Neurological Complications and Noninvasive Multimodal Neuromonitoring in Critically ill COVID-19 Patients

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Research

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Abstract

Background: The incidence and clinical presentation of neurological manifestations of coronavirus disease 2019 (COVID-19) remain unclear. No data regarding the use of neuromonitoring tools in this group of patients are available.

Methods: This is a retrospective study of prospectively collected data. The primary aim was to assess the incidence and type of neurological complications in critically ill COVID-19 patients and their effect on survival, as well as on hospital and intensive care unit (ICU) length-of-stay. The secondary aim was to describe cerebral hemodynamic changes detected by noninvasive neuromonitoring modalities such as transcranial doppler (TCD), optic nerve sheath diameter (ONSD), and pupillometry.

Results: Ninety-four patients with COVID-19 receiving mechanical ventilation and admitted to an ICU from February 28 to June 30, 2020, were included in this study. Fifty-three patients underwent noninvasive neuromonitoring. Neurological complications were detected in 47/94 patients (50%), with delirium as the most common manifestation. Patients with neurological complications, compared to those without, had longer hospital (36.8 ± 25.1 vs. 19.4 ± 16.9 days, $p < 0.001$) and ICU (31.5 ± 22.6 vs. 11.5 ± 10.1 days, $p < 0.001$) stay. The duration of mechanical ventilation was independently associated with risk of developing neurological complications (OR 1.100, 95%CI 1.046-1.175, $p = 0.001$). Patients with increased intracranial pressure (ICP) measured by ONSD (19% of the overall population) had longer ICU stays.

Conclusions: In conclusion, neurological complications are common in critically ill patients with COVID-19 receiving invasive mechanical ventilation and are associated with prolonged ICU length-of-stay. Multimodal noninvasive neuromonitoring systems are useful tools for early detection of cerebrovascular changes in COVID-19.

Registration number: 163/2020

Background

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (1–4), is primarily a disease of the respiratory system, leading to a variety of clinical manifestations including dry cough, fever, fatigue, and respiratory failure (4). However, recent data suggest that COVID-19 is not confined to the airways, but is also responsible for a syndrome of multiorgan dysfunction (MODS-CoV-2), including possible neurological involvement (5,6).

Coronaviruses may pass to the central nervous system by different routes (7,8), including hematogenous spread from the systemic to the cerebral circulation and lymphocyte invasion or dissemination from the cribriform plate and olfactory bulb to the brain (9,10). These hypothesis seem to be consistent with the loss of smell and taste described as—first atypical, then quite prevalent—presentations of COVID-19 (11). However, the neurologic manifestations of COVID-19 are highly variable, and can occur prior to diagnosis or as a complication late in the course of infection (7,8).

A recent systematic review of 37 articles revealed that 20% of COVID-19 patients present with headache, 60% with anosmia/ageusia, 25% with myalgia/myositis, 8.8% with encephalopathy, 2.8% with ischemic stroke, and 0.45% with intracerebral hemorrhage (12). Other neurological symptoms include impaired consciousness, ataxia, seizures, and neuralgia (13–17). SARS-CoV-2 has also been reported to trigger autoimmune diseases such as multiple sclerosis, acute disseminated encephalomyelitis, acute encephalitis, acute autoimmune polyneuropathy, and critical illness polyneuropathy (13,18), as well as cerebrovascular events (19,20). However, recent reports suggest that hypoxic-ischemic damage could be the main driver of neurological symptoms in COVID-19 patients (21).

Noninvasive neuromonitoring systems are widely used in Neurointensive care settings for patients with primary cerebral damage; more recently, they are also being employed in critically ill patients in general as useful tools to detect neurological complications (22,23). In particular, transcranial Doppler (TCD) ultrasonography, optic nerve sheath diameter (ONSD) measurement, and quantitative pupillometry are safe, useful methods that can be applied at the patient's bedside to assess cerebral hemodynamics, as well as to monitor cerebral perfusion pressure and intracranial pressure noninvasively (22,23). To date, no studies have investigated cerebral hemodynamics in patients with COVID-19.

The primary aim of our study was to describe the type and frequency of neurological complications in a cohort of critically ill patients with COVID-19 receiving invasive mechanical ventilation in an intensive care unit (ICU) and the effects of these complications on outcome. As a secondary aim, we sought to assess changes in cerebral hemodynamics, their effects on outcome, and their role as potential predictors of neurological complications in a subgroup of patients who underwent noninvasive neuromonitoring (ONSD, TCD, and pupillometry).

Methods

Study design

This is a single-center, retrospective, observational study of prospectively collected data. The study was carried out during the COVID-19 pandemic, from February 28 through June 30, 2020, at the ICU of the San Martino Policlinico Hospital (SMPH) IRCCS for Oncology and Neurosciences, Genoa, Italy. The SMPH is the main hospital serving both the metropolitan area of Genoa (approximate population 840,000) and the wider Liguria Region (approximate population 1,543,000). The usual ICU capacity is 52 adult beds, increased to 74 during the peak of the SARS-CoV-2 outbreak in Italy. The study protocol followed Good Clinical Practice principles in compliance with the Declaration of Helsinki. Approval was obtained from the Ethics Committee of Liguria, Italy (registry number 163/2020), which waived informed consent for participation because of the retrospective nature of the study.

Study population

Patients aged ≥ 18 years, confirmed positive for SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swab specimens at the moment of ICU admission, and who were critically ill requiring invasive mechanical ventilation were eligible for inclusion. Patients who were not neurologically evaluable due to life-threatening respiratory failure resulting in use of sedatives were excluded, as were those who died before sedation could be weaned.

Data collection

Overall population

The following data were collected from patients' electronic records at the time of ICU admission: age in years; gender; body mass index (BMI) in kg/m^2 ; sequential organ failure assessment (SOFA) score (24); a series of comorbidities, namely hypertension, diabetes mellitus, respiratory disease (defined as asthma or chronic obstructive pulmonary disease), end-stage renal disease (defined as estimated glomerular filtration rate $< 15 \text{ mL}/\text{min}/1.73 \text{ m}^2$), moderate/severe liver disease (defined as compensated/decompensated liver cirrhosis) (25), and cancer. The highest C-reactive protein (normal range 0-5 mg/L) and D-dimer (normal range 0-500 mcg/L), as well as the lowest partial pressure of oxygen (PaO_2) (normal range 72-104 mmHg), were collected from daily test results throughout each patient's ICU stay. At the time of ICU and hospital discharge, data on ICU length of stay (ICU-LOS) (days), overall hospital LOS (days), duration of mechanical ventilation (days), neurological complications (type and number), and mortality were collected.

Neuromonitoring cohort

The following data were collected from patients who underwent noninvasive neuromonitoring during the day of assessment and throughout their ICU stay: ventilatory parameters [type of ventilation, positive end-expiratory pressure (PEEP) in cmH_2O , pressure control or pressure support in cmH_2O , respiratory rate in breaths per minute, tidal volume in mL, and fraction of inspired oxygen (FiO_2)]; arterial blood gas values [PaO_2 in mmHg, partial pressure of carbon dioxide (PaCO_2) in mmHg, pH]; vital signs [mean arterial pressure (MAP) in mmHg, heart rate in beats per minute]; sedation (including type of sedative); analgesia (including analgesic agent); and neuromuscular blockade. Neurological complications and scales used for outcome measures are defined in the Electronic Supplemental Material (**ESM - Table 1-4**).

Noninvasive neuromonitoring systems

Ultrasound measurements were performed by two experienced operators (defined as having received more than 5 years of training and performing more than 70 examinations/year) (DB, CR) and three mentored trainees in Anesthesia and Intensive Care (KC, FI, MB). MAP, heart rate, mean cerebral artery

(MCA) flow velocities (diastolic, mean, and systolic), and ONSD were recorded during ICU stay, according to the clinical context and need (availability of personal protective equipment and clinical rationale).

Transcranial doppler (TCD)

A low-frequency (2 MHz) microconvex transducer (Philips SparQ®) was used to investigate intracranial vessels. The temporal window was preferred for passage of the Doppler signal for MCA assessment. Systolic (sFV), diastolic (dFV), and mean flow velocity (mFV) in the MCA were collected. MAP was also measured. The pulsatility index (PI) was calculated as the mean value between the right and left MCA flow velocities using the following formula [13]:

$$PI = \frac{(sFV - dFV)}{mFV}$$

Noninvasive ICP ($nICP_{TCD}$) was calculated according to the formula:

$$nICP_{TCD} = MAP - CPPe$$

where cerebral perfusion pressure (CPPe) was calculated as follows (27):

$$CPPe = \frac{MAP * dFV}{mFV} + 14$$

Intracranial pressure (ICP) values > 20 mmHg were considered indicative of intracranial hypertension (27).

Optic nerve sheath diameter (ONSD)

A linear probe (Philips SparQ®) was used for ONSD evaluation. The probe was placed on the closed upper eyelid, and ONSD was evaluated 3 mm behind the retinal papilla. Two measurements were obtained from each optic nerve, the first in the transverse plane and the second in the sagittal plane (28). Noninvasive intracranial pressure measured by ONSD ($nICP_{ONSD}$) was derived from a mathematic formula described elsewhere in the literature (29,30). Again, ICP values > 20 mmHg were considered indicative of intracranial hypertension (27).

Automated pupillometry

Pupillary light reactivity was measured by a handheld quantitative automated pupillometer (Neurolight Algiscan®, ID-MED, Marseille, France) in both eyes. This device measures quantitative variation in

pupillary light reactivity by using an infrared camera to record video footage of changes in the pupillary surface. Pupillary light reactivity was assessed by a calibrated light stimulation (320 lux for 1 second) with a precision limit of 0.05 mm. Quantitative reactivity was expressed as the percentage of pupillary light response, and baseline pupil size was expressed in mm. The pupillary constriction velocity (mm/sec) was also reported (31–33). Abnormal pupillary reactivity was defined as an abnormal pupillary light reflex as reported by the pupillometer (e.g., a weaker than normal or “sluggish” pupil response) (34).

Statistical analysis

The results are expressed as mean $\pm$ standard deviation, median, 1st quartile (Q1), 3rd quartile (Q3), interquartile range (IQR), and absolute and relative frequencies. No sample size calculation was performed due to the retrospective design of this study. The Shapiro–Wilk test was used to assess the normality of distribution of continuous variables. The Mann–Whitney *U*-test was used to compare continuous variables, while categorical variables were compared with Fisher’s exact test. Patient survival was estimated by the Kaplan–Meier method; the log-rank test was used to compare survival curves. Continuous and categorical variables were entered into univariate Cox proportional hazard regression models, which returned regression coefficients and hazard ratios (HRs) with 95% confidence intervals (CIs) as the main outputs. The Efron approximation was used for each Cox model. The proportional hazards assumption for each significant Cox regression model was evaluated using correlation coefficients between transformed survival times and scaled Schoenfeld residuals. Variables significant on univariate Cox regression which satisfied the proportional-hazards assumption were carried forward to the multivariate model. A forest plot and a rank-hazard plot were provided for multivariate regression. The rank-hazard plot is able to visualize the relationship between the relative hazard of variables entered in a multivariate Cox regression model [37]. Logistic regression was performed to assess the risk factors associated with neurological complications. The Hosmer–Lemeshow omnibus test was used for goodness-of-fit evaluation of each significant logistic regression model. Variables significant on univariate logistic regression were entered in the multivariate model, with regression coefficients and odds ratios (ORs) with 95%CIs as the main outputs. A receiver operating characteristic (ROC) curve was calculated for the multivariate logistic regression model, as well as sensitivity and specificity. Statistical significance was accepted at a two-tailed P-value <0.05 for all tests. Statistical analyses were conducted in the R software environment (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 116 patients with COVID-19 were admitted to the SMPH ICU. Twenty-two patients were excluded because they did not meet the inclusion criteria. Thus, 94 patients were included in the final analysis, of whom 53 underwent noninvasive neuromonitoring.

Overall population

The characteristics of the 94 patients admitted to our ICU who fulfilled the inclusion criteria—with and without neurological complications—are described in **Table 1**. Neurological complications were detected in 47/94 patients (50%). Nine patients presented more than one neurological complication. The most common complications are reported in **Table 2**. Occurrence of neurological complications did not result in increased ICU mortality ($p = 0.450$) (**Figure 1**), but was associated with longer hospital (36.77 ± 25.14 vs. 19.43 ± 16.86 days, $p < 0.001$) and ICU (31.51 ± 22.64 vs. 11.51 ± 10.14 ; $p < 0.001$) stay compared to absence of neurological complications (**Table 1**).

No reliable Cox regression model could be obtained by entering the variables collected for the overall population (data not shown). On univariate logistic regression, duration of mechanical ventilation and CRP values were associated with risk of developing neurological complications (**Table 3**). Multivariate logistic regression demonstrated that the duration of mechanical ventilation was independently associated with the risk of neurological complications (OR: 1.1; 95% CI: 1.046-1.175; $p = 0.001$) (**Table 3**), with an area under the curve (AUC) of 0.818, sensitivity of 0.658, and specificity of 0.786 (**Figure 2**). Additional results concerning the cumulative survival probability of the overall population after hospital and ICU admission are shown in **ESM - Figures 1-3**.

Table 1
Demographic and clinical characteristics of the COVID-19 patients included in the study.

Characteristics	All patients (n = 94)	Patients with neurological complications (n = 47)	Patients without neurological complications (n = 47)
Gender [male, n (%)]	74 (78.7%)	41 (87.2)	33 (70.2)
Age (y/o, mean±SD)	61.6 ± 11.1	62.4 ± 8.3	60.8 ± 13.3
Weight (kg, mean±SD)	90.0 ± 13.6	82.9 ± 14.2	80.5 ± 13.0
Height (cm, mean±SD)	176.0 ± 7.9	171.7 ± 7.5	171.8 ± 8.3
BMI (kg/m ² , mean±SD)	29.9 ± 4.2	28.1 ± 4.2	27.3 ± 4.1
Comorbidities [n, (%)]			
Hypertension	49 (52.1)	27 (57.4)	22 (46.8)
Chronic renal disease	5 (5.3)	5 (10.6)	0 (0.0)
Diabetes	14 (14.9)	6 (12.8)	8 (17.0)
Chronic respiratory disease	9	0 (0.0)	0 (0.0)
Chronic liver disease	0 (0.0)	1 (2.1)	2 (4.3)
Cancer	3 (3.2)	3 (6.4)	3 (6.4)
Cardiac failure	6 (6.4)	5 (10.6)	3 (6.4)
Neurological disease	8 (8.5)	0 (0.0)	0 (0.0)
	0 (0.0)		
Hospital length of stay (days, mean±SD)	28.10 ± 23.00	36.77 ± 25.14	19.43 ± 16.86
ICU length of stay (days, mean±SD)	21.51 ± 20.14	31.51 ± 22.64	11.51 ± 10.14
ICU outcome [n, (%)]			
Alive	61 (64.90)	31 (65.95)	30 (63.83)
Critical	2 (2.10)	2 (4.25)	0 (0.00)
Death	31 (33)	14 (29.78)	17 (36.17)

Days of mechanical ventilation (days, mean±SD)	20.00 ± 16.33	22.93 ± 19.62	8.85 ± 7.75
Days from symptoms to hospital admission (days, mean±SD)	3.98 ± 10.11	3.81 ± 7.16	4.14 ± 12.42
Days from symptoms to ICU admission (days, mean±SD)	10.92 ± 6.84	9.51 ± 6.73	12.30 ± 6.74
Higher D-Dimer during ICU stay (ng/mL, mean±SD)	17636 ± 26631	14067 ± 21401	17878 ± 31310
Higher CRP during ICU stay (mg/L, mean±SD)	266.25 ± 120.88	232.78 ± 127.49	161.47 ± 102.81
Lower PaO ₂ during ICU stay (mmHg, mean±SD)	60 ± 10.92	52.97 ± 7.80	57.96 ± 13.03

n: number; SD: standard deviation; y/o: years old; BMI: body mass index; ICU, intensive care unit; PaO₂: partial pressure of oxygen; CRP: C-Reactive Protein.

Table 2
Type and incidence of neurological complications in the overall ICU population.

Neurological complications	Number of patients (%)
Overall	47 (50)
Delirium	34 (36.17)
Critical illness neuropathy	5 (5.32)
Coma	4 (4.25)
Acute ischemic stroke	3 (3.19)
Stupor	3 (3.19)
Seizures	2 (2.13)
Encephalopathy	2 (2.13)
Cognitive deficit	1 (1.06)
Depression	1 (1.06)

Table 3

The significant variables associated with neurological complications assessed by univariate logistic regression and the output of the subsequent multivariate model, for the patients (n = 94) who fulfilled the inclusion criteria.

Variable	Univariate				Multivariate			
	RC	OR	95% CI	P value	RC	OR	95% CI	P value
Days of mechanical ventilation	0.088	1.092	1.046-1.154	<0.001	0.095	1.100	1.046-1.175	0.001
CRP	0.005	1.005	1.002-1.009	0.006	0.002	1.002	0.997-1.006	0.443

CRP: C-reactive protein; RC: regression coefficient; OR: odds ratio; CI: confidence interval.

Noninvasive neuromonitoring population

A total of 53 patients underwent noninvasive neuromonitoring. The characteristics of this subgroup are described in **ESM - Table 5**. TCD was performed in 51/53 (96.23%), ONSD in 49/53 (92.45%), and pupillometry in 29/53 (54.72%) patients. The median sFV was 99.50 [q1: 87.00; q3: 108.75] cm/s, the median dFV was 31.59 [q1: 22.87; q3: 45.00] cm/s, and the median PI was 1.16 [q1: 0.99; q3: 1.41]. The median ONSD was 5.65 [q1: 4.80; q3: 6.60] mm. The median nICP_{TCD} was 17.57 [q1: 12.68; q3: 25.21] mmHg, and the median nICP_{ONSD} was 14.33 [q1: 10.07; q3: 19.33] mmHg. High ICP was found in 21 nICP_{TCD} patients (39.62%), and in 10 nICP_{ONSD} patients (18.87%). Among the 29 patients who underwent pupillometry, 9/29 (31.03%) presented altered pupillary reactivity. The median pupillary dimensions were 3.40 [q1: 2.65; q3: 4.45] and 3.20 [q1: 2.88; q3: 4.40] mm for the right and left pupils, respectively. Patients with increased nICP_{ONSD} and nICP_{TCD}, compared to those with normal nICP_{ONSD} and nICP_{TCD}, did not experience longer hospital stay (nICP_{ONSD}: 45.00±25.27 vs. 36.33±24.70 days, p=0.222; nICP_{TCD}: 38.90±30.34 vs. 35.43±19.23 days, p=0.691), but patients with higher nICP_{ONSD} had longer ICU stays (nICP_{ONSD}: 42.30±23.21 vs. 28.26±22.28 days, p=0.042; nICP_{TCD}: 32.86±25.55 vs. 28.61±20.89 days, p=0.721). Additional descriptive data on TCD are reported in the **ESM - Table 6**. Patients with increased ICP according to ONSD and TCD values compared to those with normal ICP showed no differences in hospital or ICU mortality (**Figure 3**). Additional data from the comparison between patients with normal ICP and those with high ICP as calculated by TCD and ONSD are reported in the **ESM - Table 7**. The outcomes of the Cox regression models for the patients who underwent noninvasive neuromonitoring are reported in **ESM - Table 8** and **ESM - Figure 4-5**. The significant variables associated with neurological complications assessed by univariate logistic regression and the output of the subsequent multivariate model, for the patients (n = 53) who underwent non-invasive neuromonitoring are reported in **Table 4**.

Table 4

The significant variables associated with neurological complications assessed by univariate logistic regression and the output of the subsequent multivariate model, for the patients (n = 53) who underwent non-invasive neuromonitoring.

Variable	Univariate				Multivariate			
	RC	OR	95% CI	P value	RC	OR	95% CI	P value
Days between hospital and ICU admission	-0.092	0.912	0.815-0.988	0.058	-0.082	0.921	0.815-1.003	0.114
dFV	-0.049	0.952	0.906-0.994	0.036	-0.044	0.956	0.909-1.001	0.069

ICU: intensive care unit; dFV: diastolic flow velocity; RC: regression coefficient; OR: odds ratio, CI: confidence interval.

Discussion

The main findings of our study are: 1) neurological complications are common in COVID-19 patients and have no effect on mortality, but can be associated with increased hospital and ICU length of stay; 2) the duration of mechanical ventilation is independently associated with the development of neurological complications; and 3) increased ICP (estimated by ONSD) and pupillary abnormalities are common, and associated with longer ICU length-of-stay.

To our knowledge, this is the first study describing cerebrovascular dynamics in mechanically ventilated COVID-19 patients, which could potentially help to elucidate the underlying pathophysiology of neurological complications in this patient population. Moreover, to date, no studies have taken into account the possible secondary effects of mechanical ventilation and inflammation on neurological outcome.

There are several theories concerning central and peripheral neurological changes following SARS-CoV-2 infection: viral neurotropism, including trans-synaptic spread, endothelial or lymphocyte invasion by SARS-CoV-2; a hyperinflammatory and hypercoagulative state; or even mechanical ventilation-associated impairment (35). In our cohort, neurological complications were detected in half of the patients admitted to our ICU with confirmed COVID-19 pneumonia who fulfilled the inclusion criteria. The most frequent complication was delirium (36.70%), followed by coma, critical illness neuropathy, ischemic stroke, stupor, encephalopathy, seizures, cognitive deficit, and depression. The frequency of delirium is in line with current COVID-19 literature, in which it has ranged from 26.80–73.60% (36,37). Delirium was identified both in the acute and in the post-ICU phases during the severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS) epidemics, with a possible detrimental effect on length of stay (38). Sedatives, analgesics, pain, psychological stressors, hypoxia, metabolic and electrolyte imbalances, infection, hyperthermia, sepsis, mechanical ventilation, light, and the use of physical restraints are well-known contributors to delirium occurrence in the ICU (39,40). Delirium is

known to be associated with longer ICU stay and mechanical ventilation days, as well as increased risk of death at 6 months, disability, and long-term cognitive dysfunction (40,41). Our results are in line with these findings; patients who developed neurological complications (mainly delirium) did not show increased ICU mortality, but they did have prolonged hospital and ICU stays, often exceeding 2 weeks, with a major impact on health expenditures and resource utilization—especially in the resource-limited setting of a pandemic.

Mechanical ventilation days and inflammation (assessed by C-reactive protein) were associated with the occurrence of neurological complications at the univariate analysis. This suggests that the magnitude of the inflammatory response and the severity of respiratory impairment may strongly affect the occurrence of neurological complications in COVID-19 (35).

Several cerebral hemodynamic changes occurred in the subpopulation undergoing neuromonitoring. First, patients with COVID-19 presented higher median ONSD values compared to the normal population (5.65 mm [4.80–6.60] vs 4.10 mm [3.85–4.35] (42)). As described in the literature, the threshold of increased $nICP_{ONSD}$ is 5–6 mm (28); this suggests that increased ICP is a common finding in COVID-19 patients. In fact, increased ICP measured with both ONSD and TCD was very common, and a large portion of patients (38.71%) exhibited altered pupillary reactivity.

Several factors can potentially cause increased intracranial pressure in patients with respiratory failure and pneumonia, including increased $PaCO_2$, which can cause cerebral vasodilatation (43,44), or the use of high PEEP and consequent increased intrathoracic pressure (45). Indeed, we found that PEEP was higher in those who showed higher $nICP$, whether assessed by ONSD or TCD (as we reported in the **ESM**). Although the difference was not statistically significant, it suggests that mechanical ventilation can interfere widely with cerebral hemodynamics.

Although common, the occurrence of increased ICP had no effect on cumulative probability of survival; it did prolong ICU-LOS when measured by ONSD, but not by TCD. This confirms that, in COVID-19 patients, noninvasive ICP monitoring may be essential for early detection of patients who are at risk of longer ICU-LOS with subsequent complications and difficult recovery. The incongruity between the results of the two noninvasive methods might be explained by differences in pathophysiological sensitivity and specificity for ICP assessment between the two (27); however, recent findings suggest that ONSD is much more accurate than TCD for measurement of intracranial pressure in non-COVID-19 patients (46).

Although we found no correlation between altered neuromonitoring findings and the occurrence of neurological complications, we strongly recommend the use of these methods in critically ill patients with COVID-19. Noninvasive neuromonitoring tools are safe, quick, low-cost, easily available, and can provide relevant data at the patients' bedside.

Limitations

This study has several limitations which must be addressed. First, this was a retrospective study of prospectively collected data. Therefore, data were collected within the clinical context of the COVID-19 pandemic (limited availability of personal protective equipment, clinical reasons, and so on). Thus, neuromonitoring data are neither complete nor available for all patients. Moreover, TCD, ONSD, and pupillometer measurements were intermittent, and were obtained at different stages of the patients' ICU stays. Continuous, daily, standardized monitoring would have provided more accurate data on the behavior of cerebrovascular hemodynamics in this population. Furthermore, because of the critical demands of the pandemic, we were unable to obtain multiple neuromonitoring measurements to reduce intra- and inter-observer variability among the operators. However, our team consists of a group of specialized physicians with ample experience in the use of noninvasive monitoring. The relatively small sample size of our study—which depended on the number of COVID-19 patients admitted to our ICU and was thus beyond our control—limits the strength of our conclusions and results, but this depends. Finally, as this is not an interventional study, the sedation and analgesia protocols were not standardized, but rather were based on the clinical needs of the patients, which may have had an impact on FV, ONSD, and pupillometer-derived values.

Conclusions

Neurological complications—particularly delirium—are common in COVID-19 patients and are associated with longer hospital and ICU stay. The duration of mechanical ventilation is strongly associated with the development of neurological complications. Noninvasive neuromonitoring during ICU stay may be helpful to early detect cerebrovascular alterations. Further studies including a larger number of patients may provide new insights on the role of noninvasive neuromonitoring tools in the early detection of neurological complications in non-primarily brain-injured patients.

Abbreviations

BMI, body mass index

CI, confidence interval

COVID-19, coronavirus disease 2019

CPP, cerebral perfusion pressure

dFV, diastolic flow velocity

ESM, electronic supplemental material

FiO₂, fraction of inspired oxygen

ICP, intracranial pressure

ICU-LOS, intensive care unit length of stay

ICU, intensive care unit

IQR, interquartile range

LOS, length of stay

MAP, mean arterial pressure

MCA, middle cerebral artery

MERS, Middle East respiratory syndrome

mFV, mean flow velocity

MODS-CoV-2, multiple organ dysfunction in coronavirus disease 2019

nICP, noninvasive intracranial pressure

nICP_{ONSD}, noninvasive intracranial pressure measured by optic nerve sheath diameter

nICP_{TCD}, noninvasive intracranial pressure measured by transcranial Doppler

ONSD, optic nerve sheath diameter

OR, odds ratio

PaCO₂, partial pressure of carbon dioxide

PaO₂, partial pressure of oxygen

PcPs, pressure control or pressure support

PEEP, positive end-expiratory pressure

PI, pulsatility index

Q1, 1st quartile

Q3, 3rd quartile

ROC, receiver operating characteristic

RR, respiratory rate

RT-PCR, reverse transcriptase-polymerase chain reaction

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

SARS, severe acute respiratory syndrome

sFV, systolic flow velocity

SMPH, San Martino Policlinico Hospital

SOFA, sequential organ failure assessment

TCD, transcranial Doppler

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contribution

DB, CR conceived of the study, designed the study, acquired data, interpretation of the data, and drafted the manuscript. GS analysis of data, interpretation of the data, critical revision of the manuscript and final approval. KC, FI, MB acquisition of data, critical revision of the manuscript and final approval. FT, LB, DRG, AV, MB, PRMR, NP, IB critical revision of the manuscript and final approval. PP, helped with study design, interpretation of the data, critical revision of the manuscript and final approval. All authors read and approved the final manuscript.

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We would like the names of the individual members of the **GECOV-19Group** to be searchable through their individual PubMed records.

Ethical approval and consent to participate

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Data management, monitoring and reporting of the study were performed in accordance with the ICH-GCP Guidelines. Authorization to conduct this study was obtained from the Ethics Committee of Liguria, Italy (registry number 163/2020) prior to initiation of patients' inclusion in compliance with the applicable regulatory requirement(s). Informed consent for participation was waived because of the retrospective nature of the study.

Consent for publication

Not applicable

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Survival cumulative probability after ICU admission for the 94 patients included. Survival cumulative probability after ICU admission for the patients (n = 94) who fulfilled the inclusion criteria, stratifying for the absence/presence (No/Yes) of neurological complications.

Figure 2

Performance of the multivariate logistic regression model for assessing the factors independently associated with the risk of neurological complications. A) Overall performance of the multivariate logistic regression model presented in Table 3 (dependent variable: neurological complications; independent variables: days of mechanical ventilation and C-reactive protein). B) ROC curve of the same multivariate logistic regression model (AUC=0.818).

Figure 3

Survival cumulative probability after hospital and ICU admission for the patients who underwent noninvasive neuromonitoring. Survival cumulative probability after hospital and ICU admission for the patients ($n = 49$) who underwent non-invasive intracranial pressure (nICP), monitoring with both Transcranial Doppler (TCD) (A, B) and Optic Nerve Sheath Diameter (ONSD) (C, D).

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