Comparison of Clinical Findings in SARS-CoV-2 with Other Respiratory Viruses in Critically Ill Children during the COVID-19 Pandemic

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Abstract

Objective: The aim of this study was to compare the clinical and laboratory findings in SARS-CoV-2 (COVID-19) with those of other respiratory viruses in critically ill children.

Methods: It is a single center retrospective descriptive study conducted in a 32-bed pediatric intensive care unit (PICU). Our study was performed in Ankara City Hospital, Ankara, Turkey, between March 1, 2020, and March 1, 2021. Demographic and clinical characteristics of the patients were collected, and we recorded antibiotic use, antiviral treatments, respiratory and extracorporeal supports, PICU stay, and survival rates.

Results: A total of 202 pediatric patients who tested positive for either COVID-19 or for another respiratory virus (RVP) were included in the study. Seventy-two patients were COVID-19 positive. The median age of COVID-19 positive patients and RVP positive patients was 97 and 17 months, respectively. Hypoxia was much more common in patients with RVP than in COVID-19 patients. Low oxygen saturation in arterial blood (SaO_2), increased oxygen saturation index (OSI), and fraction of inspired oxygen (FiO_2) needs were more significant in RVP patients than in COVID-19 patients. Respiratory support therapies, such as high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV), were used more frequently in RVP patients than in COVID-19 patients.

Conclusion: It is important to distinguish between Covid-19 and RVP cases in order to prioritize intensive care needs in these patients. In addition, non-Covid diseases should not be left aside in the pandemic and appropriate care should be provided to them.

Summary

COVID-19 originated in Wuhan, China, at the end of 2019 and has since spread around the world. During the key period of the pandemic from March 1, 2020, to March 1, 2021, the pediatric intensive care unit registered a total of 72 patients testing positive for SARS-CoV-2 and 130 patients positive for RVP on the respiratory virus panel. In this single-center study, we compared the clinical differences and course of the disease in pediatric intensive care patients infected with SARS-CoV-2 with patients diagnosed with respiratory tract viruses during the COVID-19 outbreak. Unlike previous studies, this is the first to compare the clinical manifestations of COVID-19 with other respiratory pathogens requiring intensive care. Respiratory support therapy, such as high-flow nasal cannula (HFNC) and non-invasive ventilation, was prescribed more frequently in RVP patients than in COVID-19 patients. In our study, low oxygen saturation in the arterial blood (SaO_2), increased oxygen saturation index (OSI), and increased fraction of inspired oxygen (FiO_2) requirements were more significant in RVP patients than in COVID-19 patients. In parallel, the need for mechanical ventilation was higher in RVP patients than in COVID-19 patients. Therefore, we believe that RVP patients should be followed more carefully during this pandemic period.

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1. INTRODUCTION

COVID-19 disease, which emerged in Wuhan, China, at the end of 2019 and spread all over the world, is caused by severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) [1]. As of February 22, 2020, COVID-19 had been seen in more than 111 million people worldwide and resulted in the death of approximately 2.5 million people, according to World Health Organization (WHO) data [2]. While COVID-19 is asymptomatic in most infected people, 10–15% of patients require oxygen therapy in an intensive care unit, and 5% need mechanical ventilation [3]. Mortality rates differ among countries. According to the WHO, the worldwide average mortality rate is 2.2% [2].

Souza et al reported that only a small part of patients had severe (2.1%) or critical (1.2%) disease. Most of the COVID-19 patients had a mild disease or asymptomatic. The most common symptoms were fever (47.5%), followed by cough (41.5%), nasal symptoms (11.2%), diarrhea (8.1%), and nausea/vomiting (7.1%). One hundred forty-five (36.9%) children in their study were diagnosed with pneumonia, and 43 (10.9%) children were reported to have upper respiratory tract infections. Decreased lymphocyte counts were reported in 12.9% of cases [4]. RT-PCR is the best test we have for diagnosing SARS-Cov2. [5].

In this single-center study, we compared the clinical differences and disease course of pediatric intensive care patients infected with SARS-CoV-2 with those of patients with respiratory tract viruses during the COVID-19 outbreak.

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2. MATERIALS AND METHODS

2.1. Study design

This study was a retrospective single-center descriptive observational study in a 32-bed pediatric intensive care unit (PICU) in Ankara City Hospital, Ankara, Turkey, between March 1, 2020, and March 1, 2021. Real-time reverse transcriptase PCR (RT-PCR) tests were performed to detect viral infection causes. Patients whose age was between one month and 18 years old were included in the study. Patients who had upper respiratory tract symptoms but were not found to have any virus by PCR were not included in the study. Patients were divided into two groups: SARS-CoV-2 positive (Group 1) and RVP positive (Group 2). Patients with positive COVID-19 serology but negative PCR tests were excluded. Patients with positive serological findings for both COVID-19 and RVP PCR were also excluded from the study.

Swabs were taken from the nasopharyngeal region and throat for the RT-PCR test from patients with respiratory symptoms. Patients with positive RT-PCR tests for SARS-CoV-2 or any of the other viruses were included in the study. The method targets the RNA-dependent RNA polymerase (RdRp) gene using the Bio-Speedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey) for SARS-CoV-2. Upper RVP was studied with five-tube multiplex for detection of influenza A virus; influenza A (H1N1) virus (swine-lineage); influenza B virus; human rhinovirus; human coronaviruses NL63, 229E, OC43, and HKU1; human parainfluenza viruses 1, 2, 3, and 4; human metapneumovirus A/B; human bocavirus; human RSV A/B; human adenovirus; enterovirus; human parechovirus; and *Mycoplasma pneumonia*. Internal control used Fast track resp 21, and multiplex real-time PCR for detection of pathogen genes by TaqMan® technology (Rotor-gene, California, USA) was used to analyze the patients' nasopharyngeal swab samples. If at least one of these tests

was positive, it was accepted as significant. The flow chart of study was presented in Figure-

1.

2.2. Data collection

Patient demographic information, comorbidities, symptoms, indications for admission

to PICU, and physical examination findings (whole body examination, neurological,

respiratory, and circulatory systems) were recorded from patient files and computer records.

Laboratory examinations taken from the submissions were recorded, including complete

blood count (total lymphocyte count, absolute lymphocyte count, hemoglobin, and platelet

count), coagulation parameters (PT, aPTT, INR, fibrinogen, and D-dimer), C-reactive protein

(CRP), procalcitonin, troponin I/T, brain natriuretic peptide, and ferritin levels. Abnormal

values were identified according to age group and normal range [6].

2.3. Treatments and organ support methods

Antibiotics and antiviral drugs administered to the patients were recorded. Respiratory

support methods, including high-flow nasal cannula (HFNC) oxygen therapy, non-invasive

ventilation (NIV), and invasive mechanical ventilation, were recorded in patients who

received respiratory support. Complications that developed initially and during follow-up

were noted.

Organ failure in patients was defined as respiratory, circulatory, neurological, renal,

hepatic, and hematologic failure. Multiple organ dysfunction syndrome (MODS) was defined

as acute organ failure of two or more systems [7]. Extracorporeal treatments applied to

patients (renal replacement therapy RRT; total plasma exchange TPD; and extracorporeal

membrane oxygenation ECMO) were recorded. The Pediatric Risk of Mortality Score

(PRISM Ⅲ) and the Pediatric Logistic Organ Dysfunction (PELOD2) scores were calculated in all patients.

The duration of each patient's stay in the PICU and respiratory and/or neurological sequelae were recorded upon discharge from the unit. Mortality rates by group and the main factors affecting mortality were identified.

2.4. Statistical analysis and method

First, the descriptive properties (mean, median, number, and percentage) of the variables were determined. The numeric variables were checked for fit with normal distribution. While comparing the two groups, the Student's t-test was used for numeric variables with normal distribution. The Mann-Whitney U test was performed for numeric variables not normally distributed. The chi-square test was performed to compare categorical variables. A p-value < 0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS) version 17 (Chicago, Illinois, USA) software was used to analyze the results.

2.5. Ethics committee approval

Ethics committee approval was granted by the ethics committee of Ankara City Hospital (July 14, 2021; E2-21-728).

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3. RESULTS

A total of 202 pediatric patients who tested positive for COVID-19 or RVP were included in the study. Seventy-two were positive for COVID-19, and 130 were positive for another viral infection revealed in the RVP. Respiratory Syncytial Virus was the most common pathologic agent in non-COVID patients. Rhinovirus was the second common respiratory tract virus in the non-COVID group. Figure 2 presents a pie chart showing the distribution of RVP agents detected in our study. The median age of all patients was 24 months (interquartile range, IQR, was 7–96 months). COVID-19 patients were older than other group. The median age of COVID-19 patients was 96 months (IQR 17–156 months), median age of other group was 17 months (6–48 months) ($p < 0.001$). There was no significant gender difference between groups (p = 0.431). The PRISM and PELOD scores were higher in COVID-19 cases than in RVP cases. (PRISM p=0.026, PELOD $p < 0.001$, respectively). The OSI was 6 (IQR 3.6–12) in total, and a statistically significant difference was observed between COVID-19 patients (3.65; IQR 0–8.35) compared to RVP patients (7.75; IQR 5–13) ($p = 0.016$). Shortness of breath and fever were statistically significantly higher in the RVP group than in the COVID-19 group.

Hypoxia was defined as oxygen saturation values <92% within the first 48 hours of admission. Fifty-one (25.8%) patients were hypoxemic at the time of admission. There was no statistically significant difference in terms of hypoxemia between patients infected with COVID-19 ($n = 15$; 21.0%) and other viral agents ($n = 36$; 27.8%) ($p = 0.261$). The maximum FiO_2 level patients required was lower in COVID-19 patients. Median FiO2 level of COVID-19 patients was 40 (IQR 30–60), median FiO2 level of other group was 50 (IQR 40–60). This difference was statistically significant (p< 0.003). In the physical examination,

crackles and rhonchi were more common in the RVP patients than in COVID-19 cases; this difference was also statistically significant ($p < 0.001$).

In terms of organ failure, respiratory failure was observed in 164 (81.3%) of total cases. While 120 (92.4%) patients were in the RVP group, the other 44 (61.7%) were in the COVID-19 group. Thus, it is apparent that the rate of respiratory failure in RVP patients was significantly higher statistically ($p < 0.001$).

3.1. Medications and supportive treatments

One patient was treated with ECMO, while seven received therapeutic plasmapheresis treatment. No statistically significant difference was found between the two groups in terms of respiratory support treatment ($p = 0.170$). The medication and supportive treatments applied to the patients are given in Table 2.

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4. DISCUSSION

Since it began in December 2019, the COVID-19 pandemic has affected populations all over the world. COVID-19 tends to be milder in children than in adults [8]. It has been shown that most children testing positive for COVID-19 are asymptomatic, and only 2% of pediatric patients require intensive care [9]. However, a study conducted in Germany found that the viral loads of patients in the 0–6 age group were not significantly different from those of adults. Therefore, it can be assumed that children, even if they are less symptomatic, can be as contagious as adults [10]. COVID-19 is spreading rapidly around the world, and new mutations are emerging continuously. Most pediatric cases of COVID-19 occur in children under three years of age, with a slight male predominance [11]. Both RVP factors and COVID-19 can be seen at any age. In our study, patients positive for RVP were mostly infants, while patients positive for COVID-19 were mostly young children. In line with other studies in the literature, the median age of our COVID-19 patients was similar [12]. Another notable demographic feature was the lack of a significant gender difference between groups.

Children in all age groups are susceptible to SARS-CoV-2 infection, but their clinical symptoms are milder than in adults. Indeed, the clinical symptoms observed in our study were similar to those in other recent studies of mostly pediatric patients [13,14,15]. The most common symptoms reported in our two groups were respiratory distress (76%), fever (55.8% and 41.5%), and cough (40.8 and 48.5%). In our study, the symptoms in COVID-19 patients (cough, shortness of breath, physical examination findings, crackles, and rhonchi) were milder than those in RVP patients. Thus, RVP pathogens were found to cause more severe diseases in children. In some cases, patients are admitted to the PICU with severe shortness of breath,

cyanosis, fever, and cough, and even respiratory and circulatory failure may occur during their stay in the hospital [12]. The results, including those of our study, show that COVID-19 symptoms in children follow a similar pattern, albeit much less severe than in adults. Approximately 25% of patients in our study had hypoxia and were given oxygen support, but the RVP patients needed much more oxygen therapy than COVID-19 patients. Respiratory and circulatory failure is more common in RVP patients than in COVID-19 patients, indicating that non-COVID viruses are more virulent in children, increasing the rates of morbidity, mortality, and PICU hospitalizations. The rate of comorbidity was approximately 59% in both groups, and the need for conventional mechanical ventilation was higher in our RVP patients than in our COVID-19 patients (43.8% vs. 32.1%, respectively). Nevertheless, the mortality rate was higher in our COVID-19 patients (4.9% vs. 0.9%). The fact that PRISM and PELOD scores, which indicate the severity of the disease, were significantly higher statistically in the COVID-19 patients explains the mortality rates. On the other hand, the higher rate of respiratory failure and higher FiO_2 needs in RVP patients indicate that the difference in mortality rates between the two groups was impacted by organ failure other than respiratory failure. The need for invasive and aggressive treatments, such as immune plasma, RRT, plasmapheresis, and ECMO, especially in COVID-19 patients, explains why the prognosis of the disease is worse than that of RVP patients and the mortality is higher. Our study is significant since it only includes patients hospitalized in the PICU, and extensive studies have not been conducted previously on patients in PICUs.

Our abnormal laboratory findings in children infected with COVID-19 are consistent with recently published studies [16,17]. In our study, no significant difference was found between the laboratory data of COVID-19 and RVP patients. Although the frequency of leukopenia and lymphopenia was more common in COVID patients than in RVP patients, the difference was not statistically significant (COVID-19 - 21% and 50% and RVP - 16.7% and

40.8%, respectively). For example, the frequency of lymphopenia in COVID-19 patients in our study was similar to that of Zheng et al [16]. In our study, some laboratory values such as leukopenia, lymphopenia, anemia, thrombocytopenia, increased CRP and high ferritin levels were observed more frequently in COVID-19 patients than in RVP patients.

Unfortunately, at this stage, there is no consensus on the specific or proven medical treatment of COVID-19 in pediatric patients. As a supportive treatment, free oxygen was started in approximately half of the patients, antiviral treatment in half of the total patients in severe cases, and prophylactic antibiotics in 94.2%. Antibiotic and/or antifungal treatment was initiated in cases of nosocomial infection/secondary infection. As soon as the viral agent was detected, empirical treatment was discontinued in patients for whom bacterial or fungal infection was not suspected. No specific antiviral effect has been proven based on the currently available data. Hydroxychloroquine and chloroquine have been shown to have anti-SARS-CoV-2 activity in some in vitro studies [18]. A clinical study of lopinavir/ritonavir (protease inhibitors that disrupt virus formation) showed no improvement in 28-day mortality [19].

Our aim in starting early treatment with these drugs was to prevent disease progression and reduce the need for mechanical ventilation. Clinical indications for starting virus suppressive therapy (hydroxychloroquine or lopinavir/ritonavir) were patients with severe pneumonia, pediatric acute respiratory distress syndrome (PARDS), critically ill patients (shock, thrombocytopenia-associated multiple-organ failure (TAMOF), disseminated intravascular coagulation (DIC), or hemophagocytic syndrome, and suspected or confirmed COVID-19. Intravenous immunoglobulin, steroids, plasmapheresis, and RRT were also applied to these patients. We administered convalescent plasma therapy to seven of our severe PARDS patients, and three of them died. Veno-venous ECMO was applied to one patient with Stevens-Johnson syndrome and severe PARDS; unfortunately, he died three weeks later.

None of the treatments has shown a clear benefit in treating COVID-19, and the WHO does not recommend any specific treatment for children [20,21]. Respiratory support therapy, such as HFNC and NIV, was preferred for RVP patients more frequently than for COVID-19 patients because RVP factors cause more severe respiratory failure and an increased risk of aerosol formation and contamination than COVID-19 does.

In our study, low oxygen saturation in the arterial blood (SaO_2), increased OSI, and increased FiO_2 needs were more significant in RVP patients than in patients with COVID-19. Parallel to these, the need for mechanical ventilation was higher in RVP patients than in COVID-19 patients.

This study has certain limitations, such as being single-center and retrospective. We used drugs like hydroxychloroquine etc on a case-to-case basis during the epidemic when the evidence for usage was still evolving. In addition, the RT-PCR results were used as a stand-alone reference standard. Not all our cases could be tested for COVID-19 antibodies.

In conclusion, our results showed that the clinical picture of RVP agents in children is more severe than COVID-19. Therefore, we think that RVP patients should be followed more carefully during this pandemic period. RVP should be studied in conjunction with the RT-PCR tests in patients with suspected COVID-19. It caused severe PARDS in both groups. COVID-19 PCR and RVP should be studied further, and supportive therapy should be given until the diagnosis is confirmed.

There are numerous publications in the literature on the evaluation of the clinical and epidemiological findings of COVID-19. Unlike previous studies, this is the first to compare the clinical signs of COVID-19 with other respiratory pathogens requiring intensive care.

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Table 1. Demographic and clinical characteristics of patients infected with COVID-19 and other seasonal viruses.

Parameter and Tests	Total (n:202)	COVID-19 (n:72)	RVP(n:130)	P value
Demographic characteristics				
Age (month) *, median(IQR)	24(7-96)	96(17-156)	17(6-48)	**<0,001**
Male, no.(%)**	120(59,4)	39(54,1)	81(62,3)	0,431
severity of the disease				
PRISMⅢ* score	7(3-12,5)	8(4-14)	6(3-12)	**0,026**
PELOD2*score	2(1-11)	10(4-11)	1(0-10)	**<0,001**
OSI*	6(3,6-12)	3,65(0-8,35)	7,75(5-13)	**0,016**
FiO2*	50(40-60)	40(40-60)	50(40-60)	**0,003**
Clinical characteristics				
contact history**	45(30,7)	30(41,6)	15(11,5)	**<0,001**
Comorbidity**	116(57,4)	39(54,1)	77(59,2)	0,860
Cough**	80(39,6)	25(34,7)	55(42,3)	0,335
Fever**	96(47,5)	40(55,5)	56(43,1)	0,104
Shortness of breath**	150(74,2)	42(58,3)	108(83,1)	**<0,001**
Low SpO2**(<92%)	51(25,2)	15(20,8)	36(27,7)	0,261
Crackles**	125(61,8)	33(45,8)	92(70,7)	**<0,001**
Rhonchi**	83(41,1)	18(25,0)	65(50)	**<0,001**
Leukopenia **	37(18,3)	15(20,8)	22(16,9)	0,096
Lymhopenia **	89(44,1)	36(50)	53(40,8)	0,130
Anemia**	110(54,5)	40(55,5)	70(53,8)	0,217
Thrombocytopenia**	46(22,8)	18(25)	28(21,5)	0,633
Elevated CRP*** (mean± SD)	81.49±97.30	85.46±80.47	78.72±107.96	0.700
Elevated Procalcitonin***, (mean± SD)	58.55± 45.5	66.10 ±45.1	51 ± 46.53	0.473
Elevated Ferritin***, (mean± SD)	2401,68±11431,36	2902.14 ±14215.15	1760.07 ±6426.62	0.615
Elevated D- dimer***, (mean± SD)	1078.82±1265.36	1005.52 ±1291.06	1118.65 ±1264.42	0.724
Elevated PT**	162(80,2)	54(75)	108(83,1)	0,242
Elevated aPTT**	47(23,3)	12(16,7)	35(26,9)	0,376
Respiratory Failure**	164(81,3)	44(61,1)	120(92,3)	**<0,001**
Other Failure** (Circulatory,Neurological,Renal,Hematological,Hepatic)	94(46)	29(40)	65(50)	0.158

*; median (%25-75), **; number (%), *** continuous variables(mean± SD), RVP: Respiratory Viral Panel, RSV: Respiratory Syncytial Virus, OSI: Oxygen Saturation Index, FiO2: Fraction Of Inspired Oxygen

Table 2. Clinical comparison by overall and virus isolation status

Treatments and parameter	Total n:202	COVID-19 + n:72	RVP+ n:130	P value
Oxygen therapy*	99(48,9)	37(51,3)	62(47,7)	0,603
HFNC*	80(39,3)	24(33,3)	56(43)	0,170
NIV/CPAP/BIPAP*	57(28,3)	18(24,7)	39(30)	0,500
Conventional MV*	80(39,3)	23(32,1)	57(43,8)	0,106
HFO*	1(0,4)	0(0)	1(0,7)	-
Need for tracheostomy*	13(5,8)	6(7,4)	7(4,9)	0,553
Antiviral therapy*	96(47,6)	26(35,8)	70(53,8)	0,008
Antibacterial therapy *	189(94,2)	67(92,6)	122(95,1)	0,625
Antifungal therapy*	39(16,8)	13(16,3)	26(18,1)	0,875
IVIG*	39(17,4)	16(19,8)	23(16)	0,592
Steroid*	76(37,8)	23(32,1)	53(40,7)	0,188
Inotrope*	42(21,0)	16(22,5)	26(20)	0,807
Hydroxychloroquine*	22(11,1)	16(22,2)	6(4,6)	<0,001
Azithromycin*	45(22,6)	30(43,2)	15(11,5)	<0,001
Favipiravir*	28(12,4)	25(30,9)	3(2,1)	<0,001
Lopinavir/ritonavir*	9(4,0)	9(11,1)	0(0)	-
Immunoplasma*	8(3,6)	8(9,9)	0(0)	-
LMWH*	7(3,1)	7(8,6)	0(0)	-
RRT*	5(2,2)	4(4,9)	1(0,77)	0,058
Plasmapheresis*	7(3,1)	5(6,2)	2(1,53)	0,101
ECMO*	1(0,4)	1(1,2)	0(0)	-
PICU stay of length,day,median(IQR) **	6(4-14)	6(3-10)	6(4-15)	0,075
Hospital stay of length,day,median(IQR) **	10(6-22)	9(6-19)	11(7-23)	0,163
Discharge*	194(86,2)	68(84)	126(96)	0,500
Mortality Rate*	18(8,0)	4(4,9)	14(10)	0,311

*; Number (%); ** Median (%25-75)

HFNC:High Flow Nasal Cannula, NIV/CPAP/BIPAP: Non-Invasive Ventilation/Continuous Positive Airway Pressure/Bilevel Positive Airway Pressure, MV: Mechanical Ventilation, HFO: High-Frequency Oscillation, IVIG: Intravenous Immuno Globulin, LMWH:Low-Molecular-Weight Heparin, RRT: Renal Replacement Therapy, ECMO:Extra Corporeal Membrane Oxygenation , PICU: Pediatric Intensive Care Unit, Antiviral Therapy*: Oseltamivir, Immunoplasma*: Convalescent Plasma Therapy.

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Figure 1. The diagram is as follows. Study flow chart included or excluded patients.

ALGORITHM

Patients admitted to PICU between March 1, 2020 and March 1, 2021

COVID-19(-),
RVP (-)
Serology (-)
n:1402
Excluded

COVID-19(+),
RVP (-)
Serology (+)
n:8
Excluded

COVID-19(+) or
RVP (+)
Serology (-)
n:202
Included

COVID-19(+) and
RVP (+)
Serology (-)
n:16
Excluded

COVID-19(-),
RVP (-)
Serology (+)
n:62
Excluded

COVID-19(+)
n:72

RVP (+)
n:130

RSV
n:51

RHINOVIRUS
n:30

OTHERS
n:49

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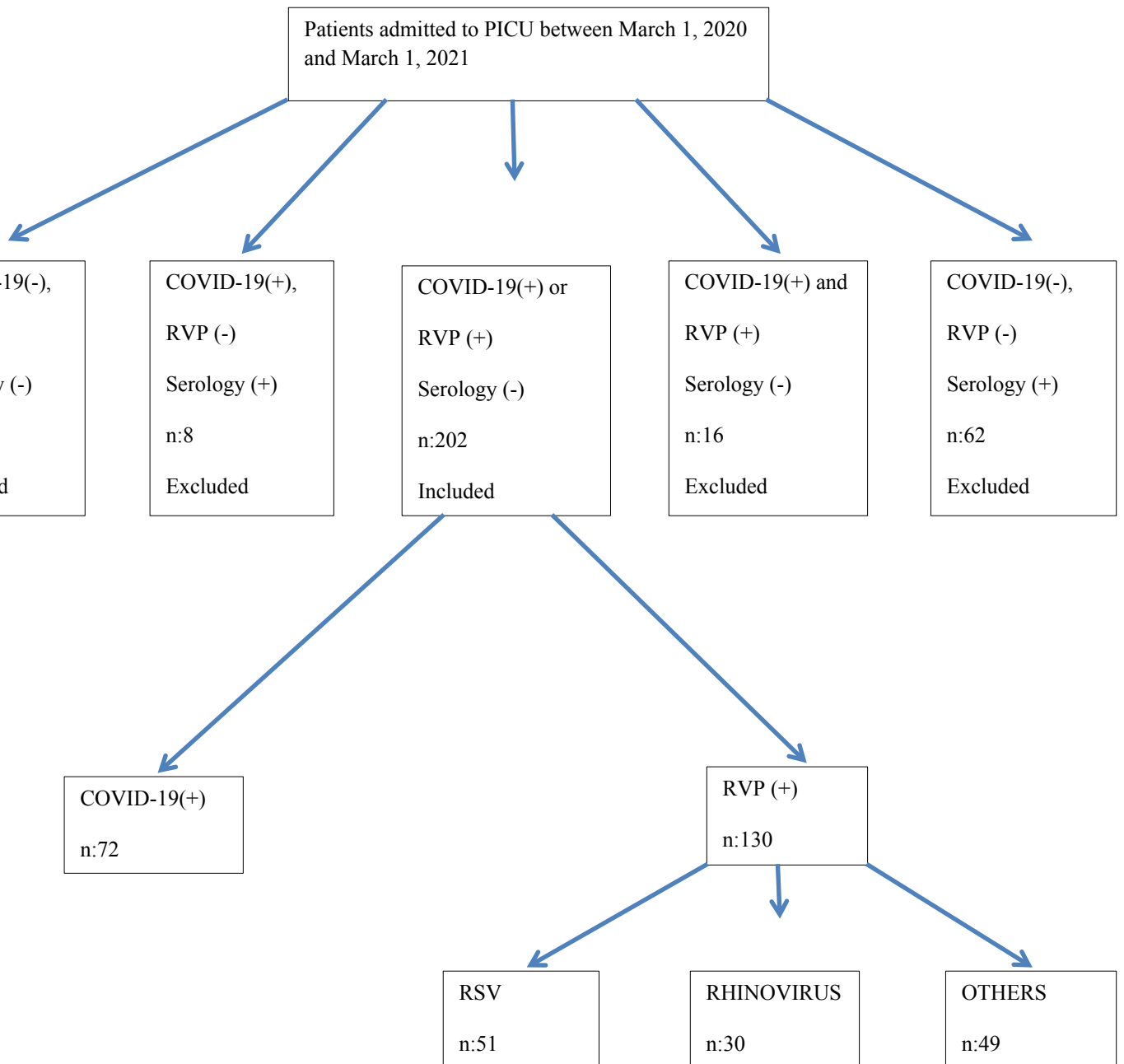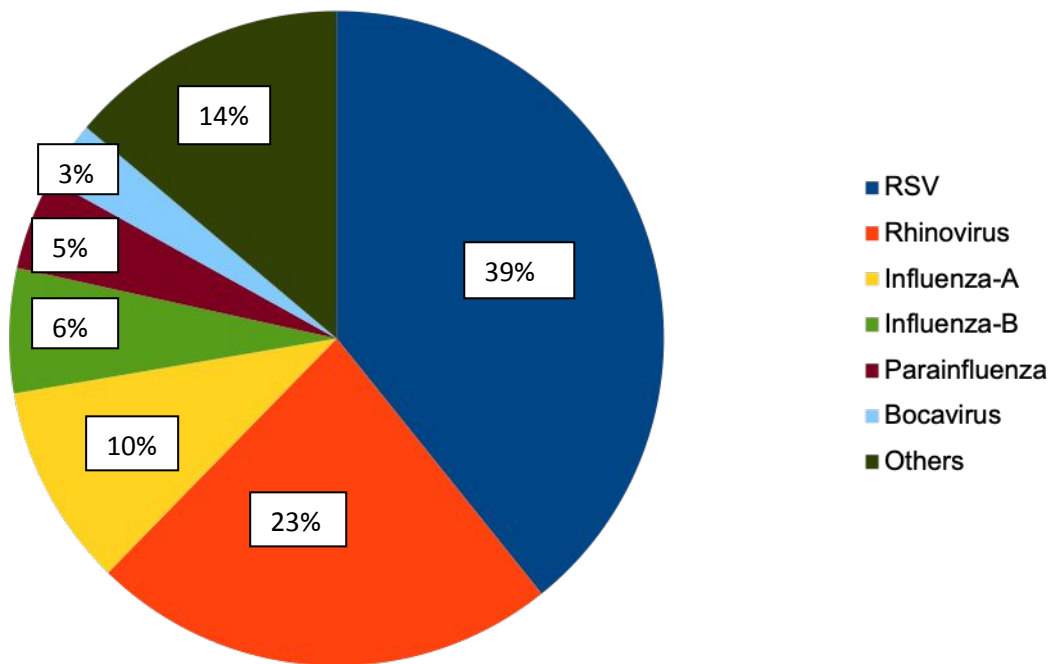42
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Figure 2. Respiratory Viral Panel. Viral etiologies detected in patients. The diagram is as follows.

RSV:51**, Rhinovirus**:30**, Influenza-A**:13, **Influenza-B**:8, **Parainfluenza:**6, **Bocavirus:**4, **Other**s:18

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authored by

Dr Oktay Perk

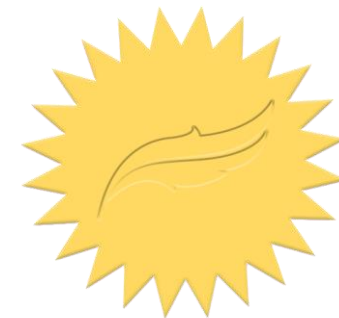was edited and/or proofread by Scribendi as order number

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