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SHORT, MEDIUM AND LONG TERM NEUROLOGICAL MANIFESTATIONS AND OUTCOME IN COVID-19 PATIENTS

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ABSTRACT

Background and objective:

There is a need to improve the understanding of Covid-19 neurological complications in a temporal manner. The objective of our study was to find out temporal relationship of neurological manifestations and outcome in Covid-19 Patients.

Methods:

This was a multi-center observational study from six centers in Pakistan. Data of covid patients with six months follow up was retrospectively collected from the hospital records. Time periods were divided into short-term (< 1 month), medium-term (2-3 months) and long-term (>4 months). SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data.

Results:

Neurological manifestations were reported in 208 out of 905 covid patients. One-hundred-twenty-five (60%) developed neurological manifestations within one month, 62 (30%) developed within 2-3 months and 21 (10%) developed between 4-6 months. Most common manifestations within one month included cerebrovascular disease (59%), neuromuscular disorders (14%) and neuropsychiatric disorders (10%). Common manifestations in 2-3 months group included neuromuscular manifestations (32%), neuropsychiatric manifestations (19%), cerebrovascular diseases (14 %), myalgia or musculoskeletal pain (14%), and vertigo, hearing problems or tinnitus (14%). Common manifestations in 4-6 months group included neuromuscular disorders (33%) cerebrovascular diseases (19%), fatigue / malaise (9%) anosmia/dysgeusia (9%) and Bell's palsy (25%). The long-term patients differed from the short-term patients by a mean younger age on presentation (44.7 vs. 59 years), female predominance (52% vs. 28%), higher asymptomatic Covid infection (29% vs. 14%), better clinical outcomes (mean mRS of 1.6 vs. 3), and low mortality (0 vs 18%).

Conclusion:

Neurological manifestations of covid infection may differ based on time duration since infection. Vascular complications are high in early period while neuromuscular manifestations are high in late period.

Key words: Coronavirus disease 2019; Covid; neurology; long term; SARS-COV-2; long covid; stroke

INTRODUCTION

Neurological manifestations involving both central and peripheral nervous systems have been reported in a range of 4.8%-36.4% in patients with coronavirus disease 2019 (Covid), especially the patients having moderate to severe covid, resulting in increased morbidity and mortality.[1-5] In a recent systematic review, the pooled prevalence of the most common neurological manifestations were reported as fatigue (32%), myalgia (20%), dysgeusia (21%), anosmia / dysosmia (19%) and headache (13%).[6] However, most of these cases are mild, transient, and occur during the acute phase of covid illness. The long-term neurological manifestations in relation to the covid infection have not been studied in detail.

It is important to study temporal relationship of neurological manifestations after covid infection because it may help in understanding pathophysiology and effects of covid virus in nervous system. Some of these neurological manifestations especially stroke occur early in course while neuromuscular manifestations and behavioral symptoms may occur late in course. The objective of our study was to find out temporal relationship of Neurological Manifestations and outcome in Covid-19 Patients.

METHODS

Study design: Retrospective cross-sectional multi-center observational study.

Place and duration of study: This is a multi-center observational study conducted from July 2020 to April 2021. Six centers from Pakistan (Aga Khan University Karachi , Ziauddin University Karachi, Liaquat college of Medicine and Dentistry Karachi , Dow University of Health Sciences Karachi , Bolan Medical University Quetta, SMBBU and Chandka Medical College Hospital Larkana) participated in this study. Both inpatients and outpatients were included in our study.

Sample size: A total of 208 patients met the inclusion criteria and were included in the study.

Sampling technique: Non-probability consecutive sampling.

Inclusion criteria: Inclusion criteria included (i) adult patient aged 18 years or above; (ii) history of covid infection, confirmed by at least one of the following: (a) reverse transcriptase-polymerase chain reaction (PCR) assay of a nasopharyngeal swab, (b) serum antibody testing for covid, or (c) serum covid antigen testing; and (iii) a new neurological manifestation within six months of covid infection.

Exclusion criteria: Patients were excluded if minimum six months follow up data (since date of covid infection) was unavailable for surviving patients. Patients were also excluded if the onset of presenting neurological complaint preceded the covid infection. Patients with diagnosis of septic metabolic encephalopathy and pre covid stroke and diabetic neuropathies were excluded.

Data collection: Data was retrospectively collected on a pre-specified questionnaire. Data was retrieved from hospital medical records and hospital based covid registries. The questionnaire included information about the patient demographics, covid status, covid treatment, neurological manifestations, timing of neurological manifestations, and outcome.

We defined the time periods as follows: (i) short-term, occurring within one month of the diagnosis of covid infection; (ii) medium-term, occurring after one month and up to three months after covid infection; and (iii) long-term, occurring at four or more than four months after covid infection. Disability was measured by modified Rankin score (mRS). All patients were evaluated and diagnosed by trained neurologist. Neurological manifestations were diagnosed based on clinical evaluation by neurologists and diagnostic tests including CT scan, MRI, EEG, EMG, CSF analysis etc.

Data analysis: Baseline characteristics were described using numbers and percentages for categorical variables. Continuous variables were reported as mean ± SD. Chi-square test was performed to examine differences in categorical variables between post-covid duration. Differences in continuous variables were examined using ANOVA. SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data.

Ethical considerations: Study protocol was approved by Ethics review committee of Aga khan University and other participating centers. Data was collected from medical records. No data relating to patients identification was collected from any participating center. All patients admitted to Aga Khan University Hospital are asked to provide consent for use of medical records in research without patients' identification.

RESULTS

A total of 1595 patients with a diagnosis of covid were presented during the study period across different centers. Out of these 1595 patients, six months follow up data was available for 965 (60%) patients. Out of 964 charts reviewed 59 (6%) excluded due to exclusion criteria or incomplete data. Out of 905 patients included in study 208 (23%) patients met the inclusion criteria and were included in our study (Figure 1).

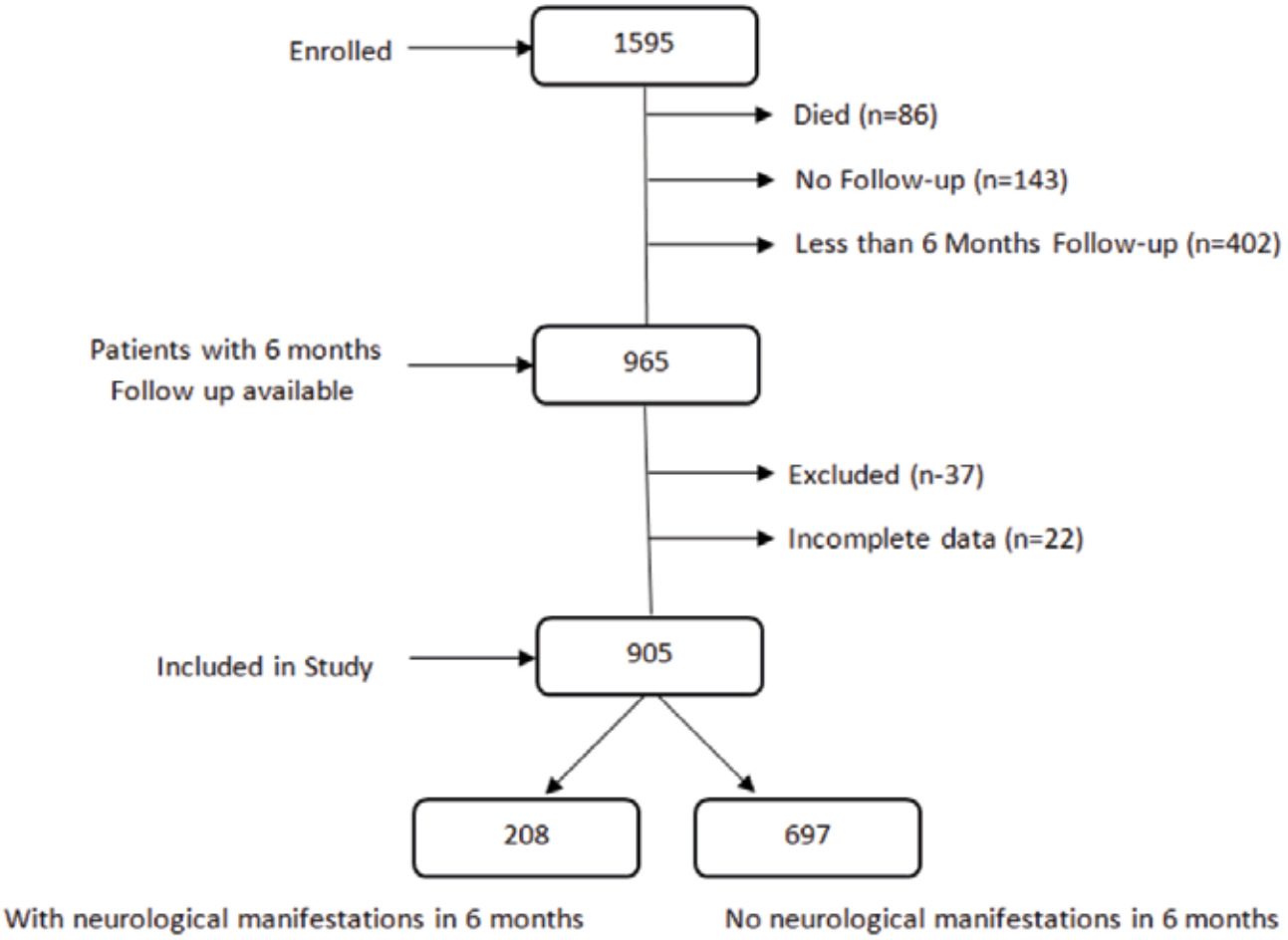

Figure 1: Flow Diagram: Patients enrolled

Mean age was 53.7 ± 17.0 years (range: 18-86 years). One-hundred-forty-four (69%) patients were male and 64 (31%) were female with a male to female ratio of 2.25:1. Hypertension (46%, n=95) and diabetes mellitus (38%, n=78) were the most common comorbidities. Covid was mostly diagnosed with a positive nasopharyngeal PCR in 76% (n=159) of the patients, followed by positive serum antibody testing (18%, n=37), and serum antigen testing (6%, n=12). Most of the patients (81%, n=168) presenting with neurological manifestations had respiratory symptoms with covid infection. Covid was managed with supplemental oxygen (61%, n=127), parenteral steroids (59%, n=122), and antiviral medicines (28%, n=58). Thirty-two patients (15%) required mechanical ventilation (Table 1).

Table 1: Clinical Characteristics of all the patients					
		Total	**< 1 month**	**2-3 months**	**>4 months**
Patients (n)		208	125	62	21
Age (Mean ± SD) in years		53.7 ± 17.0	59 ± 15	47 ± 16.7	44.7 ± 17.7
Gender	Male Female	144 (69%) 64 (31%)	90 (72%) 35 (28%)	44 (71%) 18 (29%)	10 (48%) 11 (52%)
COVID Diagnosis	PCR Antibodies Antigen	159 (76%) 37 (18%) 12 (6%)	102 (81%) 11 (9%) 12 (10%)	42 (68%) 20 (32%) --	15 (71%) 6 (29%) --
COVID Respiratory Status	Symptomatic Asymptomatic	168 (81%) 40 (19%)	107 (86%) 18 (14%)	46 (74%) 16 (26%)	15 (71%) 6 (29%)
Co-morbid:	DM HTN CAD Dyslipidemia Cancer	78 (38%) 95 (46%) 24 (12%) 22 (11%) 4 (2%)	63 (50%) 75 (60%) 21 (17%) 20 (16%) 3 (2%)	11 (18%) 17 (27%) 3 (5%) 1 (2%) 1 (2%)	4 (19%) 3 (14%) -- 1 (5%) --
COVID treatment	Intubation BiPAP Oxygen Steroids Anti-viral drugs Plasmapheresis	32 (15%) 46 (22%) 127 (61%) 122 (59%) 58 (28%) 9 (4%)	28 (22%) 36 (29%) 94 (75%) 90 (72%) 47 (38%) 7 (5.6%)	3 (5%) 8 (13%) 25 (40%) 26 (42%) 8 (13%) 2 (3%)	1 (5%) 2 (10%) 8 (38%) 6 (29%) 3 (14%) --
Outcome:	Discharged Expired	180 (88%) 24 (12%)	102 (82%) 23 (18%)	61 (98%) 1 (2%)	21 (100%) --
Mean mRS		2.9	3	2	1.6
Abbreviations: BiPAP = Bilevel Positive Airway Pressure; CAD = Coronary artery disease; Covid = Coronavirus disease 2019; DM = Diabetes mellitus; HTN = Hypertension; mRS = Modified Rankin Score; PCR = Polymerase Chain Reaction; SD = Standard deviation.					

Cerebrovascular diseases (42%, n=87) were the most common neurological manifestation, followed by neuromuscular disorders (21%, n=44) and neuropsychiatric disorders (12.5%, n=26). Twelve patients (6%) had two or more neurological manifestations. Mean modified Rankin score (mRS) was 2.9 ± 1.9 (Table 1). The mRS score in 88 (42.3%) patients was 0-2, in 96 (46.2%) patients was 3-5. Mortality reported was 11.5% (n=24), out of which 75% (18/24) was in patients with cerebrovascular disease.

Temporal Relation of Neurological Manifestations with Covid Infection

1. Short-Term (<1 month)

Majority of the patients with neurological manifestations presented during this period (60%, n=125). Mean age was 59 + 15 years with male predominance (72%). More than half (59%) of these patients had a cerebrovascular disease, followed by neuromuscular disorders (14%, n=17) and neuropsychiatric disorders (10%, n=13). Interestingly, all the patients with unexplained encephalopathy presented during this period. Mortality was the highest during this period (18.4% of total patients during this

period, 23/125), which comprised of 96% of the total mortality (23/24). Mean mRS of the discharged patients was 3.

Among cerebrovascular disorders, ischemic stroke was the most frequently seen type (77%, n=57), followed by hemorrhagic stroke (15%, n=11), and CVT (5%, n=4). All the mortality within this group occurred within the first month (n=18; ischemic stroke, 13; hemorrhagic stroke, 5). No mortality was seen in patients with CVT.

Among neuromuscular disorders (n=14), 41% (n=7) were diagnosed with a myopathy (3 of them also had an accompanying neuropathy). GBS was seen in 4 (24%) patients, 3 had AIDP and 1 had AMSAN variant of GBS. Most of the patients with severe headache (9 out of 10), CNS infection (5 out of 6), unexplained new-onset seizures (6 out of 7) with one having status epilepticus, and neuropsychiatric manifestations (13 out of 26) also presented during the short-term period (Table 2).

2.Medium-Term (2-3 months)

Sixty-two patients presented within this period having a male predominance (71%). Mean age was younger than the previous (short-term) group, 47 + 16.7 years. Neuromuscular manifestations (32%, n=20) were the most common in this group, followed by neuropsychiatric manifestations (19%, n=12), cerebrovascular diseases (14.5%, n=9), myalgia or musculoskeletal pain (14.5%, n=9), and vertigo, hearing problems or tinnitus (14.5%, n=9). All the patients with myalgia and musculoskeletal pain in our study presented during the medium-term period. Interestingly, only one patient presented with new-onset seizures or severe headache. Mortality was only seen in 2% (compared to 18% in the short-term period). Mean mRS of the discharged patients was reported to be 2 (vs. 3 in short-term).

Among neuromuscular manifestations, 30% had myopathy (one had accompanying neuropathy), and 25% had GBS (all AIDP variant). 15% of the patients (n=3) each had diagnosed with Bell's palsy or meralgia paresthetica, which were not seen during the short-term period. One-third of the patients with movement disorders, ataxia, and memory issues presented within this period (Table 2).

3.Long-Term (>4 months)

Neurological manifestations were seen in 21 patients during this period. This group had a younger mean age on presentation (44.7 + 17.7 years) and a mild female predominance (52%). Neuromuscular disorders (33%, n=7) were the most common manifestation followed by cerebrovascular diseases (19%, n=4), fatigue / malaise (9.5%) and anosmia/dysgeusia (9.5%). Bell's palsy was seen in 4 out of 7 (57%) patients with neuromuscular disorders. Only one patient presented with psychiatric manifestations. No patient presented with severe headache, myelitis, or myalgia. No mortality was seen. Mean mRS was 1.6 (Table 2).

Approximately 40% (83 out of 208) of our patients presented after one month of covid infection. The long-term patients differed from the short-term patients by a mean younger age on presentation (44.7 vs. 59 years), female predominance (52% vs. 28%), higher asymptomatic covid infection (29% vs. 14%), better clinical outcomes (mean mRS of 1.6 vs. 3), and low mortality (0 vs 18%). These patients also required less intubation (5% vs. 22%), BiPAP use (10% vs. 29%), supplemental oxygen requirements (38% vs 75%), decreased steroid use (29% vs. 72%), and less antiviral drug administration (14% vs. 38%) during the acute covid infection.

Table 2: The Temporal Relationship of Neurological Disorders in Covid Patients				
Time Duration since Covid Infection	**Total**	**<1 month**	**2-3 months**	**≥4 months**
Patients (n)	208	125	62	21
Cerebrovascular diseases • Ischemic Stroke • TIA • Hemorrhagic Stroke • CVST	87 (42%) • 69 (79%) • 2 (2%) • 11 (13%) • 5 (6%)	74 (59%) • 57 (77%) • 2 (3%) • 11 (15%) • 4 (5%)	9 (14.5%) • 9 (100%) • 0 • 0 • 0	4 (19%) • 3 (75%) • 0 • 0 • 1 (25%)
Neuromuscular disorders • Myopathy • Chronic Neuropathy • Neuropathy + Myopathy • GBS • Bell's Palsy • Meralgia Paresethetica • Others	44 (21%) • 10 (23%) • 4 (9%) • 5 (11%) • 8 (18%) • 7 (16%) • 3 (7%) • 7 (16%)	17 (14%) • 4 (24%) • 3 (18%) • 3 (18%) • 4 (24%) • 0 • 0 • 3 (18%)	20 (32%) • 5 (25%) • 1 (5%) • 1 (5%) • 4 (5%) • 3 (15%) • 3 (15%) • 3 (15%)	7 (33%) • 1 (14%) • 0 • 1 (14%) • 0 • 4 (57%) • 0 • 1 (14%)
Psychiatric (Depression, Anxiety, Insomnia, Psychosis, etc.)	26 (12.5%)	13 (10%)	12 (19%)	1 (5%)
Vertigo / Tinnitus / Hearing Problem	12 (6%)	2 (1.6%)	9 (14.5%)	1 (5%)
Anosmia / Dysgeusia	11 (5%)	4 (3%)	5 (8%)	2 (9.5%)
Headache	10 (5%)	9 (7%)	1 (1.6%)	0
Musculoskeletal Pain / Myalgia	9 (4%)	0	9 (14.5%)	0
Epilepsy / Seizures • Generalized onset ○ Status Epilepticus • Focal onset	7 (3%) • 6 (86%) ○ • 1 (14%)	6 (5%) • 5 (83%) ○ 1 • 1 (17%)	1 (1.6%) • 1 (100%) ○ 0 • 0	0
CNS Infection	6 (3%)	5 (4%)	0	1 (5%)
Myelitis	5 (2.4%)	2 (1.6%)	3 (5%)	0
Demyelinating Diseases	3 (1.4%)	1 (0.8%)	1 (1.6%)	1 (5%)
Movement Disorders	3 (1.4%)	1 (0.8%)	2 (3.2%)	0
Cerebellar Ataxia	3 (1.4%)	0	2 (3.2%)	1 (5%)
Dementia	3 (1.4%)	0	2 (3.2%)	1 (5%)
Fatigue / Malaise	3 (1.4%)	0	1 (1.6%)	2 (9.5%)
Abbreviations: CNS = Central nervous system; Covid = Coronavirus disease 2019; CVST = Cerebral venous sinus thrombosis; GBS = Guillain-Barre syndrome; TIA = Transient ischemic attack.				

DISCUSSION

Neurological manifestations differed between our different groups based on temporal profiles. Cerebrovascular diseases were overall the most common neurological diagnoses comprising of 42% (n=87) of the total patients. Majority of these patients presented within the short-term as compared to long term (59% vs. 19%). Other studies have also reported cerebrovascular diseases during the acute covid infection, with a median time ranging between 1 – 16.5 days from covid symptom onset to cerebrovascular disease.[1,2,7,8] Cerebrovascular diseases also constituted most of the mortality in our cohort (75%; 18/24). Similar poor outcome and a higher mortality was previously reported in covid patients with cerebrovascular disease.[1,9] Apart from cerebrovascular diseases, the neuropsychiatric manifestations (10%), headache (7%), and seizures (5%) were common in the short-term period. These manifestations may be related to the ACE2 receptor binding with alteration of renin-angiotensin system, direct viral CNS invasion, cytokine storm, or systemic and metabolic disturbances.[10]

The long-term patients, as compared to the short-term, had a higher percentage of neuromuscular disorders (33% vs. 14%), Bell's palsy (19% vs. 0%), fatigue and malaise (9.5% vs. 0%), dementia and cerebellar ataxia (5% vs. 0%, each). Among neuromuscular manifestation myopathy was the most common entity seen. A higher number of these patients had a history of intubation and a prolonged hospital stay. Multiple studies reported a higher incidence of myopathy, particularly the critical-illness myopathy, among the critical covid patients .[11,12]

Another important finding in our study was that three patients were diagnosed with meralgia paresthetica, all presenting during the medium-term. Case reports of meralgia paresthetica have been documented in covid patients most likely due to prone positioning.[13,14] Similarly, nine patients presented with myalgia, and all of them within the medium-term period, suggesting a post-infectious etiology. Myalgia and fatigue are proposed to be due to an underlying myopathy.[15] Unfortunately, an electrodiagnostic study (EMG/NCS) was not performed in our patients with myalgia or fatigue.

Headache is considered one of the commonest covid-related neurological manifestation but it was seen in only 5% (n=10) of our patients.[3,5,6] A similar percentage (4.2%) was reported in a recent study from Saudi Arabia.[1] We propose that the small number of headache cases in our cohort is due to the fact that most of the covid-related headaches are transient, mild, and do not require a neurological evaluation.

Pathophysiology of medium and long-term neurological syndromes following covid infection is largely elusive. However, the experience with previous pandemics and epidemics have suggested the following two main mechanisms (i) autoimmune mechanisms, and (ii) persistence of viral infection within the nervous system after the direct invasion, resulting in either continuous viral replication or virus may remain latent and reactive later with host immunosuppression.[16] The brain autopsy studies on covid patients have confirmed the presence of SARS-COV-2 RNA in more than half of the examined patients, with SARS-CoV-2 viral proteins also found in multiple cranial nerves.[17] Further studies will unravel the true pathophysiology of long-term neurological manifestations in covid patients.

The gender disparity in our study with a M:F of 2.25:1 can be explained by few observations. First, Fabiao et al. reported an increased severity of covid infection in men, with a relative risk of 1.29 (95%CI: 1.19 to 1.40; P<0.01) compared to the women, even when adjusted for age.[18] Second, cerebrovascular diseases are the most common neurological diagnoses in our study and they are epidemiologically more common in men. Third, in our society, men are more readily to consult a doctor for bothersome problems as compared to women.

There are many limitations to these findings. Number of patients have co-morbidities especially hypertension and diabetes which may lead to vascular and neuromuscular complications directly. Majority of patients were treated with steroids and antiviral medications which may potentially cause myopathy and behavioral complications. It is possible that some of these manifestations are not entirely attributable to covid infection. Data is also limited by retrospective nature of study. Patients with mild neurological manifestations may not report or it was not recorded in chart.

CONCLUSION

Neurological manifestations of covid infection may differ based on time duration since infection. Vascular complications are high in early period while neuromuscular manifestations are high in late period. Since this is a descriptive data, an association between neurological disorders and covid infection cannot be readily made, further studies are required.

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Authors' contribution:
Sajid Hameed; Concept, Data collection, data analysis, manuscript writing, manuscript revision
Bashir Soomro; Data collection, data analysis, manuscript writing, manuscript revision
Samar Iltaf; Data collection, manuscript writing, manuscript revision
Abdul Malik; Data collection, data analysis, manuscript revision
Anjum Farooq; Data collection, manuscript writing, manuscript revision
Alam Ibrahim Siddiqi; Data collection, manuscript revision
Safia Awan; Data analysis, manuscript writing, manuscript revision
Mohammad wasay; Concept, Data collection, data analysis, manuscript writing, manuscript revision