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ABSTRACT OF DOCTORAL THESIS

Neurological manifestations in SARS-CoV-2 infection

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INTRODUCTION

The SARS-CoV-2 pandemics who started by the end of 2019 represented a real challenge for public health systems around the world continuing to still have medical and psychosocial consequences.

Although it was first considered a respiratory virus, affecting primarily the lungs, proof about varied manifestations, involving also other organs and systems soon emerged (Ramos-Casals et al., 2021). One of the first researchers to remark this incredible capacity the new coronavirus holds was Mao et. al. who, in 2020, published the first observational study describing nervous system manifestations in a cohort of hospitalized patients infected with SARS-CoV-2 in Wuhan (Mao et al., 2020). Since then, many more studies proving that the virus involves both the central (CNS) and peripheral nervous system (PNS), both in the acute phase of the infection, as well as in the post infectious phase, being responsible of numerous sequelae in many patients have emerged (DosSantos et al., 2020; Hanganu et al., 2023; Siahaan et al., 2022; Silva et al., 2023; Whittaker et al., 2020).

Under the guidance of Prof. Dr. Adriana Hristea MD PhD., I set out to explore in detail the spectrum of neurological manifestations in SARS-CoV-2 infection and to identify the factors that may facilitate their occurrence, as well as their impact on prognosis, thus emphasizing the interdisciplinary nature of this research. In order to understand the ways in which the virus affects the nervous system I combined knowledge from neurology, virology, epidemiology and immunology.

As part of the PhD research, I conducted two original, retrospective studies, involving patients hospitalized with COVID-19 in "Prof. Dr. Matei Balș" National Institute of Infectious Diseases during May 2020 and December 2022, and one systematic review of literature studying the types of PNS involvement in COVID-19 (Hanganu et al., 2024a, 2024b, 2023).

This research, situated at the intersection between neurology and infectious diseases was one of the many research projects carried out at "Prof. Dr. Matei Balș" National Institute of Infectious Diseases on COVID-19. It contributes to a holistic understanding on the impact SARS-CoV-2 has on the nervous system and through its results it aims to contribute on the development of efficient strategies on improving patient outcome.

I. CURRENT STATE OF KNOWLEDGE

In the first chapter of this section, I described the microbiological characteristics of SARS-CoV-2 and pathophysiological mechanisms underlying COVID-19, as well as the clinical manifestations of the disease. One of the most frequently reported manifestations are the respiratory symptoms, cardiac rhythm disturbances, gastrointestinal symptoms, neurological, endocrine involvement, etc. Another category of conditions is represented by microvascular involvement and proinflammatory status by the viral infection (Borczuk and Yantiss, 2022; Conway et al., 2022; Lamers and Haagmans, 2022; Lorini et al., 2021).

In the second chapter I focused on the types of neurological manifestations and their pathophysiology. I conducted an exhaustive literature research regarding the ways in which SARS-CoV-2 affects the nervous system and the resulting clinical picture. It is most likely a mixed process that encompasses both direct and indirect mechanisms. Depending on the involved pathophysiological mechanism, these can be divided in four interdependent categories: direct viral invasion, parainfectious autoimmune response, endothelial disfunction and coagulopathy, and neurotoxic effects resulting from severe forms of COVID-19 (Wesselingh, 2023).

I divided the neurological involvement in CNS and PNS manifestations.

Some of the most frequent CNS manifestations were viral headache (Sampaio Rocha-Filho, 2022; Tutal Gursoy et al., 2023), COVID-19 encephalopathy (Liguori et al., 2020; Ousseiran et al., 2023), neurovascular events, mostly ischemic stroke (Luo et al., 2022; Nannoni et al., 2021; Shahjouei et al., 2020), de novo epileptic seizures (Asadi-Pooya et al., 2021; Coperchini et al., 2020).

PNS manifestations spectrum was dominated by GBS with all its subtypes, as well as varying degrees of involvement of the cranial nerves. The most frequently affected cranial nerves were VII, VI and III presenting as hypo/ageusia, peripheral facial palsy and ophtalmoparesis (Finsterer et al., 2021; Pimentel et al., 2023).

II. PERSONAL CONTRIBUTIONS TO THE STUDY OF NEUROLOGICAL INVOLVEMENT IN COVID-19

Chapter 3. Research hypothesis and general objectives

The capacity of the virus to invade the nervous system it's based on a complex physiopathological process. The virus enters the brain either directly using NRP-1 and ACE2 receptors, or through other mechanisms such as hematogenous dissemination (Gudowska-Sawczuk and Mroczko, 2021). Neurological deficits are one of the most difficult to manage and prevent and they are usually associated with more severe forms of disease (Mao et al., 2020; Zhou et al., 2020).

The aim of this paper is the exploration of neurological manifestations in patients with SARS-CoV-2 infection, identification of independent risk factors for their occurrence and the impact they have on the outcome of the affected patients.

In order to fulfill this aim, I conducted three studies who had the objectives listed below:

1. **Central and peripheral nervous system involvement in a cohort of patients hospitalized with COVID-19**
   - 1.1. Describing new onset neurological manifestations in hospitalized patients infected with SARS-CoV-2
   - 1.2. Exploring independent risk factors associated either with CNS or PNS involvement
   - 1.3. Analyzing the prognosis and identifying the characteristics of patients who had an unfavorable prognosis.
2. **Central nervous system manifestations in hospitalized patients with severe forms of COVID-19**
   - 2.1. Identifying independent risk factors for CNS involvement in patients with severe and critical forms of COVID-19
   - 2.2. Identifying independent risk factors for all cause in-hospital mortality and describing the impact CNS manifestations have on the outcome of patients with severe and critical forms of COVID-19.
3. **Peripheral nervous system involvement in COVID-19: systematic literature review.**
   - 3.1. Describing PNS manifestations in COVID-19

3.2. Exploring the association between peripheral and cranial nerve involvement and the characteristics of COVID-19 patients.

3.3. Describing the pathophysiological mechanism of PNS involvement.

Chapter 4. General methodology of research

The two original retrospective, observational, cohort studies included COVID-19 patients hospitalized in "Prof. Dr. Matei Balș" National Institute of Infectious Diseases between May 2020 and December 2022. I included adult patients (>18-year-old) who presented new onset neurological symptoms throughout hospitalization. Were considered eligible only patients who had a positive PCR or antigen SARS-CoV-2 test and who were examined by the neurologist. All patients included in the analysis were examined by myself as I was responsible with the neurological monitoring of the adult patients hospitalized in "Prof. Dr. Matei Balș" National Institute of Infectious Diseases who presented neurological manifestations. We excluded patients with pre-existent neurological diseases such as chronic migraine, epilepsy, neuroinflammatory diseases, or neurodegenerative diseases. The study was approved by the Hospital Bioethics committee (C13303/07.11.2023).

We reviewed electronic and physical medical records of the patients, which included demographic data, clinical data on comorbidities, severity of COVID-19 and respiratory parameters, laboratory pulmonary and brain imaging data. No follow-up data post hospitalization was available.

Neurological data and clinical diagnosis were extracted from the neurological clinical examinations and were divided in two categories: CNS involvement (encephalopathy, headache, neurovascular events, epileptic seizures) and PNS involvement (cranial nerve involvement, polyneuropathy, mononeuritis)

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 28, IBM Corp., Armonk, NY, USA).

Chapter 5. Central and peripheral nervous system involvement in a cohort of hospitalized patients with COVID-19 (study 1)

5.1. Objectives and population of Study 1.

Study 1 took place during October 2021 – December 2022 in four departments of "Prof. Dr. Matei Balș" National Institute of Infectious Diseases.

The objectives of the study were:

1. Describing new onset neurological symptoms in hospitalized SARS-CoV-2 infected patients.
2. Exploring independent risk factors associated with either CNS or PNS involvement
3. Analyzing patient prognosis and identification of the chacarteristics of the patients with unfavorable outcome.

5.2. Materials and Methods

During the study I reviewed 1440 patients for eligibility based on the existence of the neurological examination. Of these I included 115 patients, 72 with CNS involvement and 43 with PNS involvement

In order to study the independent value of different variables on the two events studied during the hospitalization, Cox proportional hazards regression was used: (1) independent risk factors associated with CNS/PNS manifestations and (2) unfavorable prognosis (deceased patients). To select the variables in the final model "stepwise (forward likelihood ratio)" method was used.

5.3. Results of study 1

Baseline characteristics of patients with COVID-19 and neurological symptoms

The cohort was composed of 115 patients (72 with CNS manifestation and 43 with PNS manifestations). Of these, 55 (47.8%) were males. Mean age for the whole group was 61.7±15.46 years. The median time to neurological symptoms since COVID-19 diagnosis was 9 (0-129) days and median hospitalization duration was 20 (2-139) days. Sixty-two (53.9%) patients had severe COVID-19.

In terms of cardiovascular risk factors, 66 (57.4%) patients had high blood pressure, 40 (34.8%) diabetes mellitus, 18 (15.7%) atrial fibrillation, 11 (9.6%) had ischemic heart disease, 25 (21.7%) atherosclerosis, 33 (28.7) obesity, 7 (6%) chronic kidney disease, 4 (3.5%) patients were smokers, and one (0.8%) suffered from unhealthy alcohol use. Inflammatory markers such as CRP, ferritin and fibrinogen had means (±SD) of 78.7 (±82.7), 749.5 (±574.7) and 491.1 (±189.2), respectively. Mean values for D-dimers, INR and LDH were: 816.3 (±2825), 1.17 (±.04) and 452.55 (±330.8), respectively.

Compared to patients who presented with PNS manifestations, patients who had CNS involvement were older, predominantly males, had more immunosuppressive conditions like diabetes mellitus and chronic kidney disease, and had severe forms of SARS-CoV-2 infection. The onset of CNS neurological symptoms was more likely to develop later in the course of the COVID-19 vs. PNS manifestations, but no significat difference was registered (p=.3). Furthermore, mortality was higher in the CNS group, 95.8% of all deaths being registered in this group. In Table 5.1. the comparative demographics and characteristics of patients with CNS and PNS involvement are summarized.

Table 5.1. Clinical and laboratory data on patients with new onset CNS and PNS manifestations and COVID-19

		CNS involvement n = 72	PNS involvement n = 43	*p* OR (95 CI)
Male, n (%)		40 (55.6)	14 (32.6)	0.02 2.6 (1.2-5.7)
Age, median (range)		68 (32-92)	56 (25-88)	<.001 10.75 (5.2-16.3)
Time to neurological symptoms (days), median (range)		11 (0-67)	5 (0-129)	0.3 3 (-3.8-9.9)
Severe COVID, n (%)		46 (63.9)	16 (37.2)	0.007 0.3 (0.1-0.7)
Hospitalization duration (days), median (range)		25.5 (2-115)	15 (3-139)	0.5 5.2 (-7.1-13.5)
	High blood pressure	46 (63.9)	20 (46.5)	0.08 0.5 (0.2-1.1)
	Diabetes mellitus	32 (44.4)	8 (18.6)	0.005 0.3 (0.1-0.7)
	Atrial fibrillation	14 (19.4)	4 (9.3)	0.1 0.4 (0.1-1.4)

CVD risk factors, n (%)	Ischemic cardiac disease	8 (11.1)	3 (7.0)	0.5 0.6 (0.1-2.4)
	Stroke history	6 (8.3)	4 (9.3)	0.5 1.1 (0.3-4.2)
	Atherosclerosis	17 (23.6)	8 (18.6)	0.6 0.7 (0.3-1.9)
	Obesity	22 (30.6)	11 (25.6)	0.6 0.8 (0.3-1.8)
	Chronic kidney disease	7 (9.7)	0 (0)	0.04 0.6 (0.5-0.7)
	Smoker	3 (4.2)	1 (2.3)	1 0.5 (0.05-5.4)
	Alcohol consumption	1 (1.4)	0 (0)	1 0.6 (0.5-0.7)
Laboratory data (median ±SD)	CRP (mg/dl) (n = 114)	95±88	51±65	0.005 44.5 (13.7-75.4)
	Ferritin (ng/ml) (n = 92)	81±546	633±612	0.1 185.5 (-59.4-430.4)
	Fibrinogen (mg/dl) (n = 113)	526±190	430±174	0.009 96.3 (24.8-167.6)
	D-dimers (ng/ml) (n = 107)	1051±3511	406±502	0.2 645.5 (-478.1-1769)
	INR (n = 114)	1.2±0.4	1.09±0.1	0.1 0.1 (-0.03-0.2)
	LDH (units/L) (n = 111)	480±335	406±322	0.2 74.3 (-54.5-203)
Deceased, n (%)		23 (31.9)	1 (4.2)	<0.001 0.05 (0.007-0.4)

The main CNS and PNS manifestations are available in Table 5.2.

Table 5.2: CNS and PNS manifestations associated with COVID-19 (objective 1)

CNS, n (%) (n = 72)	**PNS,** n (%) (n = 43)
At least one CNS manifestation, 72 (62.6) **COVID-19 associated encephalopathy**, 57 (79.4)	**Cranial nerves**, 34 (79) ▪ Olfactory nerve, 24 (55.8) ▪ Oculomotor nerves, 5 (11.6)

COVID-19 associated headache, 31 (43) **At least one neurovascular event,** 23 (31.9) ▪ Ischemic, 17 (23.6) ▪ Hemorrhagic, 6 (8.3) ▪ Venous thrombosis, 1 (1.4) ▪ Subarachnoid hemorrhage, 1 (1.4) **Seizures**, 8 (11.1) **Autoimmune paraviral encephalitis** 1 (1.4)	▪ Facial nerve, 1 (2.3) ▪ Vestibulo-cochlear, 26 (60.5) ▪ Polineuritis cranialis, 2 (4.7) **Mononeuritis**, 5 (11.6) **Polyneuropathy**, 4 (9.3)

Factors independently associated with CNS and/or PNS manifestations (objective 2)

After stepwise Cox PH regression, the following variables were identified to be independently associated with the development of CNS manifestations during hospitalization: older age (HR = 1.02, 95% CI: 1.003-1.037, p=.01), COVID severity (HR = 2.53, 95% CI: 1.42-4.5, p=.002), ischemic cardiac disease (HR = 2.42, 95% CI: 1.05-5.6, p=.03) and increased D-dimers (HR = 1.00, 95% CI: 1.00-1.00, p=.02).

In-hospital mortality of patients with CNS and PNS manifestations associated with COVID-19 (objective 3)

Stepwise Cox PH regression was used to evaluate the factors independently associated with death during hospitalization. In this regard, age (HR = 1.059, 95% CI: 1.024-1.096, p=.001), CRP (HR = 1.006, 95% CI: 1.00-1.011, p=.03), CNS involvement (HR = 9.155, 95% CI: 1.185-70.74, p=0.03) and white blood count (HR=1.053, 95% CI: 1.026-1.081, p<.001) were selected in the final model.

5.4. Conclusions and discussions of Study 1

CNS manifestations are more frequent than the involvement of PNS in hospitalized patients with SARS-CoV-2 infection and they are independently associated with older age, disease severity, ischemic heart disease and increased D-dimers. COVID-19 associated encephalopathy was the most common CNS manifestation in our study, but neurovascular events are also important considering the overlap between inflammatory and prothrombotic pathways, especially in severe cases. PNS findings were various, involving mostly the cranial nerves, especially the vestibulo-cochlear. Among hospitalized patients with COVID-

19 older age, CNS involvement and increased level of inflammatory markers were independent risk factor for the in-hospital mortality.

Results of this study were published in Frontiers in Neurology, Volume 14 – 2023, in *Neuroinfectious diseases* Section, in January 11th 2024, *https://doi.org/10.3389/fneur.2023.1338593* (*The outcome and risk factors associated with central and peripheral nervous system involvement in hospitalized COVID-19 patients: a retrospective cohort study;* Authors*: Andreea Raluca Hanganu, Cristian-Mihail Niculae, Adriana Octaviana Dulămea, Emanuel Moisă, Rareş Constantin, Georgiana Neagu, Adriana Hristea*), Web of Science IF 2.7.

Chapter 6. Central nervous system manifestations in patients hospitalized with severe forms of COVID-19: retrospective cohort study (Study 2)

6.1. Objectives and population of Study 2

1. Identifying independent risk factors for new onset CNS manifestations in a cohort of patients with severe forms of COVID-19.

2. Identifying independent risk factors for all causes in-hospital mortality and describing the impact CNS manifestations have on the patient outcome in severe forms of COVID-19

6.2. Materials and methods

During the study period I revised 1840 patient records hospitalized with severe forms of COVID-19. Of these I included 162 patients, of which 50 presented with specific CNS involvement manifestations and 112 had no neurologicla involvement.

Binary logistic regression was used to assess the predictive value of different variables regarding factors associated to CNS manifestations development in patients with severe COVID-19. A stepwise (backwards likelihood ratio) method was used for variable selection into the final model. The rationale for introducing the variables in the model was based both on basic inference analysis and clinical judgement.

6.3. Results of study 2

Baseline characteristics of patients with severe COVID-19

During the study period we revised 1840 files from hospitalized patients based on the severe COVID-19 diagnostic. Of these, we included 162 patients, 50 of which presented with CNS involvement. The cohort was composed of 112 (69.1%) males. Mean age for the whole group was 60.75 ± 14.35 years. In terms of medical history 87 (53.7%) patients had high blood pressure, 39 (24.1%) had diabetes mellitus, 9 (5.6%) had ischemic heart disease, 108 (66.7%) were overweight or obese, 11 (6.8%) had history of stroke, and 8 (4.9%) had chronic kidney disease. Median (range) CRP was 39.9 (.16 - 345). WBC, lymphocytes, platelets, and hemoglobin had medians (range) of 8.35 (1.7-40.5), .9 (.1-3.3), 256.75 (13.0-650.0), 13.5 (1.6-17.5) respectively. Median (range) D-dimers were 278.5 (5.4-36937.0) and median (range) LDH was 380.0 (149.0-5399.0). Median (range) values for creatinine, creatinine-kinase, alanin-amino-transferase, and aspartate-amino-transferase were: .9 (.3-5.2, 69 (20.0-2567.0), 47.0 (14.0-4990.0) and 49.0 (14.0-7102.0) respectively.

The most common CNS manifestation was the COVID-19 encephalopathy in more than half of patients, followed by neurovascular events. Of the 15 patients who presented neurovascular events, 13 had ischemic stroke, one concomitant ischemic stroke and venous thrombosis, and one ischemic stroke that transformed hemorrhagically. Other neurovascular events were hemorrhagic stroke in 5 patients, subarachnoid hemorrhage in one patient and transient ischemic attack in one patient. CNS manifestations are presented in Table 6.1. demographic and laboratory data are presented in table 6.2.

Table 6.1: Spectrum of CNS manifestations in severe COVID-19 patients

Type of CNS involvement	**Number of patients** **N= 50**
COVID-19 associated encephalopathy, N (%)	38 (76)
Neurovascular events, N (%)	22 (44)
New onset epileptic seizures, N (%)	7 (14)
COVID-19 associated headache, N (%)	7 (14)

Table 6.2. Cohort demographics and laboratory characteristics

		With neurological involvement N = 50	Without neurological involvement N = 112	p
Female, N (%)		22 (44)	28 (25)	**.018**
Age (mean±STD)		68.3 (±13.49)	57.38 (±13.46)	**<.001**
CVD risk factors	HBP N (%)	37 (74)	50 (44.6)	**.001**
	Diabetus mellitus N (%)	23 (46)	16 (14.3)	**.000**
	Ischemic heart disease, N (%)	6 (12)	3 (2.7)	**.025**
	Obesity/ overweight N (%)	13 (26)	95 (84.8)	**<.001**
Lab (Median, range)	WBC (N*10^3/μL)	6.6 (2.2-20.44)	8.35 (1.7-40.5)	.24
	Lymphocytes (N*10^3/μL)	0.7 (0.3-1.49)	1 (0.1- 3.3)	**.000**
	Platelets (N*10^3/μL)	172 (83-314)	290.5 (13-650)	**.000**
	Hemoglobin (mg/dL)	13.1 (6.92-15.58)	13.75 (1.6-17.5)	**.001**
	CRP (mg/L)	76.7 (1.5-302)	35.3 (0.16-345)	**.000**
	D-Dimers (pg/ml)	389 (5.4-5471)	242 (36-6937)	**.000**
	CK (U/L)	138 (20-1167)	53 (20-2567)	**.005**
	LDH (U/L)	397.34 (222-1872)	368.5 (149-5399)	.137
	Creatinin (mg/dl)	1 (0.3-3.2)	0.8 (0.4-4.4)	.183
	ALT (U/L)	39 (17-194)	54.5 (16-4990)	**.002**
	AST (U/L)	51 (29-151)	48.5 (20-7102)	.733
Hospitalization duration (days), median (range)		25 (6-65)	14 (6-44)	**.000**
In-hospital all cause mortality N (%)		22 (44)	8 (7.1)	**<.001**

Factors associated with CNS involvement in patients with severe COVID-19 (objective 1)

After performing binary logistic regression, the following variables were identified to be independently associated with CNS involvement in severe COVID-19 patients: female sex (p = .04, OR 3.67, 95%CI 1.05-12.85), diabetes mellitus (p = .008, OR .197, 95%CI .06-.66), lymphocyte count (.04, OR .23, 95%CI .05-.97), platelets count (p = .001, OR .98, 95%CI .98-.99) CRP value (p = .04, OR 1.007, 95%CI 1.000-1.015) and CK value (p = .004, OR 1.003, 95%CI 1.001-1.005). Obesity was a protective factor for CNS involvement (p = .00, OR 17.62, 95%CI 4.98-62.23). The results are reported in Table 6.3.

Table 6.3. Independent risk factors for CNS manifestations

			95% C.I.	
	p	OR	Lower	Upper
CKD	.063	6.513	.900	47.107
Diabetes Mellitus	.008	5.088	1.519	17.040
Obesity	<.001	.057	.016	.200
Female sex	.042	3.672	1.049	12.847
Lymphocytes	.046	.227	.053	.972
Platelets	<.001	.989	.982	.995
CRP	.046	1.007	1.000	1.015
Constant	.006	77.945		

(Method: stepwise backward likelihood ratio, p for model <0.01, Nagelkerke R square = 0.69, Hosmer-Lemeshow test, Chi-square = 4,29, p = 0.89, % cases correctly predicted = 88,6%)

Identification of independent risk factors for all causes in hospital mortality and evaluation of the impact CNS manifestations have on it (objective 2)

Age was an independent risk factors for in hospital mortality (p = .03, OR 1.06, 95%CI 1.006-1.120). New onset CNS manifestations (p =.002, OR 14.48, 95%CI 2.58-81.23) and personal history of neurovascular events (p = .007, OR 12.74, 95%CI 1.99-81.31) were also independently associated with in-hospital mortality risk factors. Laboratory variables associated with in-hospital mortality were WBC count (p = .009, OR 1.12, 95%CI 1.03-1.24), platelets count (p = .002, OR .98, 95%CI .98-.99) and LDH (p = .011, OR 1.003, 95%CI 1.001-1.005). The results are reported in Table 6.4.

Table 4. Independent risk factors for in-hospital mortality

			95% C.I.	
	p	OR	Lower	Upper
Age	,030	1,061	1,006	1,120
Stroke history	,007	12,739	1,996	81,317
WBC	,009	1,132	1,032	1,242
Platelets	,002	,988	,981	,996
LDH	,011	1,003	1,001	1,005
CNS involvement	,002	14,482	2,579	81,323
Constant	,001	,001		

(Method: stepwise backward likelihood ratio, p for model <0.01, Nagelkerke R square = 0.671, Hosmer-Lemeshow test, Chi-square = 1,61, p = 0.99, % cases correctly predicted = 88.9%)

6.4. Conclusions and discussions of study 2

In this study we identified as independent risk factors for new onset CNS manifestations in patients with COVID-19 female sex, diabetes mellitus, lymphopenia, thrombocytopenia and high titers of CRP and CK. Surprisingly, obesity was identified as protective factors for new onset CNS manifestations in COVID-19 patients.

New onset CNS manifestations and personal history of stroke were identified as independent risk factors for in hospital mortality in COVID-19 patients

Results of this study were published in *Journal of Clinical Medicine, Volume 13, Issue 13, doi: 10.3390/jcm13133948, 5 iulie 2024, (Independent risk factors and mortality implications of de novo central nervous system involvement in patients hospitalized with severe COVID-19: a retrospective cohort study;* Authors*:* **Andreea Raluca Hanganu,** *Adriana Octaviana Dulămea, Cristian Mihail Niculae, Emanuel Moisă, Adriana Hristea),* IF 3.0.

Chapter 7. Peripheral nerve system involvement in COVID-19 patients. Systematic literature review (Study 3)

7.1. Introduction

In this study I conducted a systematic literature review in order to investigate the characteristics, management and prognosis of patients with COVID-19 associated PNS manifestations, including GBS spectrum, cranial nerves, mononeuritis, dysautonomia and other types of PNS manifestations. I structured this review in two parts. We conducted this systematic literature review to investigate the characteristics, management and outcomes of patients with PNS involvement in COVID-19, including the GBS spectrum, the CN, mononeuritis, dysautonomia, and other types of PNS manifestations. We structured the review in two parts. The first part describes the peripheral nervous system manifestations associated with COVID-19. In the second part we explored associations between PNS and CN involvement and characteristics of patients with COVID-19. We also aimed to discuss possible mechanisms of the PNS findings.

7.2. Materials and method

We registered the study protocol in the PROSPERO database with number CRD42021262017. We systematically searched published studies reporting cases of adult patients diagnosed with COVID-19 and PNS involvement that matched our inclusion and exclusion criteria. The search terms were used as keywords and in combination as MeSH terms in order to maximize the output from literature findings Two authors (ARH, AC) searched PUBMED up to July 2021 using the keywords below:

((((covid-19) OR (sars-cov-2)) OR (covid)) OR (covid19)) AND ((mononeuritis) OR (mononeuritis multiplex)) OR (plexopathy)) OR (polyneuropathy)) OR (polyradiculoneuritis)) OR (miller fisher)) OR (peripheral neuropathy)) OR (neuropathy)) OR (neuritis)) OR (polyneuritis))) OR (cranial

neuropathy)) OR (olfactory nerve)) OR (optic nerve)) OR (oculomotor nerve)) OR (trochlear nerve)) OR (trigeminal nerve)) OR (abducens nerve)) OR (facial nerve)) OR (vestibulocochlear nerve)) OR (glossopharyngeal nerve)) OR (vagus nerve)) OR (accessory nerve)) OR (hypoglossal nerve)) OR (diplopia)) OR (eyelid ptosis)) OR (strabismus)) OR (facial hypoesthesia)) OR (facial palsy)) OR (facial paresis)) OR (bell's palsy)) OR (vertigo)) OR (hypoacusis)) OR (dizziness)) OR (dysarthria)) OR (dysphagia)) OR (hypoglossal palsy)) OR (guillain barre))

Using a PICO framework, our target population of interest for this systematic review was adult patients (≥18 years old) diagnosed with COVID-19 (SARS-COV-2 infection confirmed by a RT-PCR or antigen test) who had a new onset of peripheral nervous system manifestations, including CN neuropathies within the six months following the SARS-CoV2 infection, and which were presumed to be associated with COVID-19.

Inclusion criteria

- any English, Spanish or French written articles reporting on
- at least patient diagnosed with COVID-19 by either a RT-PCR or antigen test that associated a
- peripheral nervous system or CN neuropathy either at the time of infection or up to 6 months thereafter.
- we defined and included any of the following peripheral neuropathies: CN neuropathies, motor or sensitive nerve neuropathies, either mononeuropathies or polyneuropathies, Guillain Barré syndrome with all its subtypes and any autonomic nervous system manifestations.

Exclusion criteria

- pediatric cases,
- patients in whom the COVID-19 diagnosis was made clinically or using serological tests,
- articles reporting neuropathies in patients vaccinated for SARS-CoV-2 within the previous three months in whom the neurological findings could have been attributed to vaccination,
- articles reporting on patients only with anosmia and/or ageusia that were not clearly stated to be caused by direct nerve involvement,

- articles reporting cases of preexisting neuropathies secondary to other causes.

All articles were included in the qualitative synthesis and articles reporting on individual patient data were included in the quantitative synthesis as summarised in the PRISMA flow chart in Figure 7.1.

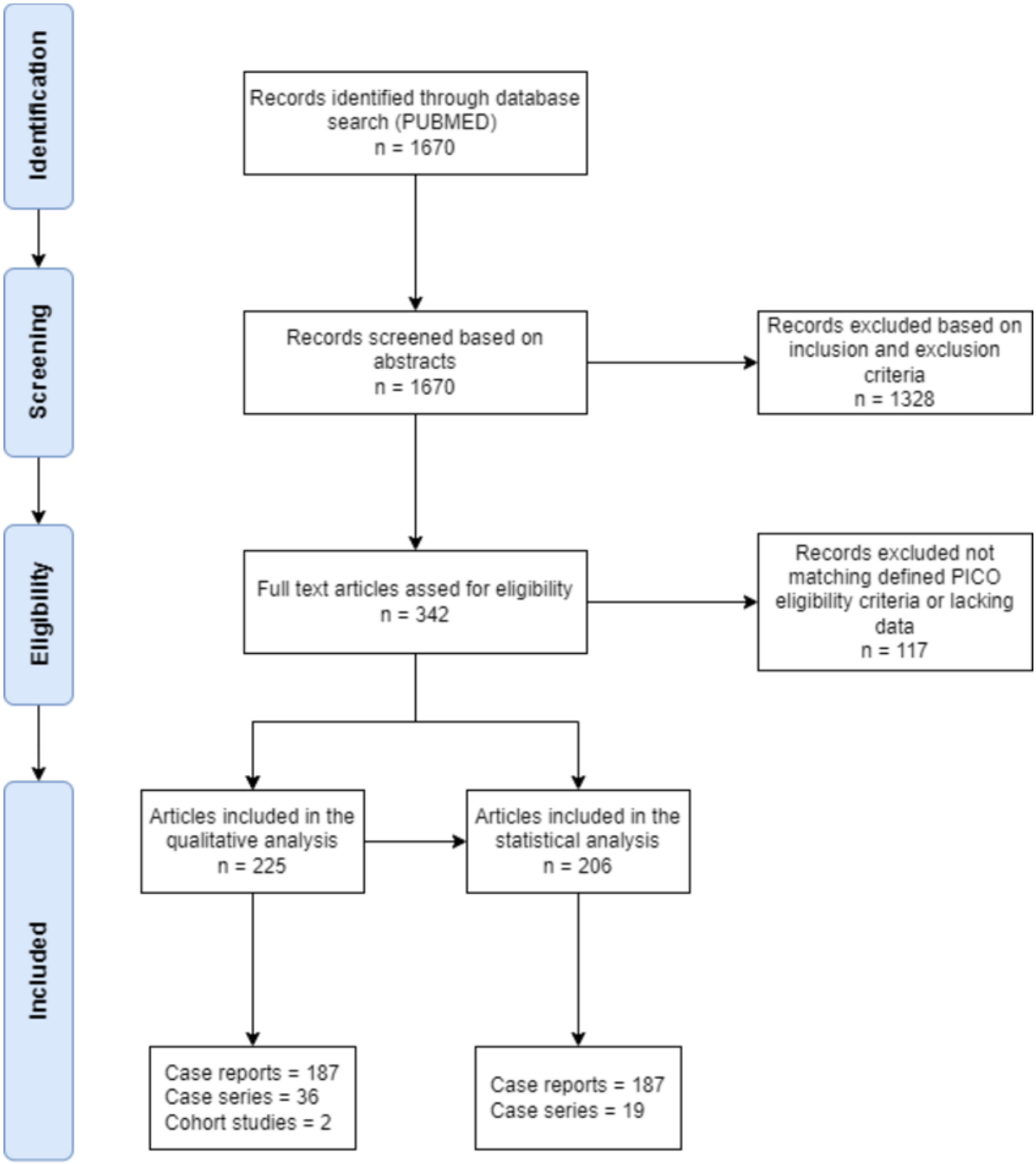

Figure 7.1.PRISMA flow diagram showing articles selection strategy.

7.3. Results of study 3

We included in our analysis data provided in 225 studies summing a total of 1320 pooled neurological events, in 1004 patients that presented with both CN involvement and PNS manifestations.

Descriptive data of the cranial nerve involvement is presented in Table 2.

Table 7.2. Types of cranial nerves involvement in patients with COVID-19

Cranial nerve (CN)	**Studies that mention CN involvement 195**	**Pooled events 957 (%)**	**Isolated CN involvement 805 (%)**	**CN + PNS Involvement 152 (%)**
I (olphactory)	11	154 (16.1)	151 (18.7)	2 (1.3) I + GBS, 1 I + MNM, 1
II (optic)	10	24 (2.5)	23 (2.8)	1 (0.6) II + GBS
III + IV + VI (oculomotor, trochlear, abducens)	29	56 (5.8)	38 (4.7)	18 (11.8) III + IV + VI + GBS, 17 III + IV + VI + dysautonomia, 1
V(trigeminal)	8	41(4.3)	15 (1.9	26 (17.1) V+ GBS, 25 V+ dysautonomia, 1
VII (facial)	70	261 (27.3)	190 (23.6)	71 (46.7) VII+ GBS, 70 VII+ dysautonomia, 1
VIII (vestibulo-cochlear)	25	243 (25.4)	241 (29.7)	2 (1.3) VIII+ GBS, 1 VIII+ dysautonomia, 1
IX (glossopharingeal),	16	99 (10.3)	86 (10.7)	13 (8.5) IX + GBS
X (vagus)	17	49 (5.1)	35 (4.3)	14 (9.2)

				X + GBS
XI (accessory)	3	20 (2.1)	17 (2.1)	3 (1.9) XI + GBS
XII (hypoglossal)	6	11 (1.1)	9 (1.1)	2 (1.3) XII + GBS

Abbreviations: N – number, CN – cranial nerves, PNS – peripheral nervous system, GBS – Guillain Barre Syndrome, MNM – mononeuritis multiplex,

The facial nerve (VII) was the most frequently involved (27.3%), followed by the vestibulo-cochlear nerve, VIII (25.4%) and olphactory, I (16.1%) The least affected by COVID-19 was the hypoglossal nerve, XII (1.1%). In patients with both types of neurological involvement, GBS spectrum was the most common type of PNS involvement, in 147/152 (96.7%) reported cases. Dysautonomia and MNM were only rarely reported. Vestibulo-cochlear nerve (VIII) involvement was most often isolated, in contrast with nerves III (oculomotors), IV (trochlear), VI (abducens), VII (facial), IX (glossopharyngeal) and X (vagus), which were affected also in combination with different types of PNS. The trigeminal nerve (V) was the only CN mostly involved in combination with PNS findings rather than isolated.

From those studies reporting on patients with PNS involvement, unclassified Guillain Barré syndrome (uGBS) was the most frequently encountered, in more than 50% of the cases, in both isolated and PNS + CN involvement, followed by AIDP and dysautonomia (Table 7.3).

The pharyngo-cervical-brachial form of GBS was the rarest one as it was found in only one patient (Liberatore et al., 2020). Most cases of GBS were diagnosed using clinical criteria and/or cerebrospinal fluid (CSF) analysis.

Table 7.3 - Type of PNS involvement in patients with COVID-19

Type of PNS involvement	**Studies 183**	**Pooled events 515(%)**	**Isolated PNS involvement N(%) 350 (68)**	**PNS + CN involvement N(%) 165 (32)**
uGBS,	75	273 (53)	183 (52.3)	90 (54.5)
AIDP	37	99 (19.2)	62 (17.7)	38 (10.8)
AMAN	13	13 (2.5)	9 (2.6)	4 (1.1)
AMSAN	19	31 (5.6)	25 (7.1)	6 (1.7)
MFS	13	18 (3.5)	-	18 (5.1)
MNM	5	14 (2.7)	11 (3.1)	3 (1.8)
Dysautonomia	8	56 (10.9)	52 (14.8)	4 (2.4)
Others	13	10 (1.9)	8 (2.3)	2 (1.2)

Abbreviations: uGBS – unclassified Guillain Barre Syndrome, acute inflammatory demyelinating polyneuropathy, AMAN – acute motor axonal neuropathy, AMSAN – acute motor and sensitive axonal neuropathy, MFS – Miller Fischer Syndrome, MNM – mononeuritis multiplex.

In table 7.4. the results of the qualitative synthesis based on the articles that reported on individual patient data are presented.

Table 7.4 - Comparative clinical data according to different types of neurological involvement

Number of patients, N = 328		**CN involvement N = 102 (%)**	**PNS involvement N = 161 (%)**	**CN + PNS involvement N = 65 (%)**	***p* value**	**Missing data N (%)**
Male sex		55 (53.9)	91 (56.5)	39/63 (61.9)	.63	2 (0.6)
Age, mean ± SD		46.2 ± 17.1	52.9 ±15.1	51.6 ± 15	**.003**	0
Severe COVID-19		25/101 (24.8)	59/158 (37.3)	22/63 (34.9)	.1	6(1.8
Duration between disease onset and neurological symptoms (days), median (range)		8 (0-90)	13.5 (0-122)	13.5 (0-42)	.06	65 (19.8)
Level of patient care	Outpatient	35/87 (40.2)	15/115 (13)	5/60 (8.3)	**<.001**	66 (20.1)
	Normal ward	33/87 (37.9)	47/115 (40.9)	28/60 (46.7)		

	ICU	19/87 (21.8)	53/115 (46.1)	27/60 (45)		
Treatment	GC	45 (44.1)	12 (7.5)	16/65 (24.6)	**<.001**	0
	IVIG	38 (37.3)	81 (50.3)	17/65 (26.2)	**.002**	
	PLEX	0 (0)	19 (11.8)	5/65 (7.7)	**.002**	
	No treatment	11 (10.8)	15 (9.3)	16 (24.6)	**.006**	
	Others	3 (2.9)	5 (3.1)	1 (1.5)	.8	
Outcome	Recovered completely	24/95 (25.3)	24/123 (19.5)	12/59 (20.3)	.1	51 (15.5)
	Mild/moderate sequelae	52/95 (54.7)	83/123 (67.5)	40/59 (67.8)		
	No improvement	17/95 (17.9)	10/123 (8.1)	4/59 (6.8)		

	Non-survivors	2/95 (2.1)	6/123 (4.9)	3/59 (5.1)		

Abreviations: CN – cranial nerves, PNS – peripheral nervous system, ICU – intensive care unit, GC – glucocorticoids, IVIG – intravenous immunoglobulins, PLEX – plasma exchange

Patients with CN involvement were younger (mean of 46.2 ±17.1 years, p=.003) than those with either isolated PNS involvement or both types of neurological involvement (mean of 52.9 ±15.1 and 51.6±15). In terms of patient care, those with CN involvement were mostly treated as outpatients compared to those with PNS involvement (either isolated or in conjunction with CN involvement), that were more likely to be hospitalized and/or ICU stay (p<.001). Patients with PNS involvement were more likely to receive intravenous immunoglobulins (p= .002) or plasma exchange (p= .002) compared to patients with isolated CN involvement that received mostly glucocorticoids (p< .001). Also, we found no statistically significant differences regarding COVID-19 disease severity among all three groups of patients, with severe forms of disease in less than 40% in all categories. When comparing the groups in table 4, duration between disease onset and the neurological symptoms was shorter for the CN groups – 8 (0-90) days, versus 13.5 (0-122) and 13. 5 (0-42) respectively (p = .06).

7.4. Conclusions and discussions of study 3.

The most affected cranial nerve was the facial nerve, followed by the vestibulo-cochlear. Of the peripheral nerve manifestations, the most commonly reported was the GBS spectrum. The mechanisms responsible for the PNS involvement are the direct viral invasion and the disimmune response.

In conclusion, PNS involvement in COVID-19 cand be an important cause of hospitalization and post COVID-19 sequelae, by raising the burden on the public health systems. Although they are usually associated with mild to moderate forms of disease, neurological sequelae can persist, thus the patients need to undertake physical recovery sessions.

The results of this study are published in *Plos ONE, https://doi.org/10.1371/journal.pone.0283827,* on April 6th 2023, (*Independent risk factors and mortality implications of de novo central nervous system involvement in patients hospitalized with severe COVID-19: a retrospective cohort study;* Authors: *Andreea Raluca Hanganu, Adriana Octaviana Dulămea, Cristian Mihail Niculae, Emanuel Moisă, Adriana Hristea),* IF 3.7.

Chapter 8. Conclusions and personal contributions

This doctoral thesis contributes significantly to the understanding of the neurological manifestations spectrum associated to COVID-19 and offers new perspectives in identifying risk factors associated with neurological manifestations and mortality, respectively. Identifying the risk factors for neurological manifestations development is essential in preventing their appearance, considering the invalidating nature of the neurological manifestations adds to the SARS-CoV-2 burden on the healthcare systems.

Through the three studies conducted in this doctoral research, it is demonstrated that neurological involvement in COVID-19 is heterogenous, by involving both the CNS and PNS systems through varied pathologies. In the general part of this paper, I emphasized the pathophysiological mechanisms the SARS-CoV-2 infection generates in the human body and the way in which they translate in general clinical manifestations, as well as neurological manifestations. I naturally transitioned to the special part in which I focused on characterising different types of neurological involvement due to these pathophysiological processes and identifying the risk factors for their occurrence, as well as the impact neurological manifestations have on mortality.

Considering that these studies took place during the pandemics, in one of the main national medical centres that were at the forefront of the fight against SARS-CoV-2, I had the advantage of treating numerous patients with extremely complex pathology, from all over the country, who frequently required interdisciplinary cooperation. Another advantage was the possibility of treating the patients at the highest standards, reinforcing the signification of the obtained results. On the other hand, because of the overload of the hospital, and of the paraclinical investigations laboratories respectively, but also due to the lack of a Neurology ward, the logistic possibility in performing all the required investigations was relatively low, such as EMG for patients with PNS involvement, or EEG for patients with encephalopathy. Another disadvantage was the difficulty of performing

lumbar punctures, usually contraindicated because of coagulopathy disturbances that required curative anticoagulation, and whose cessation, although temporary, would have overweighed the benefit of a certain neurological diagnosis. I compensated for the reduced possibility of investigating the PNS pathology by conducting a systematic review of literature whose aim was to describe the main types of PNS involvement, the management and prognosis of the affected patients.

All three studies achieved their proposed objectives, with the main conclusions being as follows:

1. the spectrum of neurological manifestations in SARS-CoV-2 infection is extremely diverse, varied manifestations having been described affecting both CNS and PNS
2. COVID-19 encephalopathy was the most common CNS manifestation, but neurovascular events are very important considering the overlap between the inflammatory and prothrombotic pathways, especially in severe cases.
3. Independent risk factors for new onset CNS manifestations in a cohort of patients with both CNS and PNS involvement are advanced age, severe form of COVID-19, personal history of ischemic heart disease, and increased D-dimers level.
4. Independent risk factors for new onset CNS manifestations in patients with severe and critical COVID-19 are female sex, diabetes mellitus, lymphopenia, thrombocytopenia and increased levels of CRP and CK respectively. Surprisingly, obesity was identified as protective factor for CNS manifestations occurrence.
5. New-onset PNS manifestations involved predominantly the CN. In the original study the most affected CN was the vestibulo-cochlear nerve, while in the systematic review it was surpassed by the facial nerve.
6. The most frequent peripheral nerve manifestation (excluding the CN) is Guillain Barré syndrome.
7. PNS manifestations are usually associated with mild and moderate forms of disease and had a favourable neurological outcome, although most patients were left with mild to moderate sequelae.
8. The management of patients with PNS manifestations due to COVID-19 is similar to the general management of these pathologies.
9. Independent risk factors for in-hospital mortality in a cohort of patients with central and peripheral new-onset neurological involvement are advanced age, severe

forms of COVID-19, CNS involvement, and increased levels of inflammatory markers.

10. New-onset CNS manifestations and personal history of neurovascular events were identified as independent risk factors for in-hospital mortality in patients hospitalized with severe and critical forms of COVID-19, along with lymphopenia, thrombocytopenia and increased LDH levels.

Personal contributions

This paper aimed a holistic approach on the neurological manifestations of COVID-19, from the risk factors responsible for their occurrence, to the influence of neurological involvement on the outcome. The novel elements were:

- Identification of independent risk factors for new-onset CNS and PNS involvement in COVID-19 patients; these factors were represented by advanced age, severe forms of COVID-19, personal history of ischemic heart disease, and increased D-dimers level (Chapter 5.3.3).
- Identification of independent risk factors for new-onset CNS involvement in patients with severe COVID-19; these were female sex, diabetes mellitus, lymphopenia, thrombocytopenia, high CRP and CK levels; surprisingly, obesity was a protective factor for CNS involvement (Chapter 6.3.3.)
- Identification of independent risk factors for in-hospital mortality in a cohort of patients with new-onset central and peripheral neurological involvement; these were advanced age, CNS involvement, and high inflammatory markers, such as CRP (Chapter 5.3.4.)
- Identification of new-onset CNS manifestations, as well as personal history of neurovascular events as independent risk factors for in-hospital mortality in a cohort of patients with severe and critical COVID-19 (Chapter 6.3.4.)

In conclusion, based on the obtained results, I wish to emphasize the importance of interdisciplinary cooperation between neurologist and infectious diseases specialist. Thus, the neurologist must consider SARS-CoV-2 infection as a possible aetiology for neurological manifestations in patients where classical causes have been excluded. Given the association between mild to moderate forms of COVID-19, as well as the important post infectious component, PNS involvement is particularly targeted in this situation. At the same time, the infectious diseases specialist who looks after SARS-CoV-2 infected patients must identify

and control the risk factors associated with the occurrence of neurological complications, especially in patients with severe forms of COVID-19.

Through this paper I aimed to integrate the neurological manifestations under the broad umbrella of non-respiratory COVID-19 manifestations, and at the same time opening new research directions, as emphasized in the subchapters constituting the personal contribution section.

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