

EFFECT OF OXYGEN THERAPY DURATION ON COGNITIVE IMPAIRMENT 12 MONTHS AFTER HOSPITALIZATION FOR SARS-COV-2 INFECTION

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Objective: To identify predictors of persistent cognitive impairment at 12 months after hospitalization due to COVID-19 (SARS-CoV-2) infection.

Design: Retrospective, single-centre study.

Subjects: All consecutive patients assessed in physical and rehabilitation medicine consultations at 3 months with a neuropsychiatric testing (NPT) at 6 months.

Methods: A Mini Mental State Examination (MMSE) was performed at 3 months and NPT at 6 and 12 months, exploring global cognitive efficiency, attention and processing speed, short-term memory and executive function. Logistic regression and receiver operating characteristic curves were used to identify predictors of persistent cognitive impairment.

Results: Among 56 patients, 64.3% and 53.6% had 1 or more impaired cognitive functions at 6 and 12 months, respectively, attention and processing speed being the most represented (41.1% at 12 months). Duration of oxygen therapy (odds ratio 0.926 [0.871–0.985], $p=0.015$) and MMSE score at 3 months (odds ratio 0.464 [0.276–0.783], $p=0.004$) were associated with cognitive impairment at 12 months by multivariable analysis (R^2 0.372–0.497).

Conclusions: Half of patients have cognitive impairment 12 months after acute SARS-CoV-2 infection requiring hospitalization. The duration of oxygen therapy in acute care could be a protective parameter. Systematic evaluation with the MMSE at 3 months after infection might be an effective tool to detect risk.

Key words: COVID-19; cognitive dysfunction; oxygen inhalation therapy; follow-up studies.

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The National Institute for Health and Care Excellence (NICE) and the World Health Organization (WHO) have defined “long COVID” (or post-COVID condition) as a group of signs and symptoms observed during or after infection compatible with COVID-19

LAY ABSTRACT

Early identification of people at risk for post-COVID-19 cognitive impairment is a major issue. This study aimed to identify predictors of persistent cognitive impairment at 12 months after COVID-19 (SARS-CoV-2) infection requiring hospitalization. Fifty-six patients from a large regional hospital were assessed by neuropsychiatric testing at 6 and 12 months after infection. Global cognitive efficiency, attention and processing speed, short-term memory and executive function were assessed. Of these patients, 64.3% and 53.6% had 1 or more impaired cognitive functions at 6 and 12 months, respectively, attention and processing speed being the most represented (41.1% at 12 months). Initial duration of oxygen therapy was associated with cognitive impairment at 12 months, as a protective parameter. The score on the Mini Mental State Examination at 3 months was also associated with a persisting cognitive impairment at 12 months and could be an easy way to detect patients at risk.

(SARS-CoV-2), and persisting for more than 12 weeks, and that cannot be explained by another diagnosis (1, 2). The most commonly described symptoms are fatigue, dyspnoea and cognitive dysfunction or “brain foginess” (1).

Various cognitive domains have been found to be impaired among patients with long COVID. In a recent meta-analysis, Tavares-Junior et al. (3) reported that executive function, attentional processes and episodic memory were the most frequently affected domains. However, the pathophysiology of post-COVID cognitive dysfunction remains to be elucidated. Several hypotheses have been proposed. The neurotropism of SARS-CoV-2 is thought to be involved, with reports of the virus being found in the olfactory nerves, for instance (4–6). However, autopsy studies of cerebral lesions do not seem to be compatible with the specific changes attributable to a virus (7). Other factors have also been proposed, such as persistent low-grade inflammation (8, 9), the accumulation of proteins involved in neurodegenerative diseases (10), baseline nutritional status (11), altered cerebral glucose metabolism in the subacute phase (12), but not in chronic phase (13), or microvascular processes (14).

In a meta-analysis, Premraj et al. (15) estimated that 32% of patients still had “brain fogginess” at 3 months after acute COVID-19 infection, while Alkodaymi et al. (16) reported that 22% of patients still had difficulty concentrating at 6 months. In another meta-analysis, Zeng et al. (17) reported that 19.7% had cognitive deficits at 12 months after COVID-19 infection, although only a few studies assessed this outcome at 12 months. In a report of 1-year follow-up after discharge from hospital for COVID-19 infection among 53 patients who underwent neuropsychiatric assessments at 1 year, Ferrucci et al. (18) reported that 49.1% had deficits on 1 or more tests. Various predictors have been investigated, but no predictive factors have been identified for persistent cognitive impairment at 1 year.

Other studies have investigated the predictors of cognitive impairment late after infection, with conflicting results in terms of the link with the severity of initial infection (19, 20), the length of hospital stay (21, 22) or the initial symptoms (20, 23, 24).

Therefore, the aim of this study was to identify the predictors of persisting cognitive dysfunction at 1 year after COVID-19 infection requiring hospitalization in a population of patients who underwent neuropsychiatric assessments at 6 and 12 months after infection.

METHODS

During the first wave of the COVID-19 pandemic, patients were assessed in the Physical Medicine and Rehabilitation (PMR) unit of Reims University Hospital, Reims, France, at 3 months after discharge from hospitalization due to COVID-19 infection and evaluated with a Mini-Mental State Examination (MMSE) and a Montreal Cognitive assessment (MoCA). In view of the uncertainty early in the pandemic surrounding the possible outcomes of patients after infection, systematic evaluation at 6 and 12 months was proposed.

A retrospective study was performed of consecutive patients evaluated in first consultation between 2 June 2020 and 13 November 2020. All patients provided informed consent. In accordance with French legislation (namely the Jardé law), this retrospective study was approved by the French national commission for personal data protection (Comité National de l'Information et des Libertés; CNIL) (number 2049775 v 0).

The results are reported in compliance with the Strengthening in Reporting of Observational studies in Epidemiology (STROBE) statement for cohort studies.

Study population

Inclusion criteria were: age > 18 years, SARS-CoV-2 infection confirmed by reverse transcriptase polymere

ase chain reaction and/or indisputable clinical and/or paraclinical arguments; need for hospitalization at the acute phase; ability to read and write French fluently; and consent to participate. Exclusion criteria were: patients under judicial or other forms of legal protection, patients with cerebral lesions or cognitive impairment before SARS-CoV-2 infection.

Study outcomes

Patient characteristics. At inclusion, socio-demographic data were recorded for all patients (age, sex, body mass, height, level of education, profession, living situation). Information about the acute phase of SARS-CoV-2 infection was collected from the patients' digital medical files, and included: initial severity, type of oxygen therapy required (if any) at the acute phase, initial blood gas findings including partial pressure of oxygen (PaO₂) and partial pressure of carbon dioxide (PaCO₂); biological findings including C-reactive protein (CRP), high-sensitivity troponin, and blood albumin levels. The total duration of oxygen therapy was defined as the total number of days on which oxygen was administered to the patient, regardless of the mode of administration (invasive mechanical ventilation, high-flow nasal oxygen therapy). The study also recorded length of initial hospital stay.

Evaluation of cognitive function. The tests used to evaluate cognitive function were chosen according to the patients' complaints and reports in the literature. The selected tests as well as the cut-offs used to interpret them are represented in Table I. The various tests used in the neuropsychological evaluation were proposed in a predefined order, which was always the same for each participant, and also the same order of performance from one session to the next. The duration of the assessment was between 60 and 75 min. All tests were scored and interpreted according to norms and recommendations of the French Working Group for reflection on cognitive evaluation (GRECO). Patients were considered to have cognitive impairment if 1 or more test was under the cut-off score, and to be

Table I. Cognitive tests used and cognitive functions explored

Function	Subtests	Pathological threshold
Processing speed and attention	Processing speed index, WAIS IV	≤1.5 SD
	TMT A (time and error in percentile)	≤5 th percentile
	Alertness test (percentile), TAP	≤5 th percentile
Short-term memory	Direct Span (percentile), WAIS IV	≤5 th percentile
	Visual Span (percentile), WMS III	≤5 th percentile
Executive function and working memory	Working memory index, WAIS IV	≤1.5 SD
	Indirect Span (percentile), WMS IV	≤5 th percentile
	Go-No-Go (percentile), TAP	≤5 th percentile
	TMT B (time in percentile)	≤5 th percentile
Overall efficiency	Brief Cognitive Status Exam (BCSE)	Low or very low

WAIS: Wechsler Adult Intelligence Scale; TMT: Trail Making Test; TAP: Test battery of Attentional Performance; WMS: Wechsler Memory Scale; BCSE: Brief Cognitive Status Exam; SD: standard deviation.

“recovering” if there was lower number of cognitive deficits at 12 months than at 6 months.

The Brief Cognitive Status Examination (BCSE) is an optional cognitive examination of the Wechsler memory scale IV (WMS-IV) used in the current study. It helps to assess global cognitive functioning. The results are expressed as very low, low, borderline, low average, and average.

The Wechsler Adult Intelligence Scale IV (WAIS-IV) (25) yields total IQ score, and 4 composite indexes, among which the working memory index (WMI), and the processing speed index (PSI) were selected. A cognitive processing deficit is usually defined by a score that is more than 1 standard deviation (SD) below the population mean (26). In the current study, for this test, -1.5 SD was chosen to diagnose a deficit.

The Trail-Making Test (TMT) examines the trajectories of visual scanning and visual movement. The score is the time, in s, to complete the task, the number of errors and the number of alternation and perseveration errors. Norms with percentiles are available for the French population (27).

The Test of Attentional Performance (TAP) (28) is a standardized software package that uses simple reaction paradigms. The performance criteria are the reaction time and any mistakes. Among the 14 proposed subtests, 2 subtests were used in the current study: TAP Alertness and TAP Go/No go. Results can be expressed as reaction time, in s, or T-scores. Percentiles are also available. The TAP version 2.3.1 was used.

Self-report questionnaires. Hospital Anxiety and Depression Scale (HADS) was used to screen for symptoms of anxiety and depression. A score of 11 or greater corresponding to the likely presence of symptoms of anxiety or depression (29, 30).

Fatigue was measured using the Modified Fatigue Impact scale (MFIS) (31). A score of 38 or higher identifies fatigued individuals (32).

Patients were also asked about the presence of any cognitive disturbances.

Quality of life was assessed using the World Health Organization Quality of Life questionnaire (WHOQoL-Bref). Norms are available in the French general population (33).

Imagery. When available, results of brain magnetic resonance imaging (MRI) taken in the year after infection were collected.

Statistical analysis

Data are described as number and percentage or median and interquartiles for qualitative and quantitative variables, respectively. No imputation was applied for missing data. Results at 6 and 12 months were compared using paired tests for repeat measures, the

Wilcoxon or McNemar test, as appropriate. Logistic regression was performed to identify the factors significantly associated with persistent cognitive impairment at 12 months. The multivariate model included factors that yielded a p -value <0.05 by univariate analysis. Results are reported as odds ratios and 95% confidence intervals (95% CI). A p -value <0.05 was considered statistically significant.

A sensitivity- and specificity-based approach with receiver operating characteristic (ROC) curves was also performed, to determine the optimal cut-off values for quantitative variables most strongly associated with 1-year cognitive impairment.

All analyses were performed using SPSS 28.0.

RESULTS

A total of 75 patients were followed up at the University Hospital of Reims, France, after the first wave of the COVID-19 pandemic. Among these, 65 underwent neuropsychiatric evaluation at 6 months after the acute infection. Nine patients did not undergo neuropsychiatric evaluation at 12 months. These 9 patients were comparable in terms of age, sex, level of education and MMSE score at inclusion to those who did undergo neuropsychiatric evaluation at 12 months. The flowchart of the study population is shown in Fig. 1. The characteristics of the 56 patients with neuropsychiatric evaluation at both 6 and 12 months are shown in Table II. The majority were men (60.7%), mean age was 65 years. All patients had been hospitalized, with (at the very least) nasal oxygen therapy, and 31 patients (55.4%) required admission to the intensive care unit (ICU) for high-flow nasal oxygen ($n=13$, 23.2%) or invasive mechanical ventilation ($n=18$, 32.1%).

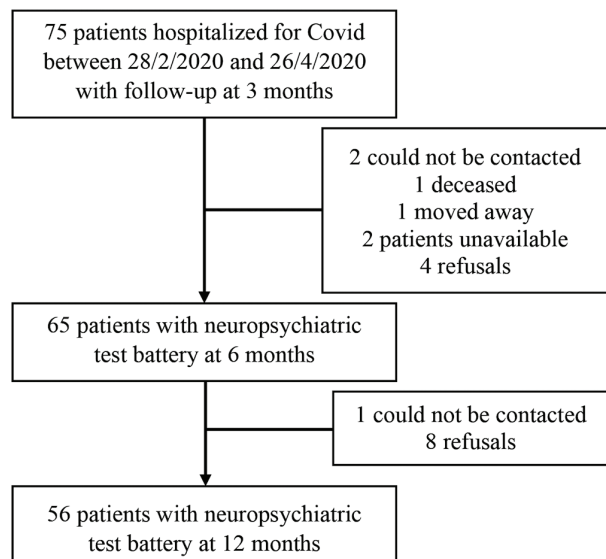


Fig. 1. Flow chart of the study population.

Table II. Characteristics of the study population

Characteristics	
Age	65 [55–72]
Women	22 (39.3)
Body mass index (BMI)	29.2 [26.3–32.4]
Obesity (BMI ≥ 30 kg/m ²)	24 (42.9)
Smokers (active or former)	26 (46.4)
Hypertension	26 (46.4)
Diabetes	12 (21.4)
Level of education	
Less than high school	29 (51.8)
High school diploma	10 (17.9)
University or higher	17 (30.4)

The results of the neuropsychiatric tests at 6 and 12 months are described in Table III. The results of the BCSE, PSI, WMI and visual reproduction tests were statistically significantly different at 12 months compared with the results observed at 6 months. The cognitive status (impaired or not) of 1 patient could not be defined at 12 months due to missing data. At 6 and 12 months, a total of 36 (64.3%) and 30 (53.6%) patients, respectively, had at least 1 cognitive deficit (Table IV). Details of function impaired are described in Table SI.

Twenty patients underwent a brain MRI scan at 1 year after acute infection. Among these, 10 had normal findings, 4 patients had white matter lesions (2 with Fazekas score 1, and 2 with Fazekas score 2), 3 patients had medial temporal atrophy (2 patients with Scheltens

score of 1, and 1 patient with Scheltens score of 2), and 3 patients had both (Fazekas score 1 associated with Scheltens score 1, 2, or 3). Finally, 1 patient also had hyperintensity in the olfactory grooves. There was no association between the presence of any MRI anomalies and cognitive impairment ($p=0.670$).

Table V compares patients with vs those without persistent cognitive deficit at 1 year. Multivariate logistic regression analysis was performed including all variables with a p -value <0.05 by univariate analysis. The duration of oxygen therapy in the acute phase and the MMSE score at 3 months after infection were found to be significantly associated with the presence of persistent cognitive impairment at 1 year (odds ratio 0.926 [0.871–0.985], $p=0.015$ and 0.464 [0.276–0.783], $p=0.004$, respectively, R^2 0.372 Cox and Snell, 0.497 Nagelkerke).

The ROC curve for oxygen therapy in acute phase is shown in Fig. 2 (area under the curve (AUC) 0.7 [0.55–0.85], $p=0.015$). Oxygen therapy lasting <10 days in hospitalized patients had a sensitivity of 71% and specificity of 52% for the identification of patients who would have persistent cognitive impairment at 1 year.

The ROC curve for MMSE score at 3 months is shown in Fig. 3 (AUC 0.766 [0.643–0.889], $p=0.0007$). An MMSE score at 3 months <25 points had 100% sensitivity, but 23.3% specificity for the detection of patients who would have persistent cognitive impairment at 1

Table III. Results of the cognitive tests at 6 and 12 months after COVID-19 infection requiring hospitalization

	6 months Median [IQR]	N < threshold at 6 months <i>n</i> (%)	12-month Median [IQR]	N < threshold at 12-month <i>n</i> (%)	<i>p</i> -value
TMT A time ^a	36.5 [27.5–49.75]	2 (3.6)	38 [28–47]	1 (1.8)	0.574
TMT A errors ^a	0 [0–1]	10 (17.9)	0 [0–0]	4 (4.1)	0.146
TMT A ^a		12 (21.4)		5 (8.9)	0.146
TMT B time	104 [76.5–152]	6 (10.7)	93 [68–151]	5 (8.9)	0.131
TMT B errors ^a	0 [0–1]	2 (3.6)	0 [0–1]	3 (5.4)	0.725
TMT B perseverance	0 [0–1]	8 (14.3)	0 [0–1]	5 (8.9)	0.375
TMT B ^a		13 (23.2)		9 (16.1)	0.219
BCSE ^a	49 [44–52]	14 (25)	52 [48–56]	8 (14.3)	<0.001
Digit span forward ^a	5 [4–6]			5 [5–6]	0.171
Digit span forward standard score ^a	9 [7–10]	2 (3.6)	9 [7–11]	2 (3.6)	0.053
Digit span backward ^a	4 [3–4]			4 [3–4]	0.461
Digit span backward standard score ^a	8 [7–10]	1 (1.8)	8 [7–10]	1 (1.8)	0.344
Symbol digit forward ^b	5 [4–6]			5 [4.75–6]	0.171
Symbol digit backward ^b	4 [4–5]			5 [4–6]	0.461
Symbol digit standard score ^b	9 [7–9]	10 (17.9)	10 [8–12]	8 (14.3)	0.004
Processing speed index ^b	100 [92–111]	6 (10.9)	102 [89–114]	5 (8.9)	0.07
Less than high school	94 [86–101.5]		97 [84–102]		
High school or higher	105 [99.2–111.7]		109.5 [103–114.7]		
University or higher	111 [94–112.5]		114 [91.5–120]		
Working memory index ^a	89.5 [83–100]	8 (14.3)	94 [83–106]	6 (10.9)	0.004
Less than high school	88 [80–95.5]		89.5 [80–103]		
High school or higher	89.5 [87.2–104.5]		100 [87.2–112.5]		
University or higher	94 [86.5–112]		100 [91–110.5]		
TAP without cue (median reaction time, <i>ms</i>) ^b	272.2 [244.3–323.2]	8 (14.3)	274.2 [247.1–317.4]	7 (12.5)	0.694
TAP with cue (median reaction time, <i>ms</i>) ^b	271.8 [242.4–344.5]	14 (25)	275.2 [241.5–330.9]	12 (21.4)	0.460
Go/No-Go (median reaction time, <i>ms</i>) ^c	403.3 [366.8–452.3]	1 (1.8)	407 [373.7–442.3]	2 (3.6)	0.783

^a1 missing data, ^b2 missing data, ^c5 missing data.

IQR: interquartile range; TMT: Trail Making Test; BCSE: Brief Cognitive Status Examination; TAP: Test for Attentional Performance.

p-value for paired samples Wilcoxon test comparing quantitative data.

Table IV. Progression of neuropsychiatric test scores from 6 to 12 months post-COVID

	6 months <i>n</i> (%)	12 months <i>n</i> (%)	<i>p</i> -value
Attention and processing speed*	26 (46.5)	23 (41.1)	0.003
Short-term memory*	11 (19.6)	10 (17.9)	<0.001
Executive function and working memory*	12 (21.4)	11 (19.6)	0.001
Overall efficiency*	14 (25)	8 (14.3)	<0.001
1 or more impairment*	36 (64.3)	30 (53.6)	<0.001
1 function impaired	19 (33.9)	16 (28.6)	0.358
2 functions impaired	9 (16.1)	8 (14.3)	0.604
3 functions impaired	8 (14.3)	6 (10.7)	<0.001

A function (among the 3 functions described in Table I) is considered to be impaired when 1 or more of the tests of this function is below the lower limit.

*1 missing data.

year. A threshold of <28 points had 76% sensitivity and 63% specificity.

Among the 36 patients with at least 1 cognitive deficit at 6 months, 18 patients (50%) were shown to be recovering, i.e. they showed a reduction in the number

of cognitive deficits at 12 months. These recovering patients had more frequently been in ICU (12 (66.7%) vs 5 (29.4%), $p=0.028$), and more frequently had prone positioning (7 (38.9%) vs 1 (5.9%), $p=0.041$). Median MMSE score at 3 months in recovering patients was 28 [26–29] vs 25 [23–28] for the 18 patients who were not found to be recovering ($p=0.014$).

DISCUSSION

This study sought to identify the characteristics that could enable early detection of patients likely to have persistent cognitive impairment at 1 year after hospitalization for acute SARS-CoV-2 infection. More than half the patients hospitalized for COVID-19 had at least 1 persisting deficit at 1 year. The only acute predictive factor identified in the current study was the duration of oxygen therapy, with a protective effect of a longer

Table V. Univariate analysis comparing patients with vs those without cognitive deficit at 12 months

	No deficit at 12 months <i>n</i> = 25	≥1 deficit at 12 months <i>n</i> = 30	<i>p</i> -value
Patient characteristics, <i>n</i> (%)			
Age > 65 years	14 (56)	14 (47)	0.491
Women	9 (36)	13 (43)	0.580
Obesity	11 (44)	12 (40)	0.765
Diabetes	4 (16)	7 (23)	0.498
Hypertension	11 (44)	14 (47)	0.843
> 2 comorbidities	14 (56)	17 (57)	0.960
Level of education			
Less than high school	13 (52)	15 (50)	1
High school diploma	6 (20)	6 (20)	
University or higher	8 (32)	9 (30)	
Acute symptoms			
Loss of smell, <i>n</i> (%)	8 (33)	10 (33)	1
Asthenia, <i>n</i> (%)	18 (75)	22 (73)	0.890
PaO ₂ at admission (mmHg), median [IQR]	74 [65–80]	76.5 [64–86]	0.291
PaCO ₂ at admission (mmHg), median [IQR]	34.5 [32–37.7]	34.5 [30–37]	0.665
Weight loss (kg), median [IQR]	9 [6–16]	6 [2.7–15.2]	0.094
Peak CRP (mg/L), median [IQR]	158 [115–239]	188 [88–188]	0.838
Troponin at admission (ng/L), median [IQR]	21 [7.5–46.5]	13 [8–18]	0.290
Acute management			
Need for ICU admission, <i>n</i> (%)	19 (76)	12 (40)	0.007
Orotracheal intubation, <i>n</i> (%)	12 (48)	6 (20)	0.028
Duration of ventilation, days, median [IQR]	17 [9.2–38.2]	9 [7–14]	0.007
Corticosteroids, <i>n</i> (%)	20 (80)	18 (60)	0.110
Evaluation at 3 months, median [IQR]			
MoCA	25 [25–27]	23.5 [19.5–26]	0.01
MMSE	29 [28–29]	26.5 [24.7–28]	<0.001
Complaints at 12 months			
Complained of cognitive impairment, <i>n</i> (%)	14 (56)	17 (57)	0.906
Complained of fatigue, <i>n</i> (%)	5 (20)	1 (3)	0.082
Complained of mood disturbance, <i>n</i> (%)	8 (25)	12 (40)	0.539
HADS-Anxiety*, median [IQR]	4 [2–8]	6 [4–7.5]	0.250
HADS-Depression*, median [IQR]	4 [1.5–7.5]	6 [2–10.5]	0.325
MFIS*, median [IQR]	35 [11.5–58.5]	46 [23.5–61]	0.45
Cognitive	3 [0–5]	4 [1.5–6]	0.201
Physical	23 [4–28]	21 [14.5–29]	0.869
Social	17 [4–24]	20 [6.5–28.5]	0.255
WHOQoL – BREF, median [IQR]			
Physical*	64.3 [53.6–82.1]	60.7 [39.3–67.9]	0.161
Psychological*	66.7 [58.3–81.2]	62.5 [54.2–72.9]	0.243
Social*	66.7 [54.2–83.3]	66.7 [54.2–79.2]	0.630
Environmental*	78.1 [68.7–90.6]	75 [64.1–87.5]	0.418

IQR: interquartile range; PaO₂: partial pressure of oxygen; PaCO₂: partial pressure of carbon dioxide; CRP: C-reactive protein; ICU: intensive care unit; MoCA: Montreal Cognitive Assessment; MMSE: Mini mental State Examination; HADS: Hospital Anxiety and Depression Scale; MFIS: Modified Fatigue Impact Scale; WHOQoL: World Health Organization Quality Of Life. *1 missing data.

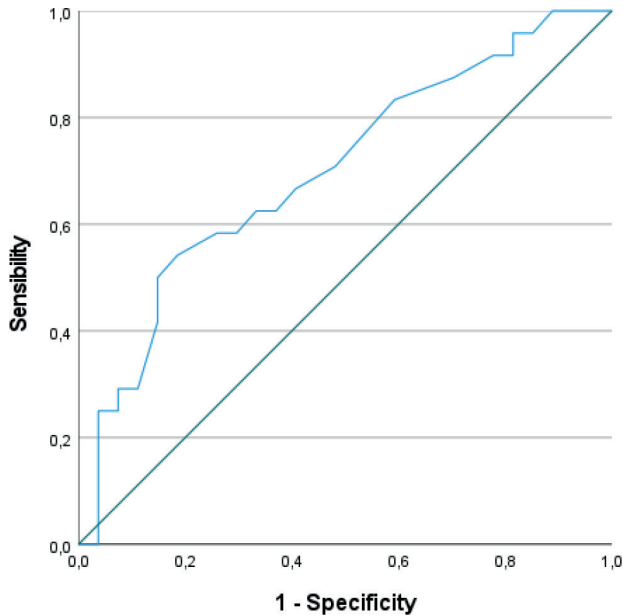


Fig. 2. Receiver operating characteristic (ROC) curve showing the sensitivity and specificity of duration of ventilation to predict persistence of cognitive deficit at 12 months.

exposition. Ferrucci et al. (18) used a methodology similar to ours, and found an association between the level of initial hypoxemia and cognitive deficits at 6 months. The duration of oxygen therapy, representing the therapeutic response to hypoxaemia, seems to protect against the risk of long-term cognitive impairment.

Pathophysiology of post-COVID cognitive impairment is not clear, but seems to be polyfactorial, involving hypometabolism (12), persistent low-noise

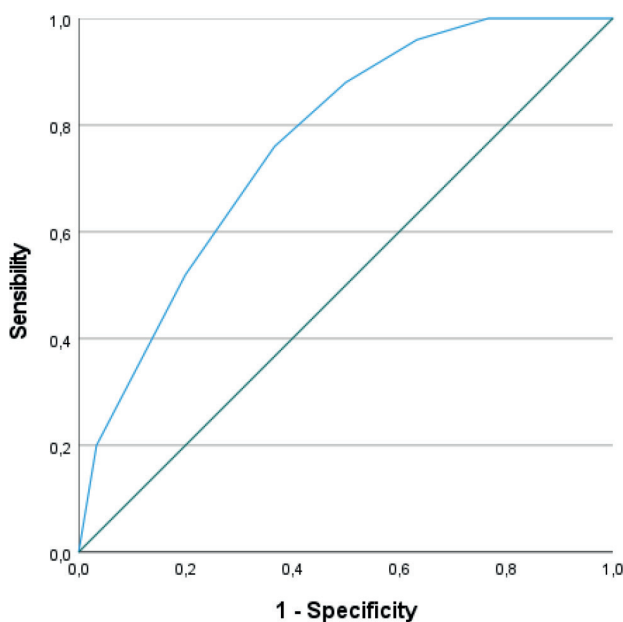


Fig. 3. Receiver operating characteristic (ROC) curve showing the sensitivity and specificity of the Mini Mental State Examination (MMSE) score at 3 months to predict persistence of cognitive deficit at 12 months.

inflammation (8, 9), immune dysfunction (34), micro-angiopathies (14) and hypoxaemia. Acute hypoxaemia is 1 of the aetiological mechanisms thought to be implicated in the persistence of neurological deficits in patients who have been hospitalized for acute SARS-CoV-2 infection (35). The appropriate duration and dose of oxygen therapy (of any form) could therefore be the best available protection against the consequences of hypoxaemia. These findings are in line with those of Alemanno et al. (20), who found that patients who had undergone orotracheal intubation had higher MMSE and MoCA scores than those with other types of ventilation, or no ventilation. A link between hypoxaemia and cognitive impairment has been reported in other nosological settings (36), providing additional support for this hypothesis. Finally, Adingupu et al. (37) used the frequency-domain near-infrared spectroscopy (NIRS) to measure cerebral tissue oxygen saturation in patient at 8 month post-SARS-CoV-2 infection. They found correlation between persisting hypoxia, supposed to be related to inflammation, and brain fog and fatigue. The use of NIRS in clinical practice seems thus to be an interesting work track.

The results of the cerebral MRIs collected retrospectively in this study did not show any abnormality in the patients with the disease. Douaud et al. (38) compared pre- and post-COVID MRIs, showing a decrease in grey matter in the orbitofrontal cortex and parahippocampal gyrus, traces of tissue damage in the piriform cortex and an overall decrease in brain size. Cerebral MRI alone therefore seems more contributory in the event of a possible comparison with the previous state. The search for hypometabolism by ^{18}F -FDG PET could be more sensitive (12, 39).

The current study did not find any association between the severity of the initial infection, and the presence of long-term cognitive impairment, and indeed, conflicting findings have been reported in this regard. Some studies have reported that initial severity, with need for ICU admission, was associated with persistent cognitive deficit at 4 (40, 41), 6 (42, 43) and 12 months (44). Others, on the contrary, have failed to show any such association at 1 (22), 2 (45), 3 (20, 46), or 8 months (47). The multicentre, prospective “Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation” (PHOSP-COVID) cohort study (48) reported similar findings to ours, since the authors also failed to observe any relationship between initial severity of physical or mental symptoms, persistent low-grade inflammation, the severity of acute illness and the occurrence of cognitive impairment. Conversely, cognitive impairments appeared to be more prevalent and persistent in moderate forms of disease among patients who did not require hospitalization (48).

Similarly, no association was found between the intensity of initial inflammation, and the persistence of cognitive deficit, which is congruent with the findings reported by Woo et al (49) in 18 young patients followed-up at 20–105 days (median 85 days) after recovery from mild to moderate disease. Mendez et al. (45) reported comparable findings at 2 months and Miskowiak et al. (50) at 3–4 months after acute illness. In the PHOSP-COVID cohort mentioned above (48); the authors purported that persistent systemic inflammation could be implicated in patient recovery, while Zhou et al. (22) reported a correlation between cognitive impairment and persistent inflammation at 3 weeks after acute infection.

The current study did not find any association between persisting cognitive impairment at 1 year and loss of taste or smell as symptoms of the initial infection. This point remains debated in the literature, with conflicting results reported at various follow-up time-points (20, 24, 51, 52). However, Dias de Melo et al. (53) recently found independence between anosmia and neuroinvasion by SARS-CoV2 in an animal model.

The absence of any established characteristics or associations that could help to quantify the risk of persisting cognitive deficit means that personalized follow-up should be systematic for all patients after COVID-19 infection (48), using screening tools that are capable of distinguishing patients at risk of long-term sequelae. Few authors have investigated the predictors of long-term cognitive impairment late after COVID-19. Aiello et al. (54) compared the MMSE and MoCA scores to screen for severe cognitive impairment, but at 2 to 3 months after COVID-19 infection. Both tools were found to be valid for this purpose, with a slightly higher sensitivity observed with the MoCA (54). Our finding that MMSE score at 3 months after infection is related to the persistence of deficits at 12 months is original and noteworthy. Although the MMSE is reputed to have less discriminant capacity for the identification of mild cognitive impairment (55), it appears to be a valid and useful tool in patients post-COVID (53). Moreover, it is easy to use in routine practice, with a short administration time (56), which also makes it attractive for use in primary care (57).

The need for systematic screening is reinforced by the fact that patients are largely unaware of their cognitive deficits. Indeed, the current data show no association between the presence of persisting cognitive impairment at 12 months, and self-reported cognitive complaints by the patients. This phenomenon has previously been described in several studies (49, 58, 59), and reflects the fact that there is a pervasive lack of awareness of these symptoms among COVID-19 patients. Nevertheless, the impact of cognitive dysfunction on social participation underpins the need to

perform careful screening and provide personalized follow-up.

In the current study there were no differences in quality of life scores between patients with, and those without cognitive deficit at 12 months, which is contrary to some previous reports (45, 50, 60), but in line with others (58). This could be explained by the study population. Indeed, Voruz et al. (58) included patients with no known cognitive complaints. The current study also evaluated patients systematically, and independently of any reported cognitive complaints, which could explain why this study and that of Voruz observed no association between quality of life and cognitive function. It is also noteworthy that there was no correlation in the current study between cognitive impairment and the presence of symptoms of anxiety or depression, as assessed by the HADS scale, or fatigue assessed by the MFIS. This point is also debated in the literature, with some authors finding an association between cognitive impairments and psychiatric disorders (23, 37, 53, 54), whereas others did not find any such relationship (49, 61). There is potential for bias, such as the presence of anxiety or depressive symptoms after SARS-CoV-2 independently of any confirmed cognitive dysfunction (40). The association between cognitive deficits and perceived fatigue has not been widely investigated, but existing studies have found conflicting results (49, 58, 62). Further studies are necessary to elucidate the interplay between all these symptoms.

Finally, when cognitive deficits are diagnosed, identifying patients with the potential to recover is a worthy and important research perspective. In this study, it appears that, among the patients with cognitive deficits at 6 months, those who were in ICU and had prone positioning at the acute phase appear to recover best, with regression of the cognitive symptoms. This is coherent with the pathophysiological hypothesis that hypoxaemia during the initial acute illness is implicated in the onset of cognitive deficits, and underlines the importance of initiating efficacious curative therapy at the acute phase. This raises the question of hypoxaemia monitoring and the acute management of hypoxaemia in patients who are cared for at home during acute infection.

Strengths and limitations

This study has some limitations; first, the absence of a control group and the small number of patients, with single-centre recruitment of patients who all required hospitalization and rehabilitation, yielding a selected population of patients with severe infection. Numerous studies have reported the existence of cognitive impairments, including in patients who did not require hospitalization, at 3–12 months after COVID-19 infec-

tion (40, 52, 62–64). Another limitation is the lack of information on functional status and the daily living impact of cognitive impairment according to neuropsychological test. In view of the aim of the study, it would be relevant to complete the evaluations with ecological tests.

This study also shows a number of strengths. First, the results of the neuropsychiatric assessments were compared with norms for the general population established in non-pandemic times. We also sought to limit the number of false-positive results, by using robust cut-off, contrary to some other studies that used more permissive thresholds (50, 60). Moreover, we used validated neuropsychiatric tests, performed by a single, experienced examiner at both 6 and 12 months, and no subjective self-report questionnaires. There is wide diversity in the tools used in the literature (65), and consequently, wide variation in the cognitive deficits described. Consensus is needed on the battery of tests to be performed in these patients, which would be of value for both research and clinical practice, to harmonize data and enable comparisons and conclusions to be drawn about the prevalence and typology of cognitive impairment post-COVID-19.

Conclusion

After hospitalization due to SARS-CoV-2 infection, half of the patients have persisting cognitive impairment at 12 months on neuropsychological test. The persistence of cognitive impairment at 12 months was not found to be related to the initial symptoms, particularly the severity of the acute illness. The total duration of oxygen therapy (regardless of the type) was found to be associated with persisting cognitive impairment at 12 months. ROC curve analysis showed that a threshold of ≥ 10 days of oxygen therapy was associated with a protective effect. There is an unmet need for a consensual screening approach to detect cognitive impairment in these patients. Performing systematic screening, notably using the MMSE at 3 months after acute COVID-19 infection, could help to identify those at risk of having persisting cognitive impairment at 12 months.

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