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ORIGINAL ARTICLE

Neurological symptoms and complications in predominantly hospitalized COVID-19 patients: Results of the European multinational Lean European Open Survey on SARS-Infected Patients (LEOSS)

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Abstract

Background and purpose: During acute coronavirus disease 2019 (COVID-19) infection, neurological signs, symptoms and complications occur. We aimed to assess their clinical relevance by evaluating real-world data from a multinational registry.

Methods: We analyzed COVID-19 patients from 127 centers, diagnosed between January 2020 and February 2021, and registered in the European multinational LEOSS (Lean European Open Survey on SARS-Infected Patients) registry. The effects of prior neurological diseases and the effect of neurological symptoms on outcome were studied using multivariate logistic regression.

Results: A total of 6537 COVID-19 patients (97.7% PCR-confirmed) were analyzed, of whom 92.1% were hospitalized and 14.7% died. Commonly, excessive tiredness (28.0%), headache (18.5%), nausea/emesis (16.6%), muscular weakness (17.0%), impaired sense of smell (9.0%) and taste (12.8%), and delirium (6.7%) were reported. In patients with a complicated or critical disease course (53%) the most frequent neurological complications were ischemic stroke (1.0%) and intracerebral bleeding (ICB; 2.2%). ICB peaked in the critical disease phase (5%) and was associated with the administration of anticoagulation and extracorporeal membrane oxygenation (ECMO). Excessive tiredness (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.20–1.68) and prior neurodegenerative diseases (OR 1.32, 95% CI 1.07–1.63) were associated with an increased risk of an unfavorable outcome. Prior cerebrovascular and neuroimmunological diseases were not associated with an unfavorable short-term outcome of COVID-19.

Conclusion: Our data on mostly hospitalized COVID-19 patients show that excessive tiredness or prior neurodegenerative disease at first presentation increase the risk of an unfavorable short-term outcome. ICB in critical COVID-19 was associated with therapeutic interventions, such as anticoagulation and ECMO, and thus may be an indirect complication of a life-threatening systemic viral infection.

KEYWORDS
COVID-19, neurological manifestations, SARS-CoV-2

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is challenging health systems worldwide and exerting a strain on patient-centered hospital care. In addition to fever and respiratory symptoms [1], involvement of the peripheral (PNS) and the central nervous system (CNS) has been observed [2]. Although evidence for direct viral infection of the CNS resulting in meningitis or encephalitis is weak [3,4], histopathological post mortem studies suggest that

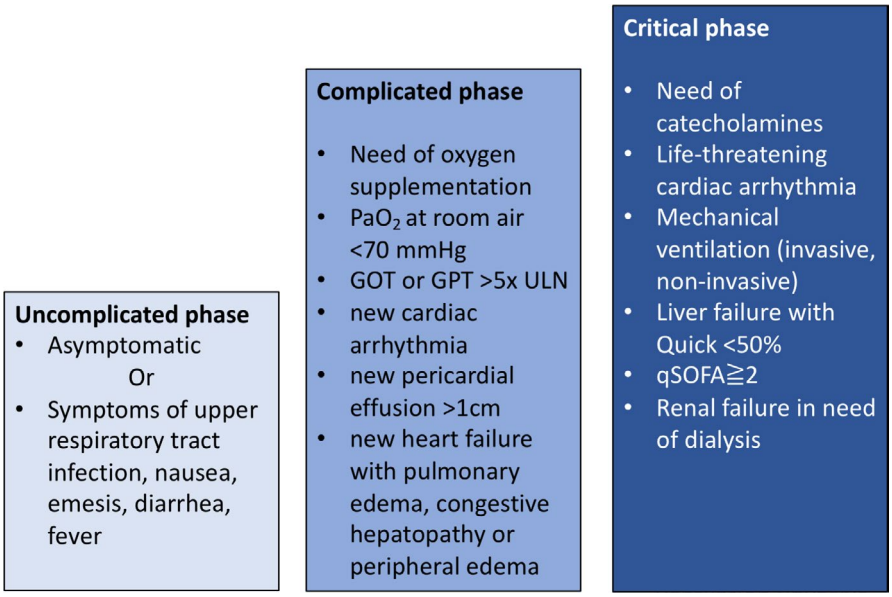

FIGURE 1 Definition of disease phases. GOT, glutamate-oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; qSOFA, quick sepsis-related organ failure assessment score [Colour figure can be viewed at wileyonlinelibrary.com]

SARS-CoV-2 can invade the nervous system, despite there being no clear evidence for CNS damage directly caused by the virus [5].

The early neurological manifestations observed range from smell and taste dysfunction, dizziness, headache, myalgia, and impaired consciousness [2,6] to severe neurological complications, such as cerebrovascular events or encephalopathy [7–10].

These neurological symptoms are likely to be of relevance for short- and long-term patient outcomes. Severe complications may be associated with increased early mortality [11], while relatively mild symptoms may persist as part of a so-called "long-COVID" or "post-COVID-syndrome" in some patients. This may contribute to prolonged morbidity after recovery from the acute respiratory infection [10,12–15]. As such, prospective large-scale studies are warranted to clarify the relevance of neurological symptoms and complications of COVID-19. Studies on neurological manifestations related to disease outcome are complicated by the fact that several variables, e.g., older age, male sex, or cardiovascular morbidity, that are consistently associated with an increased risk of a more severe COVID-19 disease course [16,17], need to be considered as possible confounders. The same is true for neurological premorbidity that may affect the symptoms reported and COVID-19 outcome.

Furthermore, dementia or stroke were reported to be independently associated with COVID-19-related deaths in one study [18]. In contrast, others did not observe an increased risk of a more severe COVID-19 disease course in patients with Parkinson's disease or dementia [19] or multiple sclerosis [20,21].

Using data from the multinational, observational cohort of patients included in the Lean European Open Survey on SARS-Infected Patients (LEOSS) registry [16], we aimed to characterize the occurrence and frequencies of neurological symptoms and complications reported during the acute phase of a SARS-CoV-2 infection and to determine the impact of these symptoms and complications, and prior neurological diseases on COVID-19 disease outcome.

METHODS

Study design and patient cohort

In this observational study, we analyzed data on patients with confirmed SARS-CoV-2 infection included in LEOSS, with diagnosed infection between January 2020 and February 2021. Submission of patients' data into LEOSS was accessible for the approved 127 partner sites, i.e., physicians from hospitals, outpatient clinics and private practices across Europe involved in the treatment of COVID-19 patients. Data were recorded retrospectively and anonymously. A dedicated form for neurological data items was developed by a working group of specialized neurologists across Germany and implemented in the registry. From this set, the following signs and symptoms were analyzed: impaired sense of smell and taste; nausea and emesis; muscle ache and weakness; delirium; excessive tiredness; headache; and meningism. Additionally, intracerebral bleeding (ICB), ischemic stroke, meningitis and encephalitis, seizures, critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) were recorded as neurological manifestations and complications.

In LEOSS, data assessments are retrieved in different disease phases, namely, at baseline (timepoint of positive SARS-CoV-2 test result), in the uncomplicated (UC) phase, in the complicated (CO) phase, and in the critical (CR) phase (for phase definitions, see Figure 1 and Jakob et al. [16]).

Statistical analyses

Descriptive analyses were performed for the entire cohort and for each of the clinical phases documented (UC, CO and CR phases). If a sign or symptom was neither reported nor the option "unknown" ticked in LEOSS, this may suggest that the symptom was absent or the data entry was incomplete. To account for reporting bias, we analyzed the

descriptive data in respect to valid data entries of each of the items collected, explaining the different denominators for several of the items analyzed. The durations of the in-patient stay in the hospital, on the intensive care unit (ICU), and of the mechanical ventilation were calculated as median with interquartile range (IQR) and mean ± standard deviation (SD). The chi-squared test was used to associate anticoagulation, interventions, and laboratory results with the occurrence of ICB.

Two clinical endpoints were defined: (i) death during hospitalization (EP1) and (ii) a combined endpoint, death or a CR phase (defined as complicated or critical phase) or no recovery until last-known status (EP2). Relationships among potential explanatory variables for the outcome (age, sex, pre-existing diseases, such as asthma, pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, neurodegenerative diseases, neuroimmunological diseases, and the signs and symptoms impaired sense of smell and taste, muscle aches and weakness, excessive tiredness, headache, delirium [Table 4]) and the two endpoints were examined using nonlinear, categorical principal component analysis (CATPCA) [22]. Their associations were evaluated primarily based on their loadings on the first two dimensions extracted by the analysis. Before CATPCA and logistic regression analyses were performed, missing data were replaced by multiple imputations, using the fully conditional specification method and producing five imputed datasets. All variables involved in CATPCA and logistic regression served as independent variables for imputation, but missing data for the two endpoints were not imputed. Age categories were treated as a continuous variable. Univariable logistic regression analyses tested the effects of individual independent variables on EP1 and EP2 (Table S2 and Figure S1). The univariable model was further adjusted for age and sex. All independent variables were entered in a multivariable logistic regression model (initial full model). Nonsignificant independent variables were then removed from the multivariable model following a stepwise-backward procedure. The level of significance was set at $p < 0.05$, two-sided. Statistical analyses were performed using SPSS version 27.

Ethics statement and anonymization processing

The study was approved by the local ethics committees, waiving the requirement for written informed consents for routine clinical data recorded anonymously. Please see Jakob et al. [16] for further information regarding ethical statements and trial registration of LEOSS, and for the anonymization procedure see Jakob et al. [23].

RESULTS

Cohort description and outcome

We analyzed data from 6537 patients with SARS-CoV-2 infection, diagnosed between January 2020 and February 2021 (for monthly enrollment, see Table S1). Most patients were reported from German study sites (93.6%, 6295/6537), the diagnosis was PCR-confirmed in 97.7% (6197/6341) and 57.7% of the patients (3773/6537) were male. The majority of patients was between 46 and 85 years old (70.7%, 4622/6537) and 8.1% (528/6537) were older than 85 years. Most patients were hospitalized (92.1%, 5972/6484) with a mean in-patient stay of 14.1 ± 14.4 days (median [IQR] 10 [13] days). Of all hospitalized patients, 37.0% (1467/3960) were treated in an ICU, with a mean duration of 15.8 ± 16.3 days on ICU (median [IQR] 11 [18] days). Of the ICU patients, 81.1% (994/1226) required mechanical ventilation, on average for 16.8 ± 15.7 days (median [IQR] 12 [17] days). A total of 47.2% of the patients (3087/6529) did not exceed the UC disease phase, one third reached the CO phase (33.5%, 2187/6529), and 19.4% the CR phase (1264/6529). The overall mortality rate was 14.7% (954/6503; Table 1).

Regarding prior neurological diseases, previous cerebrovascular disease was reported in 8.4% (531/6295), neurodegenerative diseases (dementia, movement disorders, motor neuron diseases) in 9.6% (603/6305), and neuroimmunological diseases (multiple sclerosis, neuromyelitis optica spectrum diseases, myasthenia gravis, and other autoimmune-mediated diseases) in 2.3% (146/6296; Table 1).

Neurological signs and symptoms, manifestations and complications

Commonly, excessive tiredness (28.0%, 1466/5240), headache (18.5%, 942/5096), nausea and emesis (16.6%, 867/5227), muscular weakness (17.0%, 890/5242), impaired sense of smell (9.0%, 443/4964) and taste (12.8%, 636/4972) were reported, mostly in the UC and CO phase. Delirium occurred in all phases and overall in 6.7% of patients (340/5045), peaking in the CR phase (12.9%, 127/987; Table 2). Glasgow coma scale (GCS) score at baseline was reported for 43.4% of the patients (2839/6537). Of these, 55.9% (1586/2839) presented with GCS score of 15, while 39.1% (1109/2839) showed a slightly reduced level of consciousness with GCS scores of 13 to 14 at baseline, and 2.1% (59/2839) presented with a GCS score of 8 or less.

Of the patients reaching the CO or CR disease phase (52.8%, 3451/6537), the most frequent and severe neurological complications were cerebrovascular events. ICB (2.2%, 57/2605) was more frequently observed than ischemic stroke (1.0%, 26/2578), peaking in the CR phase at 5.0% (51/1027; Table 2). Patients with ICB in the CR phase more frequently showed thrombocytopenia ($p = 0.006$) and an elevated activated partial thromboplastin time (aPPT; $p = 0.033$). In these patients, therapeutic anticoagulation, mostly heparin (leading to an elevated aPPT), as well as extracorporeal membrane oxygenation (ECMO) were associated with ICB ($p < 0.01$ and $p < 0.0001$, respectively; Table 3).

Meningitis and encephalitis were reported in 0.6% (16/2578) of the patients with a complicated or critical disease course. Steroids were administered in 7.1% (351/4947) of the patients in the UC phase, in 25.4% (679/2678) in the CO phase and in 39.4% (438/1108) in the CR phase. There was no significant association between

TABLE 1 Characteristics of the SARS-CoV-2 patient cohort

		Disease phase		
	Total	**UC**	**CO**	**CR**
	***N* = 6537** **% (*n*)**	***N* = 5487** **% (*n*)**	***N* = 2965** **% (*n*)**	***N* = 1264** **% (*n*)**
Characteristics				
Age				
<14 years	0.9 (59)	1.0 (54)	0.4 (12)	0.5 (6)
15–25 years	3.6 (233)	4.1 (225)	0.9 (27)	1.2 (15)
26–45 years	16.8 (1095)	18.6 (1022)	8.8 (261)	7.0 (89)
46–65 years	33.9 (2214)	34.4 (1887)	32.9 (975)	37.1 (469)
66–85 years	36.8 (2408)	34.7 (1904)	46.1 (1368)	47.3 (598)
>85 years	8.1 (528)	7.2 (395)	10.9 (322)	6.9 (87)
Sex				
Female	42.3 (2764)	43.0 (2358)	39.0 (1157)	28.5 (360)
Male	57.7 (3773)	57.0 (3129)	61.0 (1808)	71.5 (904)
Prior neurological diseases				
Cerebrovascular diseases	8.4 (531/6295)			
Neurodegenerative diseases	9.6 (603/6305)			
Neuroimmunological diseases	2.3 (146/6296)			
	% (*n*/*N*)	**Mean ± SD, days**		**Median [IQR] days**
Hospitalization				
No in-patient stay	7.9 (512/6484)			
In-patient stay	92.1 (5972/6484)	14.1 ± 14.4		10 [13]
ICU stay of hospitalized patients				
No ICU stay	63.0 (2493/3960)			
ICU stay	37.0 (1467/3960)	15.8 ± 16.3		11 [18]
Ventilation of patients with ICU stay				
No ventilation	18.9 (232/1226)			
Ventilation	81.1 (994/1226)	16.8 ± 15.7		12 [17]
Disease course and outcome				
Disease course, most severe phase reached				
UC phase	47.1 (3087/6529)			
CO phase	33.5 (2187/6529)			
CR phase	19.4 (1264/6529)			
Last known status				
Recovered	74.9 (4869/6503)			
Not recovered	10.5 (680/6503)			
Death	14.7 (954/6503)			

Note: Distributions are listed for the entire cohort (total), and in respect to the disease phases, thus multiple entries of a patient in the UC, CO or CR phase are possible. Neurodegenerative diseases: movement disorders, motor neuron diseases, and dementia; neuroimmunological diseases: multiple sclerosis, neuromyelitis opticum spectrum diseases, myasthenia gravis, and other unspecified immune-mediated neurological diseases.

Abbreviations: UC, uncomplicated phase; CO, complicated; CR, critical; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

steroid administration, and the occurrence of meningitis/encephalitis, intracerebral hemorrhage or ischemic stroke.

Epileptic seizures were observed in 20 patients (0.8%, 20/2577) with a CO or CR disease course, predominantly reported in the CR phase (1.2%, 12/1018). CIM and CIP occurred in 6.3% (55/874) and 7.6% of patients (66/873) during the CR phase (Table 2).

Neurological signs, symptoms, complications, and neurological premorbidity as explanatory variables of outcome

Categorical principal component analysis indicated close associations amongst cardiovascular diseases, cerebrovascular diseases,

TABLE 2 Neurological symptoms and complications

Neurological symptoms	All phases/total *N* = 6537 % (*n*/*N*)	BL *N* = 6537 % (*n*/*N*)	UC phase *N* = 5487 % (*n*/*N*)	CO phase *N* = 2965 % (*n*/*N*)	CR phase *N* = 1264 % (*n*/*N*)
Nausea/ emesis	16.6 (867/5227)	10.1 (547/5400)	10.3 (544/5303)	9.1 (227/2498)	4.2 (40/958)
Muscle aches	19.1 (976/5121)	10.2 (664/5334)	15.4 (720/4667)	9.9 (247/2491)	3.1 (29/944)
Muscle weakness	17.0 (890/5242)	11.7 (626/5336)	13.0 (603/4625)	13.5 (336/2488)	8.7 (83/958)
Delirium	6.7 (340/5045)	2.0 (107/5345)	1.6 (76/4614)	5.4 (136/2513)	12.9 (127/987)
Excessive tiredness	28 (1466/5240)	17.4 (936/5390)	19.8 (931/4709)	23.1 (588/2542)	11.5 (110/956)
Headache	18.5 (942/5096)	12.0 (642/5334)	14.5 (677/4668)	8.6 (214/2485)	3.0 (28/945)
Meningism	1.3 (64/4958)	0.4 (22/5313)	0.2 (9/4591)	0.4 (11/2472)	0.3 (3/955)
Smell sense impaired	9.0 (443/4964)	5.6 (292/5251)	7.0 (319/4563)	3.7 (89/2414)	1.1 (10/933)
Taste sense impaired	12.8 (636/4972)	8.4 (445/5267)	9.7 (445/4569)	7.6 (185/2425)	1.7 (16/934)
Glasgow Coma Scale					
15		55.9 (1586/2839)			
13–14		39.1 (1109/2839)			
9–12		3.0 (85/2839)			
3–8		2.1 (59/2839)			

Neurological complications	Total (CO or CR phase) *N* = 3451	CO phase *N* = 2965	CR phase *N* = 1264
Intracerebral bleeding	2.2 (57/2605)	0.4 (9/2565)	5.0 (51/1027)
Ischemic stroke	1.0 (26/2578)	0.5 (14/2562)	1.3 (13/1019)
Meningitis/ encephalitis	0.6 (16/2578)	0.2 (5/2564)	1.3 (13/1019)
Seizure	0.8 (20/2577)	0.3 (8/2564)	1.2 (12/1018)
CIM	2.6 (55/2146)	0.0 (0/2114)	6.3 (55/874)
CIP	3.2 (68/2150)	0.1 (3/2113)	7.6 (66/873)

Note: The here listed percentages are in respect to the valid data entries (as listed in brackets for each item, missing values per item excluded). Neurological symptoms "all phases" depicts the occurrence of a symptom in the entire cohort. The neurological complications in total (CO or CR phase) represent the sum score of the patients that underwent the CO or CR phase.

Further, a symptom in the respected disease phase (BL, or UC, CO or CR phase) or a neurological complication (CO, CR phase) is reported. In the presentation by phase, multiple entries of a patient in UC, CO, or CR phase are possible, when a patient underwent various disease phases in the longitudinal course.

Abbreviations: BL, baseline; CO, complicated phase; CR, critical; CIM, critical illness myopathy; CIP, critical illness polyneuropathy; UC, uncomplicated phase.

pulmonary as well as neurodegenerative diseases, age, and the two endpoints "death" and "death / CR phase / no recovery" (Figure 2, cf. Table 4 for variable definition). Asthma, neuroimmunological diseases, and other baseline symptoms (headache, muscle aches and weakness, impaired sense of smell and taste, excessive tiredness and delirium) were not closely related.

In the multivariable final model, the strongest predictor of death (EP1) was older age (odds ratio (OR) 2.78; 95% confidence interval [CI] 2.48–3.12), followed by chronic pulmonary disease (OR 1.98, 95% CI 1.62–2.43), male sex (OR 1.84, 95% CI 1.57–2.16), neurodegenerative diseases (OR 1.56, 95% CI 1.27–1.93) and cardiovascular (OR 1.54, 95% CI 1.28–1.87) diseases. The baseline symptom headache was associated with a lower risk of death (OR 0.60, 95% CI 0.41–0.89; Table 5).

The strongest predictors of EP2 (death or a CR phase or no recovery until last-known status) were cardiovascular diseases (OR 1.71, 95% CI 1.51–1.93), pulmonary diseases (OR 1.72, 95% CI 1.41–2.11), older age (OR 1.54, 95% CI 1.44–1.64), the baseline symptom excessive tiredness (OR 1.42, 95% CI 1.20–1.68), male sex (OR 1.37, 95% CI 1.23–1.53) and asthma (OR 1.37, 95% CI 1.08–1.75), respectively. The baseline symptom headache (OR 0.76, 95% CI 0.63–0.93) and pre-existing neuroimmunological diseases (OR 0.64, 95% CI 0.44–0.92) were associated with a lower risk for the combined endpoint (Table 5 and Figure S1).

TABLE 3 Laboratory results and anticoagulation/interventions in relation to intracerebral bleeding

Laboratory results	Total (CR phase) % (*n*/*N*)	No ICB (CR phase) % (*n*/*N*)	ICB (CR phase) % (*n*/*N*)	*p*-value
Platelet count				
<10,000/µl	1.7 (16/941)	1.6 (14/892)	4.1 (2/49)	**0.006**
10,000–49,999/µl	6.5 (61/941)	6.2 (55/892)	12.2 (6/49)	
50,000–119,999/µl	14.7 (164/941)	16.5 (147/892)	34.7 (17/49)	
120,000–449,999/µl	57.9 (545/941)	59.1 (527/892)	36.7 (18/49)	
450,000–799,000/µl	15.5 (146/941)	15.7 (140/ 892)	12.2 (6/49)	
800,000–1,199,999/µl	0.7 (7/941)	0.8 (7/892)	0.0 (0/49)	
>1,199,9999/µl	0.2 (2/941)	0.2 (2/892)	0.0 (0/49)	
aPTT				
>25 s	5.6 (44/780)	5.7 (42/738)	4.8 (2/42)	**0.033**
25–39 s	31.5 (246/780)	32.5 (240/738)	14.3 (6/42)	
40–54 s	16.2 (126/780)	16.4 (121/738)	11.9 (5/42)	
55–69 s	10.5 (82/780)	9.9 (73/738)	21.4 (9/42)	
70–84 s	10.0 /78/780)	9.6 (71/738)	16.7 (7/42)	
>84 s	26.2 (204/780)	25.9 (191/738)	31.0 (13/42)	
INR				
<1.25	45.7 (364/797)	46.6 (351/754)	30.2 (12/43)	0.199
1.25–2	41.0 (327/797)	40.3 (304/754)	53.5 (23/43)	
2–3.5	8.4 (67/797)	8.2 (62/754)	11.6 (5/43)	
>3.5	4.9 (39/797)	4.9 (37/754)	4.7 (2/43)	
Anticoagulation/ Intervention				
Prophylactic heparin[a]	48.3 (475/983)	48.7 (455/934)	40.8 (20/49)	0.281
Subtherapeutic heparin[b]	7.9 (67/848)	7.9 (64/806)	7.1 (3/42)	0.852
Therapeutic Anticoagulation[c]	43.1 (420/975)	42.1 (389/924)	60.8 (31/51)*	**0.009**
Antiplatelet agents[d]	23.3 (198/848)	23.1 (186/806)	28.6 (12/42)	0.412
ECMO administration	17.0 (149/878)	14.7 (123/829)	53.1 (26/49)	**<0.0001**

Statistics were calculated as cross tables and *p*-values assessed by chi-squared tests. $p < 0.05$ was considered statistically significant.

Abbreviations: CR, critical; ICB, intracerebral bleeding; aPTT, activated partial thromboplastin time; INR, international normalized ratio; ECMO, extracorporeal membrane oxygenation.

[a]Heparin or low-molecular weight heparin in prophylactic dose.

[b]Heparin or low-molecular weight heparin in subtherapeutic dose, i.e., more than prophylactic, but less than therapeutic dose.

[c]Therapeutic anticoagulation, either heparin or low-molecular weight heparin, or argatroban or direct oral anticoagulation in therapeutic dose, *hereof: 23 patients treated with heparin in therapeutic doses.

[d]Antiplatelet agents: either aspirin, Adenosine-diphosphate (ADP) -receptor antagonists or glycoprotein-inhibitor IIa/IIIb.

DISCUSSION

The present large-scale analysis from LEOSS, a European multinational registry-based cohort study, focused on neurological signs, symptoms and complications in predominantly hospitalized (92.1%) SARS-CoV-2-infected patients who were mostly enrolled from German study sites (92.6%).

Olfactory and gustatory dysfunction, which can also occur in the absence of respiratory symptoms and nasal congestion, is considered a rather specific feature of COVID-19 patients, and may suggest direct involvement of the nervous system [24]. The rate of impaired sense of smell (9.0%) and taste (12.8%) in our cohort fell into the lower range compared to other studies reporting a prevalence between 5% and 88% [6,24,25]. The fact that the LEOSS cohort consists of predominantly hospitalized patients (>90%) with a comparably severe disease course, and the recruitment of patients was mainly by physicians not specialized in neurology, may explain this finding, leading to underreporting of this rather mild, albeit specific symptom [16]. Olfactory and gustatory dysfunction had no impact on the early disease course. However, as these symptoms were consistently shown in previous studies to persist in a relevant proportion of patients far beyond recovery from the acute respiratory infection [12–14], these symptoms may still cause prolonged morbidity and neurological sequelae in a subset of patients.

Most of the other neurological signs and symptoms reported at baseline in our study were non-specific, with a high prevalence of excessive

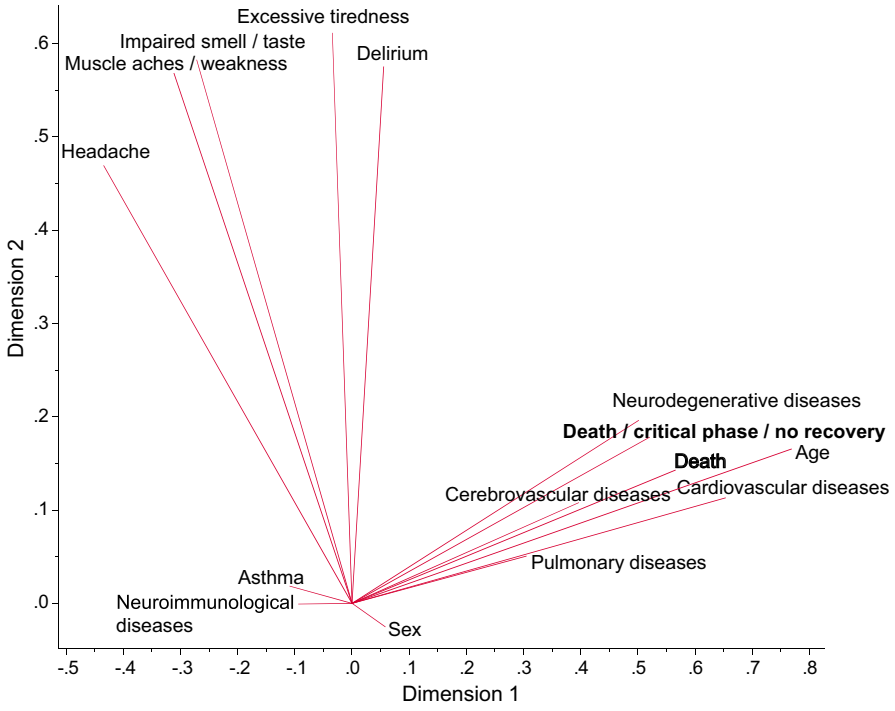

FIGURE 2 Component loadings of variables for Dimensions 1 and 2, extracted by categorical principal component analysis [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Variables analyzed with categorical principal component analysis and logistic regression

Variable	Definition
EP1	Death
EP2	Death or CR phase or no recovery until last-known status
Age	Ranging from <14 to >85 years in six categories: (i) <14 years (reference category); (ii) 15–25 years, (iii) 26–45 years, (iv) 46–65 years; (v) 66–85 years 6) >85 years
Sex	Male; Female
Asthma	Baseline comorbidity asthma
Pulmonary diseases	Baseline comorbidity chronic obstructive pulmonary disease (COPD) or other chronic pulmonary disease
Cardiovascular diseases	Baseline comorbidity myocardial infarction or coronary artery disease or hypertension or diabetes mellitus
Cerebrovascular diseases	Baseline comorbidity cerebrovascular disease
Neurodegenerative diseases	Baseline comorbidity movement disorder or dementia or motor neuron disease
Neuroimmunological diseases	Baseline comorbidity multiple sclerosis or myasthenia gravis or neuromyelitis optica spectrum disorder or other immune-mediated neurological disease
Delirium	Baseline symptom delirium
Headache	Baseline symptom headache
Excessive tiredness	Baseline symptom excessive tiredness
Smell and taste impaired	Baseline symptom impaired sense of smell or taste
Muscle aches and weakness	Baseline symptom muscle aches or muscle weakness

tiredness, headache, muscular weakness, and nausea/emesis, which was within the range of previously published articles studying COVID-19 patients [1,6,26–28]. We observed a relatively high prevalence of nausea and emesis (10%) at baseline and the UC phase. Considering this high frequency reported during the UC phase, we regard this as a non-specific sign of COVID-19, and not an indication of direct involvement of the nervous system as previously hypothesized [28].

The prevalence of neurological complications in the present study was mostly in line with previous studies, which reported overall neurological complications in 3.5%–13.5% of hospitalized patients [11,29]. The most common acute neurological events found in the present study were strokes. In patients with a CO or CR disease course, we noted ischemic stroke in 1.0% (26/2578), and hemorrhagic stroke in 2.2% (57/2605), a prevalence overall comparable

TABLE 5 Multivariable logistic regression models

		Multivariable, full model				Multivariable, final model, adjusted for age and sex			
Outcome	**Independent variable**	**OR**	**95% CI lower limit**	**95% CI upper limit**	***p*-value**	**OR**	**95% CI lower limit**	**95% CI upper limit**	***p*-value**
Death	Older age	2.731	2.431	3.069	0.000	2.781	2.478	3.121	0.000
	Male sex	1.820	1.551	2.136	0.000	1.841	1.569	2.159	0.000
	Pulmonary d.	1.974	1.609	2.423	0.000	1.982	1.619	2.427	0.000
	Asthma	0.666	0.429	1.034	0.070				
	Cardiovascular d.	1.534	1.268	1.856	0.000	1.544	1.279	1.865	0.000
	Cerebrovascular d.	1.052	0.836	1.326	0.664				
	Neurodegenerative d.	1.486	1.197	1.846	0.000	1.564	1.267	1.930	0.000
	Neuroimmunological d.	0.657	0.337	1.282	0.218				
	Excessive tiredness	0.944	0.723	1.233	0.662				
	Headache	0.671	0.452	0.994	0.047	0.602	0.408	0.887	0.011
	Muscle aches/weakness	0.927	0.661	1.299	0.637				
	Impaired smell / taste	0.514	0.276	0.959	0.037				
	Delirium	1.716	0.914	3.223	0.088				
Death or complicated phase or no recovery	Older age	1.532	1.434	1.637	0.000	1.535	1.437	1.640	0.000
	Male sex	1.373	1.233	1.528	0.000	1.374	1.234	1.529	0.000
	Pulmonary d.	1.716	1.402	2.101	0.000	1.724	1.409	2.110	0.000
	Asthma	1.381	1.081	1.764	0.010	1.372	1.076	1.749	0.011
	Cardiovascular d.	1.713	1.515	1.937	0.000	1.711	1.514	1.933	0.000
	Cerebrovascular d.	1.000	0.810	1.235	0.998				
	Neurodegenerative d.	1.274	1.027	1.581	0.028	1.320	1.067	1.632	0.010
	Neuroimmunological d.	0.655	0.455	0.941	0.022	0.639	0.443	0.920	0.016
	Excessive tiredness	1.398	1.176	1.661	0.000	1.421	1.204	1.676	0.000
	Headache	0.772	0.626	0.952	0.017	0.764	0.625	0.934	0.010
	Muscle aches/weakness	1.043	0.861	1.263	0.655				
	Impaired smell/taste	0.765	0.575	1.018	0.066				
	Delirium	1.654	0.938	2.915	0.079				

Pooled results from analyses on five imputed data sets. In the final multivariable model, only significant predictors ($p < 0.05$) were included.
Abbreviations: CI, confidence interval, d., diseases; OR, odds ratio.

to previously reported studies reporting strokes (range 1.1%–1.9%) [11,29,30]. In the present study, the occurrence of ischemic stroke increased with disease severity (CO phase: 0.5%; CR phase: 1.3%), possibly explained by the association of COVID-19 with coagulopathy [31].

Interestingly, while in most previous studies ischemic strokes were more frequent than hemorrhagic strokes [6,32–35], we found the opposite, with cerebral hemorrhages peaking in the CR phase (5.0%). This is probably explained by a higher frequency of interference with the blood coagulation system (Table 3), in particular, in the 53.1% of patients (26/49) with ICB treated with ECMO [36].

In the 16 patients with meningitis or encephalitis, cerebrospinal fluid findings were reported incompletely, not allowing further conclusions. To date, detection of SARS-CoV-2 RNA was only reported in a few patients in the literature [37–41], suggesting that direct replicative infection of the CNS is rare.

Regarding the impact of neurological manifestations on COVID-19 disease outcome, we noted that excessive tiredness at baseline was associated with an increased risk for a more severe COVID-19 disease course. As this item was not further specified in LEOSS, the term may include motor and cognitive fatigue secondary to the severe infection, respiratory failure, or an involvement of the CNS.

Among the baseline signs and symptoms, headache was the only predictor of a lower risk of mortality and the combined endpoint considering the transition to a CO or CR phase or death. A possible explanation may be that individuals with a new onset of headache may seek early medical attention, possibly resulting in an earlier diagnosis of COVID-19 and optimized therapy. Further, patients who

are able to complain of headache at baseline, may be in a less severe medical condition, while patients at more severe disease stages may be unable to express this complaint. In line with these considerations and our findings, in a smaller cohort study of COVID-19 patients, there was a trend of headache being more frequently reported in the group without Acute Respiratory Distress Syndrome (ARDS) than with ARDS [42].

Extending previous work, the present study shows that a pre-existing neurodegenerative disease (comprising dementia, movement disorders, and motor neuron diseases) is an independent risk factor for mortality and a more severe COVID-19 disease course. This finding persisted after adjusting for sex and age, and was consistently seen across the different age strata of the study. Indeed, patients with prior neurodegenerative diseases are at higher risk of reduced lung function and respiratory system-related complications, e.g., aspiration pneumonia due to dysphagia [43]. Further, patients who are experiencing advanced stages of dementia, movement disorders, or motor neuron disease may opt not to receive all the possible options of intensive care medicine, such as mechanical ventilation or ECMO, considering the invasive nature of such procedures and the anticipated limited expectations of success. Therefore, a higher mortality rate and worse outcomes in patients with neurodegenerative diseases appear plausible and fit with the literature. One study reported a higher case fatality rate for patients with Parkinson's disease [44]. Another study in a cohort of 16,749 patients hospitalized with COVID-19 reported that the combined prior conditions "dementia or stroke" were independently associated with COVID-19-related deaths [18]. Our study seems to contrast with a previous study [19] that found no association of outcome in patients affected by Parkinson's disease or dementia compared to matched controls without neurodegenerative diseases. This earlier study, also from the LEOSS registry, differs with regard to the overall population studied (4310 patients vs. 6537 in the present study), and the statistical methods used: Parkinson's disease or dementia were studied separately in a case-control-matching design, while we used a multivariable logistic regression approach and grouped the neurodegenerative diseases—dementia, movement disorders, and motor neuron diseases—to increase the power. While in the previous study a systematic sampling strategy was applied, randomly extracting 15 controls from the study population for each of the 40 patients with Parkinson's disease (1:15) and randomly selecting two controls for each of the 290 dementia patients (1:2), we adjusted for age and sex in our final multivariable model. Our approach, looking at a larger population of patients with neurodegenerative disease (total $n = 603$) and a different statistical approach likely explains the different findings, although we were unable to prove causality in the present study.

Concerns have been expressed that patients with immune-mediated diseases treated with immunosuppressive drugs, such as patients with neuroimmunological diseases, might be at higher risk of a more severe COVID-19 disease course. A review of 873 SARS-CoV-2-infected patients with multiple sclerosis suggested no increased mortality and even possible beneficial effects of disease-modifying treatment [20,21]. In contrast, recent data from the Swedish multiple sclerosis registry suggests that B-cell-depleting therapy with rituximab may increase the risk of hospitalization (see Footnote[1]).

Our findings of an inverse association of neuroimmunological diseases with the combined endpoint "death or severe disease course" after adjusting for age and sex might partially be explained by a selection bias. A relatively high proportion of patients with neuroimmunological diseases was recruited from outpatient clinics, fitting the lower hospitalization rate (58.3%) compared to the entire cohort (92.1%). This observation is in line with recent literature [45,46], further demonstrating that higher Expanded Disability Status Scale (EDSS), progressive disease course, male sex, older age and comorbidities (e.g. obesity) are risk factors for a severe COVID-19 course in patients with multiple sclerosis [45,47].

The present study has obvious limitations, inherent to the study design. We analyzed anonymized registry data precluding, for instance, the analysis of imaging source, or individual cerebrospinal fluid data. The analysis had to rely on data obtained in predefined reporting forms, including items not further specified such as nausea/emesis or excessive tiredness. These signs and symptoms can possibly be explained by various, often non-neurological causes, in particular, when mainly entered by non-neurologists. Further, some neurological conditions like critical illness encephalopathy or sepsis-associated encephalopathy, as well as sinus thromboses, were not included in the LEOSS report forms. Additionally, missing values and incongruent answers may further limit data quality, and, due to a lack of follow-up data and inclusion of patients early after the confirmed infection with SARS-CoV-2, post-infectious neurological complications such as Guillain–Barré syndrome or long- or post-COVID-19 syndrome could not be assessed as part of this study. Concerning the generalizability of the data reported here, it is crucial to consider that 92.1% of the patients were hospitalized. As a result, asymptomatic SARS-CoV-2 infections and patients with only mild symptoms are underrepresented, while certain patient populations with specific comorbidities, in particular, patients with neuroimmunological or cerebrovascular diseases, or those treated with ECMO, might be overrepresented, resulting in a reporting bias.

The strength of this registry and the present study is the large-scale real-world patient data from a high number of patients with a PCR-confirmed SARS-CoV-2 infection (97.7%), representing a multicentric and multinational, European cohort, with unified and predefined data entry, accessible for registration of patients via personal accounts by treating medical doctors. This approach enabled the analysis of neurological aspects of COVID-19 in more than 6500 individuals.

In conclusion, non-specific frequent neurological signs and symptoms at baseline, such as headache, muscular weakness, impaired sense of smell and taste, and delirium are not associated with an unfavorable outcome early during the COVID-19 disease course. Rates of severe acute neurological complications overall were compatible with previous reports, although a comparably high rate of ICB was noted in our cohort of patients with a critical disease course. This was likely related to a high rate of ECMO and anticoagulation therapy. This indicates that at least a fraction of the complications observed during

critical COVID-19 are not due to direct viral effects, but occur secondarily during the attempt to save the life of a critically ill ICU patient, using invasive management strategies such as ECMO. Prior cerebrovascular and neuroimmunological diseases are not associated with an unfavorable short-term outcome of COVID-19, whereas patients with prior neurodegenerative diseases and those presenting with excessive tiredness appear to be at higher risk. Further investigations are needed to assess delayed-onset, prolonged, or persisting neurological symptoms and sequelae following the SARS-CoV-2 infection.

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CONFLICT OF INTERESTS

All authors report no disclosures relevant to the manuscript.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

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ENDNOTE

[1] Pre-print, not yet peer reviewed: Spelman, Tim and Forsberg, Lars and McKay, Kyla and Glaser, Anna and Hillert, Jan, Increased Rate of Hospitalisation for COVID-19 Amongst Rituximab Treated Multiple Sclerosis Patients: A Study of the Swedish MS Registry. Available at SSRN: https://ssrn.com/abstract=3801769 or http://dx.doi.org/10.2139/ssrn.3801769

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Figure S1

Table S1 and S2

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