower scores indicating less arousal, higher scores indicating more agitation, and 0 indicating an alert and calm state[24]. The presence of delirium or agitation was derived from the clinical notes by the nurses and bedside physicians or when the RASS score was plus 2 or more. The presence of delirium or agitation was assessed by one investigator (LV), who was unaware of the neurocognitive outcomes at the time of scoring. Due to the challenging work environment during the COVID pandemic, some routine registrations, such as Delirium Observation Screening (DOS) scale, were temporarily halted by nursing staff.

Statistics

Data were expressed as mean ± SD or median and interquartile range (IQR), as appropriate, for continuous variables and numbers with percentages for categorical variables. The student t-test or Wilcoxon test was used to compare continuous parameters between groups.

The Chi Square test was used to compare categorical parameters between groups.

To get an indication of which factors affect cognitive outcome in C-ARDS patients, multivariable logistic regression analyses were conducted for RBANS <1.5 SD and IQCODE >3.2. The covariates of long-term outcome after critical illness (APACHE IV score, CCI and clinical frailty) and the level of education were included in these models.

Logworth values, area under the curve (AUROC), R^2 and lack of fit (Hosmer-Lemeshow test) were reported. Results were considered significant if $p<0.05$. JMP, version 15.0.0 (SAS Institute Inc, Cary, NC, USA) was used for statistical analyses.

Approvals by the ethics committee

The cohort study was approved by the independent ethics committee of both hospitals, chairman Dr. Patrick Noyens (ZOL, 20/0075U and ZMK 2020-004, Eudract/B-nr: B3712020000016) and registered on ClinicalTrials.gov (NCT04593069). This study was approved by the Ethics committee on 30 September 2020.

Finally, This manuscript adheres to the applicable STROBE guidelines.

Results

Between March and June 2020, 117 COVID-19 patients were admitted to the ICU (Figure 1). The median length of stay in the ICU was 8 days (IQR 5-21). 32 patients (27%) died during hospital stay or within 6 months after discharge. The sample size of the study was therefore limited by the total number of surviving patients (n=85). In 67 (79%) patients the IQCODE was obtained after informed consent. 22 patients (26%) had a language barrier, precluding reliable cognitive testing, making only IQCODE testing possible. Hence, cognitive impairment (RBANS) and executive functioning (TMT) six months after ICU admission could

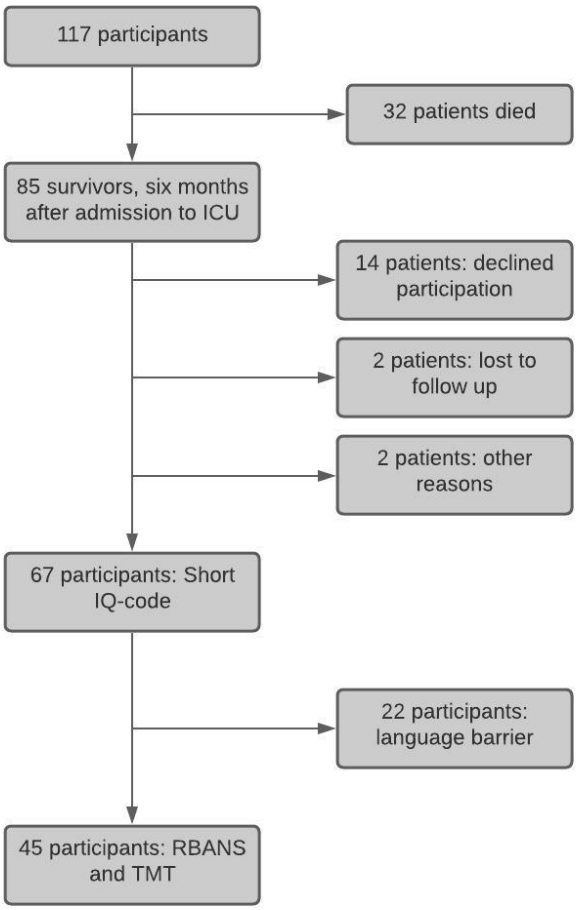

Fig. 1 — Flowchart of the COGCOV patients.
This figures shows the process of our study with the in and exclusion of patients. Boxes to the right show the number of excluded patients with the exclusion criterium. Of the 117 potential patients, 32 died after which the remaining patients were included or excluded. 67 patients were ultimately included and short IQ code was obtained. 22 patients could not partake in the RBANS and TMT due to their language barrier.

be measured in 45 (53%) COVID-19 survivors (Figure 1).

Baseline characteristics did not differ between the IQCODE (n=67) and RBANS/TMT (n=45) cohort (Table I). On admission, patients had a normal level of consciousness (GCS mean 14.9). More than 51% had a clinical frailty score of at least 4 (vulnerable). The level of education in the 45 patients who could do the RBANS, and TMT did not differ statistically from the ones unable: median 3 (IQR 2-6) versus 2 (IQR 1-3) (p=0.06).

We found that COVID-19 survivors had lower total RBANS cognition scores than the age-adjusted population norms (Figure 1). Fifteen (33%) patients had a global cognition score 1.5 SD below the population means and 8 patients (18%) a score 2 SD below the population means. RBANS-subscale performance revealed that memory (both immediate and delayed recall) and attention suffered most (all at minus 1 standard deviation below normative means), while the higher cognitive functions of language and visuospatial cognition were spared.

Furthermore, executive function was considerably affected, shown by a median TMT B score of 40 (IQR 10-65). These findings were consistent with elevated scores of the short form IQCODE (mean 3.4 (SD 0.4). The health utility score of the EQ-5D was median 0.74 (IQR 0.51-0.86) and its Visual Analogue Scale median 65 (IQR 50-77). At baseline, patients with RBANS below 1.5 SD, hence RBANS <77.5, were older (68 ± 8 versus 61 ± 12 years), had higher APACHE IV scores (64 ± 16 versus 55 ± 16) and lower level of education (median 2 (1-2) versus 5 (3-6)), compared to patients with higher RBANS scores (Table II).

Duration of hospitalization was also longer in patients with RBANS scores below 77.5 (median 32 (16-49)) compared to patients with higher RBANS scores (median 14 (10-31)). There were no statistical differences in duration of deep sedation

Table I. — Patient characteristics.

	IQCODE cohort n=67	RBANDS/TMT cohort n=45
Age, y, mean (SD)	63 (12)	63 (11)
Sex, male, n (%)	39 (58)	29 (64)
BMI, kg/m², median (IQR)	30.2 (26.9-34.6)	30.2 (26.8-34.3)
APACHE-IV scores, mean (SD)	59 (17)	58 (16)
Frailty score, median (IQR)	4 (3-5)	4 (3-4.5)
CCI, median (IQR)	3 (1-4)	3 (2-4)
Level of education, median (IQR)	3 (2-6)	3 (2-6)
ICU LOS, days, median (IQR)	8 (5-21)	9 (5-25)
Hospital LOS, days, median (IQR)	17 (12-37)	18 (12-41)
Duration of delirium, days, median (IQR)	1 (0-3)	1 (0-3)
Duration of deep sedation, days, median (IQR)	0 (0-10)	1 (0-10)
Patients' characteristics in the RBANS/TMT group and the IQCODE group.		

Table II. — Comparison of patient characteristics according to RBANS lower or equal/higher than 1.5 SD.

	RBANS <1.5 SD n=15	RBANS >1.5 SD n=30	P-value
Age, y, mean (SD)	68 (8)	61 (12)	**0.03**
Sex, male, n (%)	8 (53)	21 (70)	0.27
BMI, kg/m², median (IQR)	32.8 (28.9-36.7)	30.9 (28.1-33.6)	0.16
APACHE-IV score, mean (SD)	64 (16)	55 (16)	**0.03**
Frailty score, median (IQR)	4 (3-4)	4 (3-5)	0.65
CCI, median (IQR)	4 (3-5)	3 (1-4)	0.05
Level of education, median (IQR)	2 (1-2)	5 (3-6)	**0.0002**
ICU LOS, days, median (IQR)	14 (7-38)	8 (5-19)	0.11
Hospital LOS, days, median (IQR)	32 (16-49)	14 (10-31)	**0.02**
Duration of delirium, days, median (IQR)	2 (0-4)	0.5 (0-2)	0.19
Duration of deep sedation, days, median (IQR)	0 (0-8)	8 (0-18)	0.05
Comparison of patient characteristics, according to RBANS lower or equal/higher than 1.5 SD. A lower RBANS was more prevelant in older patients, a higher APACHE score and a lower level of education. Patients with a lower RBANS were longer hospitalized.			

and days of delirium (Table II). Multivariable nominal logistic regression analysis with the predefined baseline risk factors for RBANS score < 1.5 SD showed that level of education and frailty were the only independent baseline risk factors for poor cognitive outcome (Table III) A similar nominal logistic regression analysis in the entire study population (n=67) for IQCODE >3.2 showed that level of education is the only independent predictor of poor cognitive outcome (Table IV).

Table III. — Multivariable nominal logistic regression analysis of RBANS <1.5 SD at 6 months.

N=45	Logworth	P-value
- Level of education	1.87	0.01
- Frailty	1.31	0.04
- CCI	0.52	0.30
- APACHE IV	0.08	0.82
Pre-existing risk factors were analyzed with multivariable logistic regression analysis with level of education most indicative of a lower RBANS outcome (p=0.01). AUROC = 0.94, R^2=0.53, lack of fit p=0.60.		

Table IV. — Multivariable nominal logistic regression analysis of IQCODE >3.2 at 6 months.

N=67	Logworth	P-value
- Level of education	1.26	0.05
- Frailty	0.46	0.34
- CCI	0.41	0.38
- APACHE IV	0.37	0.42
Multivariable logistic regression analysis for IQ-CODE showed that level of education is the only independent indicator of poor cognitive outcome AUROC = 0.91, R^2=0.47, lack of fit p=0.99.		

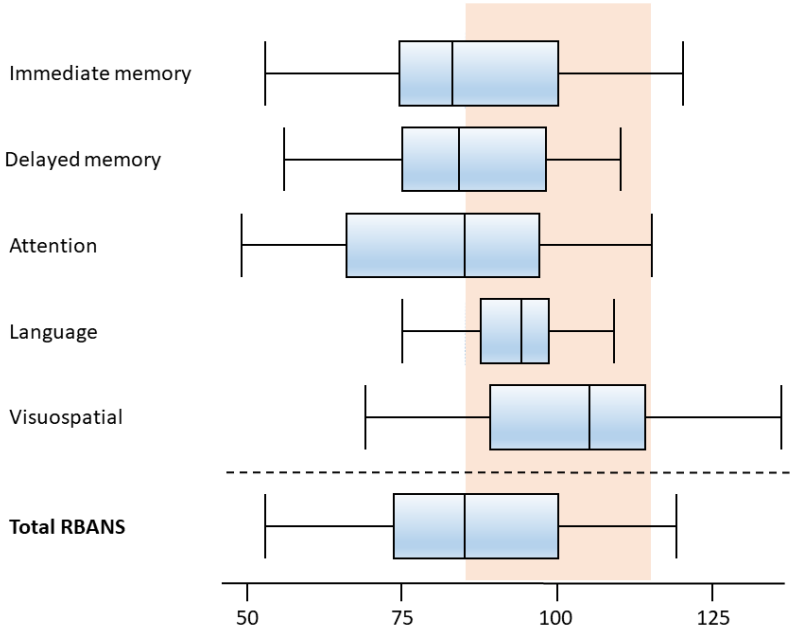

Fig. 2 — Cognition scores in COVID-19 survivors.
The boxplots show the age adjusted cognitions scores on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; with a population age-adjusted mean of 100 with a standard deviation of 15, which is depicted as a red band) at 6 months in 45 COVID-19 survivors. For each boxplot, the line within the box shows the median, while the lower and higher box lines represent the percentile 25 and 75, respectively. The whiskers represent the minimum and maximum, excluding the outliers.

Discussion

Our results suggests that C-ARDS negatively affects long-term cognitive function with the most noticeable impact on memory and attention. These findings are in line with the results of the BRAIN-ICU study[14]. In the latter, 40% of patients had a global cognition score 1.5 SD below the population means and 26% of patients had a score 2 SD below the population means. Comparable results were found by Birberg Thornberg et all with RBANS below 1.5 SD in 36% and below 2 SD in 23% of patients in a five month follow up after COVID hospitalization[25].

Apart from similar deterioration in global RBANS score, similar indices were affected (attention and short-term memory). In the latter study only 27% of patients were admitted to the ICU and a much higher proportion had a university degree. Birberg Thornberg et all noted no correlation between need for ICU admission and either global RBANS score or in the affected indices[25]. Similar finding were reported by Langravinese et all who reported a decrease in attention and memory functions based on RBANS in hospitalized patient, with a more severe impact on ventilated patients[26].

An alternative method of global cognitive assessment is the Montreal cognitive Assessment or MoCa. The large PHOSP-COVID multicenter, prospective cohort study in the UK found that 16.9% of patients had cognitive impairment, defined as a MoCa score <23. Cognitive impairment was only modestly related to the severity of the acute illness[27]. Mild cognitive impairment, as determined by a MoCA score of <26, was detected in 26% of COVID-19 ICU survivors in another small, single center study[28]. At the time of writing there is still debate whether the severity of acute COVID-19 illness is correlated with decrease in neurocognitive function. A study conducted by Hampshire at all showed a more severe impact on cognitive function in patients who were admitted to an ICU than outpatient individuals[29]. Pihlaja et all detected a more significant impact on cognitive impairment in ICU patients compared to patients on wards or no hospitalization[30]. Another prospective study done by Evans et all however showed no clear correlation between disease severity and cognitive impairment[27]. This (lack of) correlation can partially be explained by new literature being released showing significant brain changes even in mild cases of COVID[31,32]. It remains however important to note that MRI imaging does not always correlate with clinical impact and neurological testing. The lack of correlation between the severity of critical illness and impaired cognition was confirmed by our multivariable regression analyses.

We found that a low level of education could be a risk factor of cognitive impairment after C-ARDS. Other studies have shown that in ARDS, lower level of education is a risk factor for cognitive

impairment[33,34]. Sociodemographic factors like fewer years of education, advancing age and pre-COVID neurological comorbidities like baseline cognitive impairment and a higher burden of comorbidities have been described as preadmission risk factors for cognitive impairment after critical illness and not the admission diagnosis[14,35,36]. Reduced cognitive reserve could serve as a possible explanation for the significant relation between low education and cognitive impairment following COVID. Cognitive reserve refers to the brain's resilience against increasing damage of the brain[37]. Healthy lifestyle, high education, and stimulating occupation are said to increase a person's cognitive reserve[37]. Low education limits the neural resources and compensatory cognitive strategies to deal with global neural damage, and this may also explain why more diffusely organized basic cognitive functions like attention and memory suffer most, whereas more focal functions like language and spatial cognition remain spared[38]. Since our study only evaluate a limited amount of patients, this finding needs to be validated in larger studies.

Whereas a longer duration of delirium in the hospital is associated with worse global cognition and executive function scores[14,39], our study did not find a significant association between patients with delirium or number of deep sedation and worse cognitive outcome.

Our findings are in line with studies on non-COVID ARDS, where similar results can be found. The underlying pathophysiology on why ARDS is associated with cognitive decline is unclear but to the systemic inflammatory dysregulation and impairment of cerebrovascular perfusion might be an important contributor.

Our study has some limitations though. First, it is a small, hypothesis generating study, prompting further validation in larger cohorts. Secondly, delirium and delirious days, well-known determinants of post-ICU cognitive impairment, could not be reliably scored by a validated test due to the patient overload together with the allocation of non-ICU trained nursing personnel during the first wave of the COVID pandemic. Third, we neither had a healthy control group nor a non-C-ARDS group from the same setting available to compare with or have assessed the cognitive function of the patients before their infection It also remains difficult to draw comparisons with other studies on cognitive outcome due to the methodological variations[45].

In conclusion, this prospective cohort study confirmed that C-ARDS results in cognitive impairment, to a similar extend as after other types of critical illness. Fewer years of education appears to be the strongest preadmission risk factor for this cognitive impairment.

Funding: The study was supported by the "Interreg Euregio Meuse-Rhine" (Covid Data Plat-form (CoDaP) grant: Interreg-EMR 187.

References

1. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8(12).
2. Mattioli F, Piva S, Stampatori C, Righetti F, Mega I, Peli E, et al. Neurologic and cognitive sequelae after SARS-CoV2 infection: Different impairment for ICU patients. J Neurol Sci. 2022;432.
3. Levine RL. Addressing the Long-term Effects of COVID-19. JAMA. 2022.
4. Thaweethai T, Jolley SE, Karlson EW, Levitan EB, Levy B, McComsey GA, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA [Internet]. 2023;329(22):1934–46. Available from: https://doi.org/10.1001/jama.2023.8823
5. WHO. Post COVID-19 condition (Long COVID) [Internet]. who.int. 2022. p. 1. Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition
6. Perrottelli A, Sansone N, Giordano GM, Caporusso E, Giuliani L, Melillo A, et al. Cognitive Impairment after Post-Acute COVID-19 Infection: A Systematic Review of the Literature. Vol. 12, Journal of Personalized Medicine. 2022.
7. Tavares-Júnior JWL, de Souza ACC, Borges JWP, Oliveira DN, Siqueira-Neto JI, Sobreira-Neto MA, et al. COVID-19 associated cognitive impairment: A systematic review. Cortex. 2022 Jul;152:77–97.
8. Velichkovsky BB, Razvaliaeva AY, Khlebnikova AA, Manukyan PA, Kasatkin VN, Barmin A V. Systematic Review and Meta-Analysis of Clinically Relevant Executive Functions Tests Performance after COVID-19. Behav Neurol. 2023;2023:1094267.
9. Diamond A. Executive functions. Vol. 64, Annual Review of Psychology. 2013.
10. Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: A randomized controlled trial. JAMA. 2012;308(16).
11. Sterken C, Lemiere J, Vanhorebeek I, Van den Berghe G, Mesotten D. Neurocognition after paediatric heart surgery: a systematic review and meta-analysis. Open Hear. 2015;2(1).
12. Sterken C, Lemiere J, Van Den Berghe G, Mesotten D. Neurocognitive development after pediatric heart surgery. Pediatrics. 2016;137(6).
13. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med. 2011;364(14).
14. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-Term Cognitive Impairment after Critical Illness. N Engl J Med. 2013;369(14).
15. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding EDEN Trial follow-up. Am J Respir Crit Care Med. 2013;188(5).
16. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory

distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185(12).
17. Sakusic A, Rabinstein AA. Cognitive outcomes after critical illness. Vol. 24, Current Opinion in Critical Care. 2018.
18. Saraçli Ö, Akca ASD, Atasoy N, Önder Ö, Senormanci Ö, Kaygisiz I, et al. The Relationship between Quality of Life and Cognitive Functions, Anxiety and Depression among Hospitalized Elderly Patients. Clin Psychopharmacol Neurosci. 2015;13(2).
19. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int psychogeriatrics. 2004 Sep;16(3):275–93.
20. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998 Jun;20(3):310–9.
21. Phillips R, Qi G, Collinson SL, Ling A, Feng L, Cheung YB, et al. The Minimum Clinically Important Difference in the Repeatable Battery for the Assessment of Neuropsychological Status. Clin Neuropsychol [Internet]. 2015;29(7):905–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26548428
22. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery and REHABIT: A model for integrating evaluation and remediation of cognitive impairment. Cogn Rehabil. 1988;6.
23. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MATI, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: A prospective longitudinal multicentre cohort study. Intensive Care Med. 2013;39(5).
24. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal P V., Keane KA, et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10).
25. Birberg Thornberg U, Andersson A, Lindh M, Hellgren L, Divanoglou A, Levi R. Neurocognitive deficits in COVID-19 patients five months after discharge from hospital. Neuropsychol Rehabil. 2022 Oct;1–25.
26. Lagravinese G, Castellana G, Castellana F, Genco M, Petrelli R, Ruccia M, et al. Cognitive Deficits among Individuals Admitted to a Post-Acute Pneumological Rehabilitation Unit in Southern Italy after COVID-19 Infection. Brain Sci. 2023 Jan;13(1).
27. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021;9(11).
28. Van Gassel RJJ, Bels J, Remij L, Van Bussel BCT, Posthuma R, Gietema HA, et al. Functional Outcomes and Their Association with Physical Performance in Mechanically Ventilated Coronavirus Disease 2019 Survivors at 3 Months following Hospital Discharge: A Cohort Study. Crit Care Med. 2021;
29. Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. eClinicalMedicine. 2021;39.
30. Pihlaja RE, Kauhanen LLS, Ollila HS, Tuulio-Henriksson AS, Koskinen SK, Tiainen M, et al. Associations of subjective and objective cognitive functioning after COVID-19: A six-month follow-up of ICU, ward, and home-isolated patients. Brain, Behav Immun - Heal. 2023 Feb;27:100587.
31. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604(7907).
32. Y L, X L, D G, N M, PY W, CC H, et al. Cerebral Micro-Structural Changes in COVID-19 Patients - An MRI-based 3-month Follow-up Study. EClinicalMedicine. 2020;25.
33. Hartung TJ, Neumann C, Bahmer T, Chaplinskaya-Sobol I, Endres M, Geritz J, et al. Fatigue and cognitive impairment after COVID-19: A prospective multicentre study. EClinicalMedicine. 2022 Nov;53:101651.
34. Liu YH, Wang YR, Wang QH, Chen Y, Chen X, Li Y, et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. Mol Neurodegener. 2021 Jul;16(1):48.
35. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Vol. 101, Brain, Behavior, and Immunity. 2022.
36. Rengel KF, Hayhurst CJ, Pandharipande PP, Hughes CG. Long-term Cognitive and Functional Impairments After Critical Illness. Vol. 128, Anesthesia and Analgesia. 2019.
37. Stern Y. Cognitive reserve. Vol. 47, Neuropsychologia. 2009.
38. Mungas D, Gavett B, Fletcher E, Farias ST, DeCarli C, Reed B. Education amplifies brain atrophy effect on cognitive decline: implications for cognitive reserve. Neurobiol Aging. 2018;68.
39. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW. Delirium in critical illness: clinical manifestations, outcomes, and management. Intensive Care Med. 2021 Oct;47(10):1089–103.
40. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270).
41. Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. Crit Care. 2019 Nov;23(1):352.
42. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ, et al. Neural origins of human sickness in interoceptive responses to inflammation. Biol Psychiatry. 2009 Sep;66(5):415–22.
43. Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Ann N Y Acad Sci. 2001 Mar;933:222–34.
44. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003 Apr;31(4):1226–34.
45. Raman R, Desautels SJ, Lauck AM, Scher AM, Walden RL, Kiehl AL, et al. Instruments Assessing Cognitive Impairment in Survivors of Critical Illness and Reporting of Race Norms: A Systematic Review. Vol. 4, Critical Care Explorations. 2022.

doi.org/10.56126/75.1.05