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3 **Neurological manifestations of paediatric acute COVID infections: A single centre**
4 **experience**
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7 Short running title: **Evaluation of neurological manifestations in children of a paediatric**
8 **COVID-19 center**
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Neurological manifestations of paediatric acute COVID infections: A single centre experience

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) usually leads to a mild infectious disease course in children, while serious complications may occur in conjunction with both acute infection and neurological symptoms, which have been predominantly reported in adults. The neurological complications in these patients vary based on patient age and underlying comorbidities. Data on clinical features, particularly neurological features, and prognostic factors in children and adolescents are limited. The present study provides a concise overview of neurological complications in pediatric COVID-19 cases.

Materials and Methods: The retrospective study reviewed medical records of all patients who were admitted to our hospital and were diagnosed with COVID-19 by real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay between March 11, 2020 and January 30, 2021. Patients with a positive PCR result were categorized into two groups: Out Patient Departments (OPD) patients and In Patient Departments (IPD).

Results: Of the 2,530 children who underwent RT-PCR during the study period, 382 (8.6%) were confirmed as COVID-19 positive, comprising 188 (49.2%) girls and 194 (50.8%) boys with a mean age of 7.14 ± 5.84 (range, 0-17) years. Neurological complications that required hospitalization were present in 34 (8.9%) patients, including seizure (52.9%), headache (38.2%), dizziness (11.1%) and meningoencephalitis (5.8%).

Conclusion: The results indicated that neurological manifestations are not rare in children suffering from COVID-19. Seizures, headaches, dizziness, anosmia, ageusia, and meningoencephalitis major neurological manifestations during acute COVID-19 disease. Although seizures were the most common cause of hospitalization in IPD patients, the frequency of meningoensalitis was quite high. Seizures were observed as febrile seizures for children under six years of age and afebrile seizures for those over 6 years of age. Febrile seizure accounted for half of all seizure children.

Key words: COVID-19, neurological manifestations, adolescence, infant, neonates

INTRODUCTION

Coronavirus disease (COVID-19) is a serious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease spread from a Chinese cluster to almost all other countries within a few weeks in late December 2019. Ever since, the COVID-19 outbreak has drastically changed the world's health concerns and the disease has rapidly spread worldwide, becoming the first pandemic of the 21st century. As of August 31, 2020, more than 25 million patients have been infected with the disease. (1).

Neurotropic and neuroinvasive capabilities of coronaviruses have been described in humans. Neurological problems found in patients with coronavirus infection include febrile seizures, convulsions, loss of consciousness, encephalomyelitis, and encephalitis. Moreover, neurological manifestations have also been reported in adults with COVID-19 (2). Despite the high number of people affected, data on clinical features and prognostic factors in children and adolescents are limited (1-3). The incidence curves of hospitalized patients increase with age, with most severe cases including adults aged over 80 years. Mortality follows this trend and mainly burdens the elderly, but rarely children (4-5). Therefore, children comprise a minority of hospitalized patients (6). Given the limited number of diagnosed pediatric cases and the low associated morbidity rate in children, the literature on pediatric COVID-19 cases is relatively scarce in comparison with the reports on affected adults. Neurological complications in children have only been reported in a few case reports and reviews (4-25). Mao L, Lu X et al. also reported that they did not observe neurological complications in pediatric patients during the acute COVID-19 period (23-24). Twenty-one studies/case series and five case reports include in study; non-specific neurological manifestations, presenting altogether in 16.7% cases and 1% were found to have been reported with definite neurological complications (13), to our knowledge, there has been no single-center study evaluating children and infants with COVID-19 and neurological complications. In our study, neurological complications requiring hospitalization were seen in 8.9%. The present study provides a concise overview of neurological complications in pediatric COVID-19 cases and aimed to investigate neurological complications in pediatric COVID-19 cases admitted to a tertiary care hospital.

MATERIALS AND METHODS

This retrospective, observational single-center study reviewed medical records of all patients who were admitted to our hospital and were diagnosed with COVID-19 between March 11,

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3 2020 and January 30, 2021. Our hospital is the only COVID-19 hospital in our city, a
4 scientific committee was established in our hospital to determine a management algorithm for
5 the detection and treatment of pediatric COVID-19 patients. Based on this algorithm, the
6 patients were classified as outpatients or inpatients.
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10 All the children admitted to our emergency department with fever, cough, or breathing
11 difficulties were initially evaluated in our COVID-19 examination rooms and then a detailed
12 examination consisting of contact history, underlying comorbidities, physical examination,
13 and laboratory and radiographic workup was performed. A suspected case was defined as an
14 individual presenting with the symptoms of COVID-19 and/or a contact history with an
15 individual diagnosed with COVID-19.
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22 All the patients had at least one nasopharyngeal swab specimen positive for SARS-CoV-2
23 nucleic acid on real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay,
24 either with a positive result for immunoglobulin G (IgG)/immunoglobulin M (IgM) antibodies
25 against SARS-CoV-2. Electronic medical records, serum and biochemical parameters
26 (complete blood count [CBC], creatinine kinase, lymphocyte count, C-reactive protein [CRP],
27 ferritin, and D-dimer), radiological examinations (cranial computed tomography [CT] and
28 magnetic resonance imaging [MRI], and electroencephalogram (EEG) findings were reviewed
29 for each patient. Demographic and clinical characteristics including age, gender, presenting
30 symptoms, and exposure history were retrieved from our hospital database and were recorded.
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38 Patients with a positive PCR result were categorized into two groups: (i) Out Patient
39 Departments (OPD) patients with neurological manifestations of nonspecific symptoms
40 shown that headache, dizziness, anosmia/dysgeusia, vertigo and (ii) Inpatient Departments
41 (IPD) patients with CNS disorders shown like that direct viral infection, disorders of
42 consciousness, refractor headache and dizziness, and seizures (afebrile/febrile seizures, and
43 acute symptomatic seizure).
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49 As per our hospital protocol, more than 3 month children; a diagnostic lumbar puncture is
50 performed at the time of admission in all patients presenting with $\geq 2/4$ of the classic clinical
51 features of meningitis including headache, fever, meningismus, and altered mental status, less
52 than 3 month children; not sucking, hypoactivity, lethargy, apnea, seizure, fontanel bloating,
53 vomiting, respiratory distress and body temperature changes restlessness, irritability, fever or
54 late sepsis. Patients with focal neurological deficits do not undergo lumbar puncture due to the
55 likelihood of space-occupying lesions and the risk of herniation after lumbar puncture and
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3 thus CT is performed in such patients. Cerebrospinal fluid (CSF) is sent to the laboratory for
4 standard investigations including Gram stain, India ink stain, bacterial culture, and
5 cryptococcal antigen. Pleocytosis of CSF was defined as a CSF a white blood cell count
6 (WBC) of over 5 cells/ μ L or neonatal term patients 20 cells/ μ L. CSF protein levels of >45
7 mg/dL, neonatal term patients 100 mg/dL were considered abnormal. CSF glucose levels of
8 <40 mg/dL, neonatal term patients 30 mg/dL were considered low. Suspected cases with no
9 positive RT-PCR results were excluded from the study.

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16 In this retrospective and non-invasive study, no experiments were conducted on the
17 participants. The study was registered in the database of our medical center (identifier:
18 2021/53) and an approval was obtained from the local ethics committee. A written informed
19 consent was obtained from each patient.

20 21 22 23 24 ***Statistical analysis***

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26 Data were evaluated using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.).
27 Descriptives were expressed as median and minimum-maximum for continuous variables and
28 as frequencies (n) for categorical variables. Categorical variables were compared using Chi-
29 square test or Fisher's Exact test. Multiple comparisons were performed using Kruskal-Wallis
30 test. A two-tailed p value of <0.05 was considered significant.

31 32 33 34 35 **RESULTS**

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38 Of the 2,530 children who presented with the symptoms of COVID-19 and/or a contact
39 history with an individual diagnosed with COVID-19 during the study period, 382 (8.6%)
40 were confirmed as COVID-19 positive, comprising 188 (49.2%) girls and 194 (50.8%) boys
41 with a mean age of 7.14 ± 5.84 (range, 0-17) years. No significant difference was observed
42 between the percentage of boys and girls ($p > 0.05$). Mean age was 8.12 ± 3.2 months in patients
43 aged less than one year, 3.2 ± 1.8 years in patients aged 1-5 years, 7.2 ± 2.8 years in patients
44 aged 6-10 years, and 14.2 ± 3.6 years in patients aged 10-17 years (Table 1). OPD and IPD
45 patients were detected in 259 (%67.8). Additionally, 34 (8.9%) patients had complications
46 that required hospitalization, including seizure (52.9%), headache (38.2%), dizziness (11.1%)
47 and meningoencephalitis (%5.8). Figure 1 presents the flow-chart of the study. Among the 54
48 neonates who were admitted to the neonatal intensive care unit (NICU) with maternal contact
49 for 0-30 days, 14 patients were diagnosed positive for SARS-CoV-2 infection and only one
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3 neonate was diagnosed with meningoencephalitis. No neurological symptoms were detected
4 in other patients.
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7 Out Patient Departments patients included headache, dizziness, anosmia/dysgeusia, and
8 ageusia/dysgeusia. Neurological complications of OPD patients were detected in 225 (58.9%)
9 patients. Of these, headache was the most common presenting symptom (23%) and the rate of
10 hospitalization due to headache was 38.2%. All the patients with headache were adolescents,
11 who had a mean age of 14.2 ± 3.6 (range, 4-17) years. In severely symptomatic children who
12 received inpatient care, cranial MRI findings were normal and the longest hospitalization
13 period was 5 days. These patients benefited from hydration and antipyretic and analgesic
14 treatment. The second most common nonspecific symptom was dizziness (14.3%), followed
15 by anosmia (10.2%), and ageusia/dysgeusia (7.3%). No patient was hospitalized due to
16 anosmia and ageusia/dysgeusia. Dizziness was observed in 14.3% of the patients, and 0.7% of
17 them were hospitalized. The patients hospitalized due to dizziness showed a good response to
18 diphenylhydantoin and hydration therapy.
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29 Inpatient Departments patients were detected in 34 (8.9%). Of the 18 (4.7%) patients who
30 presented with seizure as the first symptom, 9 (2.3%) of them had experienced their first
31 febrile seizure. Of the children who were otherwise healthy and presented to our clinic after
32 their first seizure, 1.8% of them had simple febrile seizures and 0.5% of them had complex
33 febrile seizures. Five (1.3%) patients who were being followed up with a diagnosis of
34 epilepsy presented with an increased frequency of seizures (Lennox–Gastaut syndrome (n:2),
35 Dravet Syndrome (n:2), and benign rolandic epilepsy (n:1). Two patients who presented with
36 seizure as the first symptom had no fever before or during the follow-up. ~~Cranial and spinal.~~
37 No seizure activity was detected on EEG. Patients diagnosed as having Todd's paralysis had
38 no seizures throughout the follow-up period.
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47 Two patients who presented with meningoencephalitis (a 4-day old and three months old)
48 were also confirmed positive for SARS-CoV-2 on RT-PCR test. Cranial MRI was normal.
49 The CSF examination revealed the following values: WBC $1,190 \text{ cells/mm}^3$ (89% segmented
50 neutrophils and 9% lymphocytes), glucose level 35 mg/dL, and protein level 352
51 mg/dl. Streptococcal pneumonia and SARS-CoV-2 were detected in CSF culture. Phenytoin
52 loading and levetiracetam treatment twice daily were continued. Both contrast/noncontrast
53 cranial MRI were normal except for mild meningeal enhancement. The patients were
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3 discharged with full recovery after a meningoencephalitis treatment. No sequela occurred in
4 any patient.
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6 7 **DISCUSSION** 8

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10 Children with SARS-CoV-2 infection have different clinical manifestations and outcomes
11 compared to adults. Literature indicates that pediatric cases of SARS-CoV-2 infection are
12 remarkably rare and only a few cases have been reported thus far (1-3). The present study
13 investigated the frequency and characteristics of neurological complications in pediatric
14 COVID-19 cases. All the patients, including those with comorbidities, recovered fully and
15 had no sequelae at the time of hospital discharge. Additionally, neurological symptoms were
16 detected in 67.8%, the rate of hospitalization due to neurological complications was 8.9%, and
17 the rate of children that were positive for SARS-CoV-2 infection and had seizures was 4.7%.
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24 Clinical symptoms of COVID-19 show a wide variation across age groups and the rate of test
25 positivity decreases as the age decreases (5-9). Although, several factors have been proposed
26 regarding the lower effect of COVID-19 in children, there is no substantial evidence to
27 support any of these mechanism (18-21).. SARS-CoV-2 has a neuroinvasive potential since
28 36% of adult patients have been reported to have a variety of neurological manifestations
29 including headache, vertigo, acute cerebrovascular events, and changes in mental status (22).
30 A previous study evaluated 171 Chinese children with COVID-19 infection and did not detect
31 neurological involvement in any patient (23). In recent reports published in Western
32 countries, nonspecific headache has been reported as the only neurological symptom in
33 COVID-19-infected children, accounting for 4-28% of all cases (24). A study by the CDC
34 COVID-19 Response Team evaluated a total of 2,572 pediatric patients with a mean age of 11
35 years, among whom 91% of the patients were infected with COVID-19 through family cluster
36 infection and 57% of them were male. Of the 291 (11%) symptomatic children, 81 (28%)
37 children were followed up due to headache (15). Pairi et al. reported that 4%, Cura et al.
38 detected headache in 9.1%, of the patients (14, 25). In our study, headache was the most
39 common nonspecific presenting symptom and the headache frequency increased with age.
40 Moreover, the frequency of headache in symptomatic COVID-19 pediatric patients was
41 23.0% and the rate of hospitalization due to headache was 38.2%. Hypogeusia and hyposmia
42 are frequently reported in COVID-19 cases and have become a cardinal factor in the early
43 diagnosis of the disease (26, 27). Moreover, anosmia and ageusia have been 30–80% cases
44 and have been rarely reported in children as well. Cura et al. detected anosmia and ageusia in
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3 5% of the patients (25). Despite these varying rates, in our study, we found a lower frequency
4 of anosmia/ageusia (17.5%) among OPD patients. The frequency of dizziness has been less
5 studied in children. According to the CDC COVID-19 Response Team study, 23% of
6 pediatric patients required follow-up due to dizziness (15). In our study, dizziness and
7 hospitalization of dizziness were detected in 14.3% and 8.8% of our patients.
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12 Febrile seizure is the most common seizure in childhood and is defined as seizures occurring
13 in children aged older than 6 month associated with a febrile disease not caused by an
14 infection of CNS, without previous neonatal seizures or a previous unprovoked seizure, and
15 not meeting the criteria for other acute symptomatic seizures and its incidence varies between
16 2-5% (28-30). Even so, these children are at risk of developing seizures and encephalopathy,
17 particularly those suffering from severe disease (13). A review by Panda et al. evaluated 21
18 studies and case reports and reported the prevalence of nonspecific neurological
19 complications as 16.7% and the prevalence of specific neurological complications
20 (encephalopathy, seizure, meningeal irritation) as 1%. Although there are only a limited
21 number of studies reporting on neurological complications, these complications remain a
22 serious problem (13). A previous study reported that all the seizures were in the form of acute
23 symptomatic seizures and occurred during febrile episodes while only one seizure was in the
24 form of status epilepticus (13). To our knowledge, definite demographic variables have not
25 been reported for children with nonspecific/specific neurological complications in other case
26 reports and few small case series. In a multi-center Italian study investigating SARS-CoV-2
27 infection in children and adolescents, Garazzino et al. evaluated 168 pediatric patients and
28 reported the prevalence of afebrile and febrile seizures as 1.8% and 1.2%, respectively (12).
29 In contrast, the CDC COVID-19 Response Team study reported that no serious neurological
30 complications occurred in their patients, except for nonspecific neurological symptoms (15).
31 In our study, 4.7% of children that were positive for SARS-CoV-2 infection had seizures,
32 among whom 1.8% of them had febrile seizures, 1.3% of them had acute symptomatic
33 seizures, 0.05% of them had afebrile seizures, and 0.05% of them had meningoencephalitis.
34 The rate of hospitalization due to seizure was 52.9%. Literature indicates that pediatric
35 COVID-19 patients aged over six years who present with afebrile seizures should not be
36 considered epileptic since their seizures may show a wide variety of clinical manifestations as
37 in seizures in pediatric practice (35). In our patients, seizures resolved after the administration
38 of antiepileptic therapy. And a 3-month-old meningoencephalitis with pediatric patient with
39 an incomplete vaccination status was families should be asked.
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3 As recommended by pediatric associations, it is essential to include the SARS-CoV-2 PCR
4 test in the workup of infants aged less than 3 months (47). In neonatal children, SARS-CoV-2
5 test positivity is remarkably low and the most common presenting symptoms include seizure,
6 hypotonicity, and encephalopathy (32,48-52). Stafstrom et al. reported several cases with
7 neurological symptoms of COVID-19 in the neonatal and infantile period on a case-by-case
8 basis (32). In our study, a four-day-old infant with positive maternal contact who had seizures
9 and hypotonia was not detected with SARS-CoV-2 in CSF by RT-PCR, while neuroimaging
10 and lumbar puncture findings were suggestive of meningoencephalitis.
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18 In conclusion, the results indicated that neurological manifestations are not rare in children
19 suffering from COVID-19, particularly in those suffering from severe disease who are at
20 increased risk of developing nonspecific neurological symptoms, febrile/afebrile seizures, and
21 meningoencephalitis. We suggest that COVID-19 should be investigated in the etiology of
22 febrile seizures. Pediatric COVID-19 patients aged over six years who present with afebrile
23 seizures should not be considered epileptic since their seizures may show a wide variety of
24 clinical manifestations as in the seizure semiology in epileptic patients. We also suggest that
25 acute symptomatic seizures in COVID-19-infected children who present with temporal lobe
26 epilepsy can be managed successfully with antiepileptic drugs with favorable short-term
27 outcomes. Care should be taken against COVID-19 meningoencephalitis in infants younger
28 than 3 months, particularly in those with an incomplete vaccination status.
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38 Our study was limited since it was a single-center study and had a relative small sample size
39 for the determination of the frequency of neurological findings in pediatric COVID-19
40 patients. Further studies evaluating pediatric patients with different neurological clinical
41 symptoms are needed. Available literature about neurological manifestations of COVID-19 is
42 rather limited; therefore, our study will hopefully contribute to increased alertness for both
43 neurologists and non-neurologists about the manifestations of pediatric COVID-19 patients.
44 Further studies involving larger numbers of patients with various neurological complications
45 are needed to provide precise information regarding the treatment and semiology of seizures,
46 EEG, lumbar puncture, and cranial MRI findings, and long-term prognosis.
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We devote this study to all the people in our region who have suffered the consequences of COVID-19 and to all the healthcare workers in our hospitals who have shown extraordinary effort in the fight against this terrible disease.

Conflict of interest

There is no conflict of interest among the authors. We would like to thank all the staff of our hospital for their contributions to patient follow-up and care during the pandemic process.

Ethical approval

The study was approved by the Public Health Agency, Turkey Ministry of Health and by Kanuni Training and Research Hospital Ethics Committee, Trabzon, Turkey (Approval No: 2021/53).

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Table 1. Demographic and clinical characteristics

Parameters	Total	%	
Age			
Mean age (years)	7.14±5.84	NA	
Age groups			
<1 year	71	18.5	
1-5 years	104	27.2	
6-10 years	76	19.9	
10-17 years	131	34.2	
Total (n)	382	100	
Gender			
Female	188	49.2	
Male	194	50.8	
OPD patients	225		
IPD patients	34		
Headache	88	23.0	
Hospitalized due to headache	13	3.4	
Mean age (years)	14.2±3.6 (4-17)		
Anosmia	39	10.2	
Ageusia	28	7.3	
Dizziness	55	14.3	
Vertigo / nausea	15	3.9	
Hospitalized due to dizziness	3	0.7	
Seizures	18	4.7	
Febrile seizure	9	2.3	
Acute symptomatic seizure	5	1.3	
Afebrile seizure	2	0.5	
Meningoencephalitis	2	0.5	

COVID-19 RT-PCR test was performed, Out Patient Departments (OPD) patients and In Patient Departments (IPD), n: patients

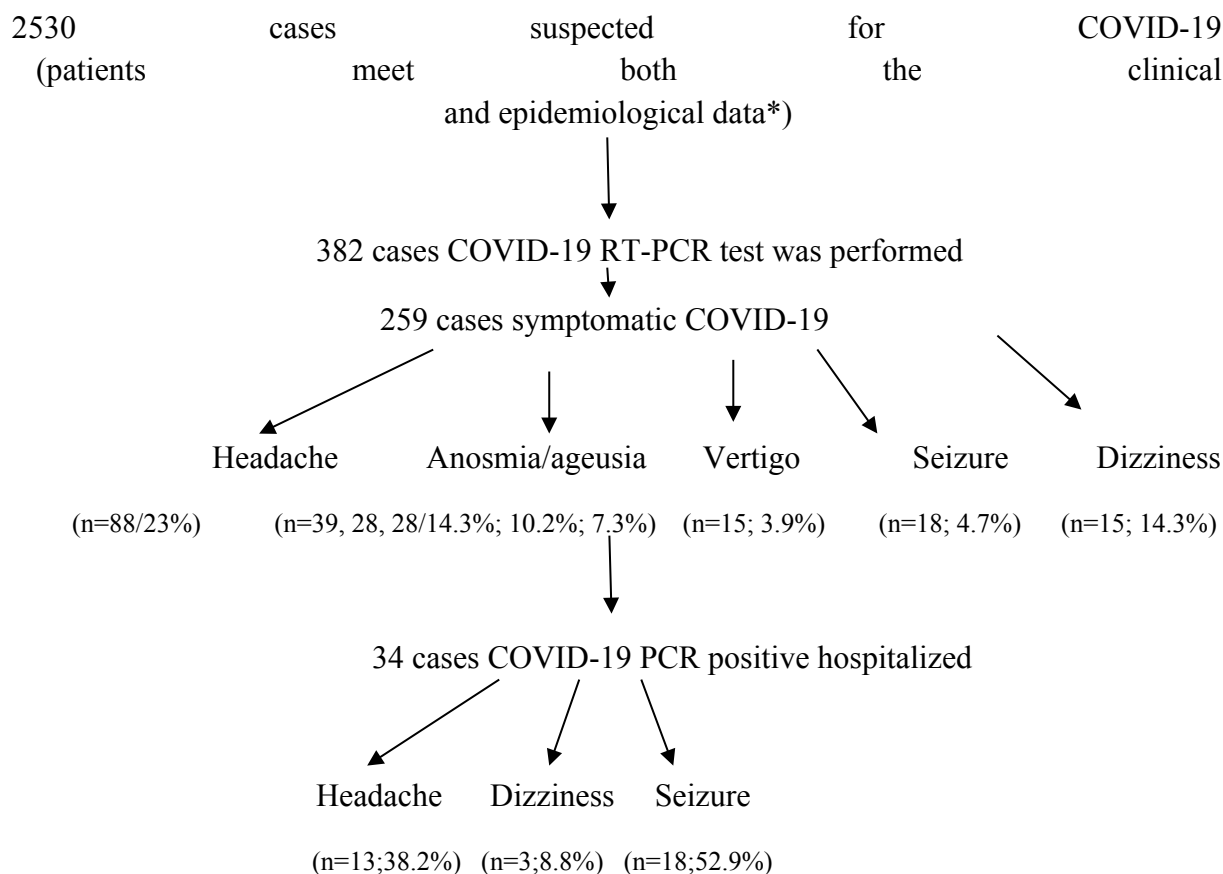


Figure 1. Flow-chart of the study

*Clinical: Acute respiratory infection of any severity, including at least one of shortness of breath, or cough (with or without fever), or fever with no other symptoms. Epidemiological: In the 14 days travel to abroad, or contact with a confirmed COVID-19 case