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Human Bocavirus Infection in Turkish Children

Abstract

The human bocavirus (HBoV) in children have been identified with an acute lower respiratory tract disease (LRTD). Its prevalence, clinical characteristics, and function as an RTD causal agent are unclear. This study sought to evaluate the laboratory and clinical data of HBoV patients, pinpoint the clinical characteristics linked to HBoV, and examine the distinctions between detecting HBoV alone and in combination with other agents. We used molecular testing to confirm the presence of HBoV DNA and 20 other respiratory pathogens in 1739 nasopharyngeal samples from hospitalized children at the Pediatric Infectious Diseases Service. 73 children, whose median age was 15 months, had HBoV. Concomitant infection of Bocavirus with another virus was observed in 41 (56.1%) of the patients. Coinfections were observed most frequently with rhinovirus (n=17) and RSV (n=10). There was no difference between the isolated bocavirus and coinfection groups in terms of age, clinical presentations, chest X-ray findings, or laboratory results. A role of HBoV in RTD is supported by the fact that the majority of patients were admitted to the hospital with a diagnosis of pneumonia or bronchopneumonia. HBoV mainly affects the respiratory tract, but it can also cause different clinical manifestations.

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INTRODUCTION

Human bocavirus (HBoV) is predominantly located in the respiratory tract. The respiratory system can host unidentified viruses that induce both mild and severe symptoms (1, 2). Bocavirus is present globally, spreading and infecting individuals throughout the entire year. Nevertheless, it tends to be more prevalent during the winter and spring months (3). In patients with positive human bocavirus in respiratory tract infections, the co-infection rate varies from

8.3% to 100%. Meanwhile, for gastrointestinal findings, the associated co-infection rate is 46.7% (4). The seroprevalence of human bocavirus increases with age, reaching around 40% in children aged 18 to 23 months and approximately 100% in children aged 2 years and older (5).

Bocavirus genotypes belong to the Parvovirinae subfamily within the Parvoviridae family. Human infections have been associated with a specific parvovirus known as B19. Despite their close phylogenetic relationship, parvovirus B19 and bocavirus exhibit notable differences (6).

The virus gains entry into the host through the respiratory tract, bloodstream, or direct uptake, subsequently infiltrating the gastrointestinal system. HBoV has been observed in both the respiratory and gastrointestinal tracts (7). HBoV1 has been associated with both upper and lower respiratory tract infections in various studies. Common clinical signs and symptoms in this context include cough, fever, runny nose, asthma exacerbation, bronchiolitis, wheezing, and pneumonia (3, 8, 9). Although bocavirus infections can occur alone, about 36% of cases occur in conjunction with other infectious pathogens. (10). Co-infection with other viral and bacterial respiratory and gastrointestinal pathogens, such as rhinovirus, adenovirus, RSV, and rotavirus, is prevalent in cases of bocavirus infection (11, 12). The high prevalence of co-infections in bocavirus cases may be attributed to its persistence and reactivation. Nevertheless, the specific effects and mechanisms of bocavirus persistence and reactivation remain unclear. Additionally, the role of bocavirus in active disease is not well-understood (13).

The sole treatment for bocavirus is palliative care, as there is currently no specific antiviral treatment available. Symptomatic treatment is provided based on the clinical presentation it induces (14).

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Our objectives were to investigate the prevalence of HBoV in children, identify the clinical features associated with HBoV, and explore the differences between detecting HBoV as a sole agent and its co-detection with other agents.

MATERIALS AND METHODS

Study design and patients. The study was a retrospective single-centre cohort investigation encompassing patients admitted to the Pediatric Infectious Diseases Service for acute respiratory infection (ARI), between January 2016 and December 2018. The study included patients who were diagnosed with respiratory tract infection using clinical, laboratory, and imaging assessments, and who underwent bacterial and viral testing of respiratory samples. The study eliminated participants who did not receive concurrent PCR testing for viral and bacterial agents.

Virus detection. During the study period, all respiratory tract samples (including nasopharyngeal swabs/aspirates, sputum, endotracheal aspirates or bronchoalveolar lavage fluid) from which respiratoy viral +/- bacterial pathogen molecular detection tests were requested, were evaluated by multiplex real-time PCR analysis by using the Fast Track Diagnostics Respiratory Pathogens 33 (FTD-33) Kit (Fast-Track Diagnostics, Germany). Besides bocavirus, the FTD-33 assay detects influenza viruses -A (H1N1) -B, and -C, parainfluenza viruses 1-4, respiratory syncytial viruses (RSV) A and B, seasonal coronaviruses (229E, HKU1, NL63 and OC43), picornaviruses (enterovirus, rhinovirus and parechovirus), adenovirus and human metapneumoviruses (hMPV)A and B. This assay also detects the presence of Mycoplasma pneumoniae, Chlamydia pneumonia, Haemophilus influenzae (plus H. influenzae type b), Streptococcus pneumoniae, Moraxella catarrhalis, Bordetella pertussis, Staphylococcus aureus, Legionella pneumophila, Klebsiella pneumoniae, Salmonella spp. and the fungal pathogen Pneumocystis jirovecii. In patients requiring urgent results, the QiaStat-Dx

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Respiratory Panel v1 (Qiagen, Germany) was used to analyze the samples for the presence of influenza A (H1N1, H1, H3) and B viruses, seasonal coronaviruses, parainfluenzaviruses 1-4, RSV A/B, hMPV, adenovirus, bocavirus, rhinovirus/enterovirus, Mycoplasma pneumoniae, Legionella pneumoniae, and Bordertella pertussis.

Clinical characteristics. We conducted a retrospective analysis of demographic, clinical, and laboratory data about patients diagnosed with bocavirus infection. The study highlights the difference between detecting bocavirus as the sole agent (the mono-infection group) and detecting bocavirus together with other respiratory tract infection agents (the co-infection group). The mono-infection group and the co-infection group were collectively examined, considering parameters such as white blood cell count (WBC), C-reactive protein (CRP) levels, clinical characteristics (upper respiratory tract disease, lower respiratory tract disease, gastrointestinal disease, fever, lymphadenitis), duration of hospitalization, requirement for oxygen therapy or respiratory support, chest X-ray findings, and the necessity for intensive care.

Statistical analyses. IBM SPSS Statistics 21 was employed for statistical analysis. Descriptive statistics were generated using central and prevalence criteria, including numerical indicators such as count, percentage, smallest and largest values, mean, median, and standard deviation. To assess differences between categorical variables, Pearson, Chi-square, and McNemar tests were employed. Throughout the study, statistical significance was set at a p-value below 0.05.

Permission to carry out the study was approved by the local ethics committee. (Date: 25/06/2018 Number: 11-725-18)

RESULTS

Between January 2016 and December 2018, bocavirus was detected in 73 (4.1%) of 1739 patients whose nasopharyngeal samples were investigated by multiplex PCR.

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Demografic Datas, Seasonality

65.8% (n=48) of the research population were male. In our study, the mean age of diagnosis was found to be 25.6±33.5 months, the patient diagnosed at the youngest age was 18 days old, and the oldest patient was 240 months old (median age: 15 months). 16.4% (n=12) of the patients were between 0-6 months, 21.9% (n=16) were between 6 months-1 year, 52.1% (n=38) were between 1-5 years, 9.6% of them (n=7) were diagnosed over the age of 5 years (Table 1).

Bocavirus infection was most common in the winter months, with positive patients hospitalised most frequently in January and February (Figure 1).

Chronic Diseases

19 (26%) of 73 patients with bocavirus infection have an underlying chronic disease, and 11 (57.8%) of them use medication. A wide range of these diseases has been observed, from neurological diseases to metabolic diseases, from gastroenterological diseases to polycystic kidney disease. One of the patients was followed up with a diagnosis of dilated cardiomyopathy. Four patients have Down syndrome. Mono infection and co-infection groups with and without chronic illness were the two distinct groups in which all results were presented (Table 1).

Symptoms, Physical Examination

The most common complaints of the patients in the study were cough (90.4%), wheezing (76.7%), fever (72.6%) and rhinorrhea (46.6%), respectively. Seven patients presented with diarrhea (9.6%) and 15 patients with vomiting (20.5%). One patient presented with the complaint of a seizure. This patient was previously followed up with a diagnosis of epilepsy (Table 1).

In the study, the most common physical examination of the patients was crackles (rales) (63%), prolonged expiratory phase (52.1%) and rhonchi (34.2%). 50.4% of the patients had

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tachypnea. Hepatosplenomegaly was detected in 29 patients (39.7%). Cardiac murmur was present in 15.1% of patients. While nine patients were followed in pediatric cardiology due to atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), operated truncus arteriosus and dilated cardiomyopathy, 2 patients had a physiological murmur. 3 of the patients had rash; nonspecific viral rash was detected in 2 of them, and 1 of them had erysipelas-like cellulitis while being examined for fever of unknown focus. In addition to bocavirus in the respiratory viral panel of this patient, adenovirus and *Staphylococcus aureus* in the respiratory tract bacterial panel were detected (Table 1).

Coinfection

In 32 patients, bocavirus was the only causative agent, whereas in 41 patients (56.1%), bocavirus was associated with other respiratory viruses. Dual and triple infections were detected. The greatest association was with rhinovirus (n=17). This was followed by RSV (n=10), metapneumovirus (n=9), influenza (n=8) and parainfluenza (n=7). Other agents found together are coronavirus (n=5), adenovirus (n=5) and enterovirus (n=1) (Figure 2, Table 2).

All patients were divided into two groups: patients with chronic diseases (n=19) and patients without chronic diseases (n=54). Bocavirus monoinfection and coinfection were investigated in two distinct groups, one for each of the groups with and without chronic illness. Bocavirus was most common in both groups during the winter. Bocavirus infection was found to be mono-infection in 32 (43.8%) of the 73 patients studied, and co-infection in 41 (56.2%). Bocavirus was most common in children aged 1 to 5 years old in both groups. Males are more common in both groups (Table 1).

Of the patients, 53 (72.6%) presented with a complaint of fever. Among those with a fever complaint, 27 out of 32 patients (84.4%) who had the bocavirus as the sole agent and 26 out of 41 patients (63.4%) identified with multiple agents were determined. The incidence of fever complaints in the group with bocavirus as the sole agent is higher in the history (p=0.046).

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Among those who presented with cough, 30 (93.8%) had bocavirus as the sole agent, and 36 (87.8%) were identified with multiple agents. Seven patients presented with a complaint of diarrhea, with isolated bocavirus detected in 2 of them (6.3%); however, this is statistically insignificant.

In the physical examination of both groups, respiratory tract infection findings were most commonly observed. Tachypnea, rales, and rhonchi were frequent in both groups.

Laboratory findings

Leukocytosis (>15,000/mm3) was found in 10 (31.2%), high sedimentation rate was found in 12 (37.5%), and elevated CRP was seen in 16 (50%) of the patients in whom bocavirus was found as the only agent. Sedimentation rate and CRP elevation did not differ statistically significantly between the two groups ($p>0.05$). Of the total number of patients, 15% had >5,5 x10^9/L lymphocyte and 19.1% (14 patients) had <1,5 X10^9/L lymphocyte. (Table 1).

Blood cultures from four patients were positive. They were all found to have methicillin-resistant coagulase-negative Staphylococcus (MRCoNS) growth in blood cultures, which was discovered late (19th, 21st, 24th, and 25th hours). The second blood culture did not show any growth, and none of them had clinical signs of a bloodstream infection. They all don't require medical attention. They were regarded as contaminated.

Radiological findings

The comparison of the lung X-ray findings of both groups is provided in Table 1. Among the 40 patients with infiltration detected in the lung X-ray, isolated bocavirus was found in 20. Atelectasis was observed in 4 patients with isolated bocavirus.

Respiratory support

Out of all patients (n=73), 67 (91.8%) required respiratory support, while 6 patients (8.2%) did not need respiratory assistance. For patients experiencing increased respiratory effort while receiving oxygen therapy through nasal cannula or reservoir mask, advanced

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respiratory support was provided in the form of high-flow nasal cannula oxygen (HFNCO2) (n=20) and continuous positive airway pressure (CPAP) (n=4). In cases where these measures proved insufficient, mechanical ventilatory support was administered to one patient, and even extracorporeal membrane oxygenation (ECMO) support was given to another patient. The patient under ECMO was diagnosed with necrotising pneumonia. This patient was monitored under ECMO for a total of 24 days, received mechanical ventilator support for 11 days, and continued treatment in the pediatric infectious disease service for 35 days after 10 days of intensive care follow-up. The lung parenchyma improved, and the patient was discharged. In addition to bocavirus, the patient tested positive for influenza, parainfluenza, and metapneumovirus in the respiratory viral panel. No statistically significant difference was found in terms of respiratory support between the two groups in our study ($p>0.05$) (Table 3).

Intensive Care Unit

Out of the entire patient population (n=73), 12 patients (16.4%) required intensive care either during their initial hospitalisation or throughout the course of treatment. Isolated bocavirus was identified as the causative agent in 5 (41.7%). No statistically significant difference was found between the two groups ($p=0.868$). The distribution of the need for intensive care among all patients is presented in Table 3.

Clinical Characteristics

While the presence of bocavirus in the nasopharynx plays a role in the aetiology of respiratory tract diseases, it can also lead to other clinical conditions. The clinical diagnoses of patients with bocavirus infection are shown in Table 4. Three patients had acute otitis media (4%), 58 patients had bronchiolitis (80%), 3 patients had gastroenteritis (4%), 1 patient had myocarditis (1%), 2 patients had fever without a focus (3%), 1 patient had convulsion (1%), 1 patient had submandibular abscess (1%), 2 patients had necrotizing pneumonia (3%), 1 patient had lymphadenitis (1%), and 1 patient was diagnosed with lobar pneumonia (1%).

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DISCUSSION

In our study, we employed multiplex PCR to identify human bocavirus (HBoV) and various other viruses among hospitalised children. Out of the cases studied, we found 73 (4.1%) to be HBoV-positive. The prevalence of HBoV detection demonstrates variability across different countries. Past reports indicate a global average prevalence of HBoV in respiratory tract samples ranging from 1.0% to 56.8%, with an overall prevalence estimate of 6.3% in respiratory infections (4).

Bocavirus emerges as the predominant causative agent among children below the age of 5 (15). In our investigation, the average age at diagnosis was determined to be 25.6±33.5 months. Notably, 16.4% (n=12) of the patients were under 6 months, 21.9% (n=16) fell within the 6 months to 1-year age group, and 52.1% (n=38) were diagnosed between the ages of 1-5. This aligns with existing literature, where 90.4% (n=66) of the cases were diagnosed in children under the age of 5. Despite the commonly held belief that maternal antibodies protect during the first 6 months, the frequent occurrence of cases within this timeframe suggests that this protection may not be entirely comprehensive.

Some investigations found that human bocavirus was often found in the summer, whereas other studies found it more often in the winter (16)(17, 18). In our research, 46.6% (n=34) of patients sought medical attention during the winter. These findings supporting the notion that the higher prevalence of bocavirus during winter months is likely attributed to its strong association with respiratory tract infections, which are more prevalent in clinical settings during the winter.

Debates persist regarding whether bocavirus functions as a singular pathogen. A notable aspect of respiratory tract infections attributed to bocavirus is the frequent co-infection with other respiratory viruses. Numerous studies suggest a correlation between disease severity and

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viral load, indicating that a high viral load may serve as a determining factor in bocavirus's causative role in respiratory diseases (19-21). The virus commonly triggers infections alongside respiratory pathogens such as influenza, rhinovirus, parainfluenza, RSV, and metapneumovirus, with rates reaching up to 90% (22).

In our research, we compared the clinical manifestations caused by bocavirus alone with those induced by other viral agents. Among our patients, the co-infection rate stood at 56.2%, and unfortunately, viral load measurement was not feasible in our study. The most prevalent accompanying agents with HBoV were rhinovirus (n=17) and RSV (n=10), aligning with existing literature.

Our patient group was heterogeneous in terms of underlying conditions, and there was no difference between those with chronic diseases regarding the detection of bocavirus as a single or multiple pathogen. In some patients, the presence of an underlying disease may have contributed to their symptoms and clinical findings.

In a study, it was discovered that 86% of patients with sole bocavirus infection experienced upper respiratory tract infections (23). Longtin et al. identified pneumonia in 42% and bronchiolitis in 42% of pediatric patients with bocavirus infection (24). Our study revealed that 80% of patients were diagnosed with bronchiolitis, consistent with existing literature. Concurrently, our investigation into the clinical characteristics of bocavirus-infected patients unveiled diverse clinical presentations. A minority, 4% of patients, presented with gastroenteritis, while 1% each exhibited symptoms of myocarditis, fever without a focus, submandibular abscess, lymphadenitis, lobar pneumonia, and acute otitis media. Like other respiratory viruses, bocavirus may have a characteristic that makes it more susceptible to bacterial infections, as demonstrated by these clinical images and patients with blood culture growth.

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Bocavirus infection can manifest clinically as gastroenteritis, a significant infectious disease affecting individuals of all ages worldwide, with notable morbidity in children (25). While HBoV1 primarily induces respiratory system infections, HBoV2, HBoV3, and HBoV4 can be identified in stool samples and lead to gastroenteritis (26). Bocavirus-induced gastroenteritis may occur in isolation or in conjunction with other gastrointestinal pathogens such as rotavirus, sapovirus, and adenovirus (27). In our study, isolated bocavirus was identified in two (28.6%) of seven patients presenting with diarrhea. However, contrary to existing literature, bocavirus was not examined in stool samples but in respiratory tract viral PCR examinations. Respiratory samples were collected from these patients due to the concurrent presence of symptoms related to upper respiratory tract infection alongside diarrhea. Bocavirus subtypes were not investigated in our research, and our laboratory does not currently detect bocavirus in stool samples. In the analysis of other viruses in stool samples, rotavirus was found in two patients, and adenovirus was detected in one patient.

In a study carried out in the United States, patients with bocavirus infection exhibited white blood cell counts ranging from 3,000/mm^3 to 31,000/mm^3, with a median count of 13,300/mm^3 (28). Consistent with these findings, our study observed white blood cell counts ranging from 4,000/mm^3 to 22,500/mm^3. Lymphopenia and lymphocytosis are conditions that may be observed in viral infections (29), and we found similar findings in our patients.

In a study conducted by Volz et al., the reported C-reactive protein (CRP) values ranged from 0.3 to 114 mg/L (10). In our study, we observed CRP values ranging from 0.1 to 214 mg/L, aligning with the existing literature.

Patients suffering from acute bronchiolitis or viral pneumonia may necessitate oxygen and ventilator support (30, 31). In our study, 56.1% of the patients received oxygen therapy through a mask/nasal cannula, 27.3% were administered high-flow nasal cannula oxygen (HFNCO2), and 5.4% required oxygen therapy with continuous positive airway pressure

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(CPAP) due to escalating respiratory distress. However the rates of mechanical ventilation (1%) and extracorporeal membrane oxygenation (ECMO) (1%) were low.

In a retrospective study by Ajda et al., which compared children diagnosed with bronchiolitis under the age of 2 with those monitored in the pediatric emergency department and pediatric intensive care, the most frequently detected agents were RSV (57.5%), rhinovirus (25.6%), and bocavirus (18.4%) (32).

In our study, 12 patients (16.4%) out of the entire patient population required monitoring in intensive care during their initial hospitalisation or treatment follow-up, a rate consistent with the literature. Simultaneously, isolated bocavirus was identified as the causative agent in 5 out of the 12 patients (6.8%) who needed intensive care. No statistically significant difference was observed between the groups (p=0.868).

Before the COVID-19 pandemic, this study was performed. More research in this field is required, including on the COVID-19 pandemic and beyond.

Our study is subject to several limitations. Firstly, the retrospective nature of the investigation resulted in missing data, both in electronic records and in written patient files. Missing data were addressed by evaluating rates after their removal. Additionally, bocavirus comprises four distinct subtypes: HBoV1, HBoV2, HBoV3, and HBoV4. Among these, HBoV1 is most commonly found in respiratory secretions, while HBoV2, HBoV3, and HBoV4 are typically identified in stool samples. Unfortunately, our hospital laboratory does not conduct examinations for HBoV subtypes, and bocavirus is not tested in stool samples, representing a further limitation.

Moreover, our study focused on the clinical impact of bocavirus primarily through respiratory tract PCR examination. While it was inferred that bocavirus contributed to the observed clinical manifestations without direct tissue biopsy, this assumption could not be

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conclusively proven. These limitations should be considered when interpreting the findings of our study, and future research might benefit from addressing these constraints.

In conclusion, our study underscores the significance of bocavirus as a notable pathogen, particularly in respiratory tract infections. The PCR method emerges as a highly sensitive diagnostic tool. Not only is the detection of the virus in respiratory tract secretions associated with respiratory tract infections, but it may also contribute to other clinical conditions. The research has shed light on the pathogenic nature of bocavirus, revealing its potential to cause various clinical conditions independently. While some patients diagnosed with bocavirus may exhibit mild symptoms, others may present with severe respiratory failure necessitating intensive care monitoring. Our study provides valuable insights for future investigations in this field.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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FIGURES LEGENDS

Figure 1. Monthly distribution of HBoV

Figure 2. Co-infective agents with bocavirus

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TABLES

Table 1. Comparison of clinical and demographic data for Bocavirus identification as a singular or multiple agent in patients with chronic diseases, those without chronic diseases, and the whole patient population

	Patients with chronic diseases (n=19			*Patients without chronic diseases (n=54)*			*All patients (n=73)*		
Characteristic	Bocavirus mono-infection (n=7)	Bocavirus co-infection (n=12)	p	Bocavirus mono-infection (n=25)	Bocavirus co-infection (n=29)	p	Bocavirus mono-infection (n=32)	Bocavirus co-infection (n=41)	p
Season									
Spring	2 (28.6%)	2 (16.7%)	0,666	8 (32%)	6 (20.7%)	0.088	10 (31.3%)	8 (19.5%)	0.061
Summer	2 (28.6%)	2 (16.7%)		1 (4.0%)	3 (10.3%)		3 (9.4%)	5 (12.2%)	
Autumn	1 (14.3%)	1 (8.3%)		8 (32%)	3 (10.3%)		9 (28.1%)	4 (9.8%)	
Winter	2 (28.6%)	7 (58.3 %)		8 (32%)	17 (58.6%)		10 (31.3%)	24 (58.5%)	
Age Group									
<6 months	1 (14.3%)	2 (16.7%)	0.865	2 (8%)	7 (24.1%)	0.357	3 (9.4%)	9 (22%)	0.316
6 m-1 year	3 (42.9%)	3 (25%)		6 (24%)	4 (13.8%)		9 (28.1%)	7 (17.1%)	
1-5 years	2 (28.6%)	4 (33.3%)		16 (64%)	16 (55.2%)		18 (56.3%)	20 (48.8%)	
>5 years	1 (14.3%)	3 (25%)		1 (4%)	2 (6.9%)		2 (6.3%)	5 (12.2%)	
Sex									
Female	4 (57.1%)	3 (%25)	0.161	10 (40%)	8 (27.6%)	0.335	14 (43.8%)	11 (26.8%)	0.131
Male	3 (42.9%)	9 (%75)		15 (60%)	21 (72.4%)		18 (56.3%)	30 (73.2)	
Complaints									
*Fever**	5 (71.4%)	9 (%75)	0.634	22 (88%)	17 (58.6%)	0.016	27 (84.4%)	26 (63.4%)	0.046
Cough	7 (100%)	10 (%83.3)	0.386	23 (92%)	26 (89%)	0.767	30 (90.3%)	36 (87.8%)	0.456
Wheezing	1 (14.3%)	4 (33.3%)	0.366	2 (8%)	2 (6.9%)	0.877	3 (9.4%)	6 (14.6%)	0.498
Rhinorrhea	1 (14.3%)	8 (66.6%)	0.027	10 (40%)	15 (51.7%)	0.389	11 (34.4%)	23 (56.1%)	0.065
Diarrhea	1 (14.3%)	2 (16.7%)	0.891	1 (4%)	3 (10.3%)	0.375	2 (6.3%)	5 (12.2%)	0.456
Vomiting	1 (14.3%)	1 (8.3%)	0.683	5 (20%)	8 (27.6%)	0.516	6 (18.8%)	9 (22%)	0.737
Seizure	0	0	NS	0	1 (3.4%)	1	0	1 (2.4%)	1
Examination									
*Fever **	2 (28.6%)	0	0.039	1 (4%)	2 (6.9%)	0.896	3 (9.4%)	2 (4.9%)	0.459
Tachypnea	4 (57.1%)	5 (41.7%)	0.650	14 (56%)	14 (48.3%)	0.571	18 (56.3%)	19 (46.3%)	0.401
Crackles (Rales)	5 (71.4%)	8 (66.7%)	0.829	14 (56%)	19 (65.5%)	0.474	19 (59.4%)	27 (65.9%)	0.569
Rhonchi	3 (42.9%)	4 (33.3%)	0.678	10 (40%)	8 (27.6%)	0.335	13 (40.6%)	12 (29.3%)	0.310
Prolonged expiratory phase	5 (71.4%)	5 (41.7%)	0.210	16 (64%)	12 (41.4%)	0.097	21 (65.6%)	17 (41.5%)	0.040
Hepatosplenomegaly	5 (71.4%)	5 (41.7%)	0.210	6 (24%)	13 (44.8%)	0.110	11 (34.4%)	18 (43.9%)	0.409
Murmur	3 (42.9%)	6 (50%)	0.764	1 (4%)	1 (3.4%)	0.915	4 (12.5%)	7 (17.1%)	0.746
Rash	2 (28.6%)	0	0.05	0	1 (3.4%)	0.349	2 (6.3%)	1 (2.4%)	0.578
Laboratory Findings									
White blood cell									
<5.000/mm³	1 (14.8%)	0	0.236	1 (4%)	0	0.548	2 (6.3%)	0	0.251
5.000-15.000 /mm³	3 (42.9%)	9 (%75)		17 (68%)	20 (69%)		20 (62.5%)	29 (70.7%)	
>15.000/mm³	3 (42.9%)	3 (%25)		7 (28%)	9 (31%)		10 (31.3%)	12 (29.3%)	
Lymphocyte									
>6.5 x10^9/L	2 (28.6%)	3 (25%)	0.858	2 (8%)	4 (13.8%)	0.549	4 (12.5%)	7 (17.1%)	0.792
<1.5 x10^9/L	1 (14.3%)	3 (25%)		6 (24%)	4 (13.8%)		7 (21.9%)	7 (17.1%)	
***ESR** >20 mm/h*	4 (57.1%)	4 (33.3%)	0.311	8 (32%)	14 (48.3%)	0.225	12 (37.5%)	18 (43.9%)	0.581
***CRP** >5 g/L*	5 (71.4%)	7 (58.3%)	0.568	11 (44%)	12 (41.4%)	0.038	16 (50%)	19 (46.3)	0.756
Imaging/Chest X-ray									

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Infiltration	3 (42.9%)	7 (58.3%)	0.515	17 (68%)	13 (44.8%)	0.088	20 (62.5%)	20 (48.8%)	0.243
Hyperaeration	3 (42.9%)	4 (33.3%)	0.678	11 (44%)	12 (41.4%)	0.846	14 (43.8%)	16 (39%)	0684
Atelectasis	1 (14.3%)	3 (25%)	0.581	3 (12%)	8 (27.6%)	0.156	4 (12.5%)	11 (26.8%)	0.133

P-values <0.05 were considered statistically significant.

** Complaints of fever: Refers to patient-reported symptoms*
***Examination of fever: Refers to clinician-observed findings*

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Table 2. Triple co-infection

Triple co-infection	n (%)
Bocavirus + RSV + Rhinovirus	4 (5.4)
Bocavirus + RSV + Adenovirus	2 (2.7)
Bocavirus + RSV + Influenza	2 (2.7)
Bocavirus + Metapneumovirus + Rhinovirus	2 (2.7)
Bocavirus + Metapneumovirus + Parainfluenza	2 (2.7)

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Table 3. Comparison of respiratory support, medication and hospitalization for bocavirus identification as a singular or multiple agent in patients with chronic diseases, those without chronic diseases, and the whole patient population

	Patients with chronic diseases (n=19)			*Patients without chronic diseases (n=54)*			*All patients (n=73)*		
	Bocavirus mono-infection (n=7)	Bocavirus co-infection (n=12)	p	Bocavirus mono-infection (n=25)	Bocavirus co-infection (n=29)	p	Bocavirus mono-infection (n=32)	Bocavirus co-infection (n=41)	p
Respiratory support									
Not required	1 (14.3%)	4 (33.3%)	0.363	5 (20%)	12 (41.4%)	0.092	6 (18.8%)	16 (39%)	0.061
Required	6 (85.7%)	8 (66.7%)		20 (80%)	17 (58.6%)		26 (81.3%)	25 (61%)	
Nasal/mask oxygen	3 (42.9%)	4 (33.3%)		9 (36%)	9 (31%)		12 (37.5%)	13 (31.7%)	
HFNCO2	2 (28.6%)	4 (33.3%)		8 (32%)	6 (20.7%)		10 (31.3%)	10 (24.4%)	
CPAP	1 (14.3%)	0		3 (12%)	0		4 (12.5%)	0	
Mechanical ventilation	0	0		0	1 (3.4%)		0	1 (2.4%)	
ECMO	0	0		0	1 (3.4%)		0	1 (2.4%)	
Medication									
Antibiotic usage	5 (71.4%)	10 (83.3%)	0.539	17 (68%)	20 (69%)	0.939	22 (68.8%)	30 (73.2%)	0.679
Antiviral (Oseltamivir)	0	5 (41.7 %)	0.047	2 (8%)	6 (20.7%)	0.191	2 (6.3%)	11 (26.8%)	0.023
Salbutamol	5 (71.4%)	8 (66.7%)	0.829	21 (84%)	17 (58.6%)	0.042	26 (81.3%)	25 (61%)	0.061
Systemic steroids	3 (42.9%)	4 (33.3%)	0.678	11 (44%)	8 (27.6%)	0.165	14 (4 3.8 %)	12 (29.3%)	0.200
Intensive care unit									
No	5 (71.4%)	10 (83.3%)	0.539	22 (88%)	23 (79.3%)		27 (84.3%)	33 (80.5%)	
Yes	2 (28.6%)	2 (16.7%)		3 (12%)	6 (20.7%)	0.393	5 (15.7%)	8 (19.5%)	0.764
Duration of hospitalisatio *Median (min-max)*	8 days (4-20 days)	8.5 days (2-30 days)	NS	5 days (3-11 days)	5 days (2-45 days)	NS	5 days (3-20 days)	5 days (2-45 days)	NS
Mortality	0	0	NS	0	0	NS	0	0	NS

P-values <0.05 were considered statistically significant.

NS: No statistics.

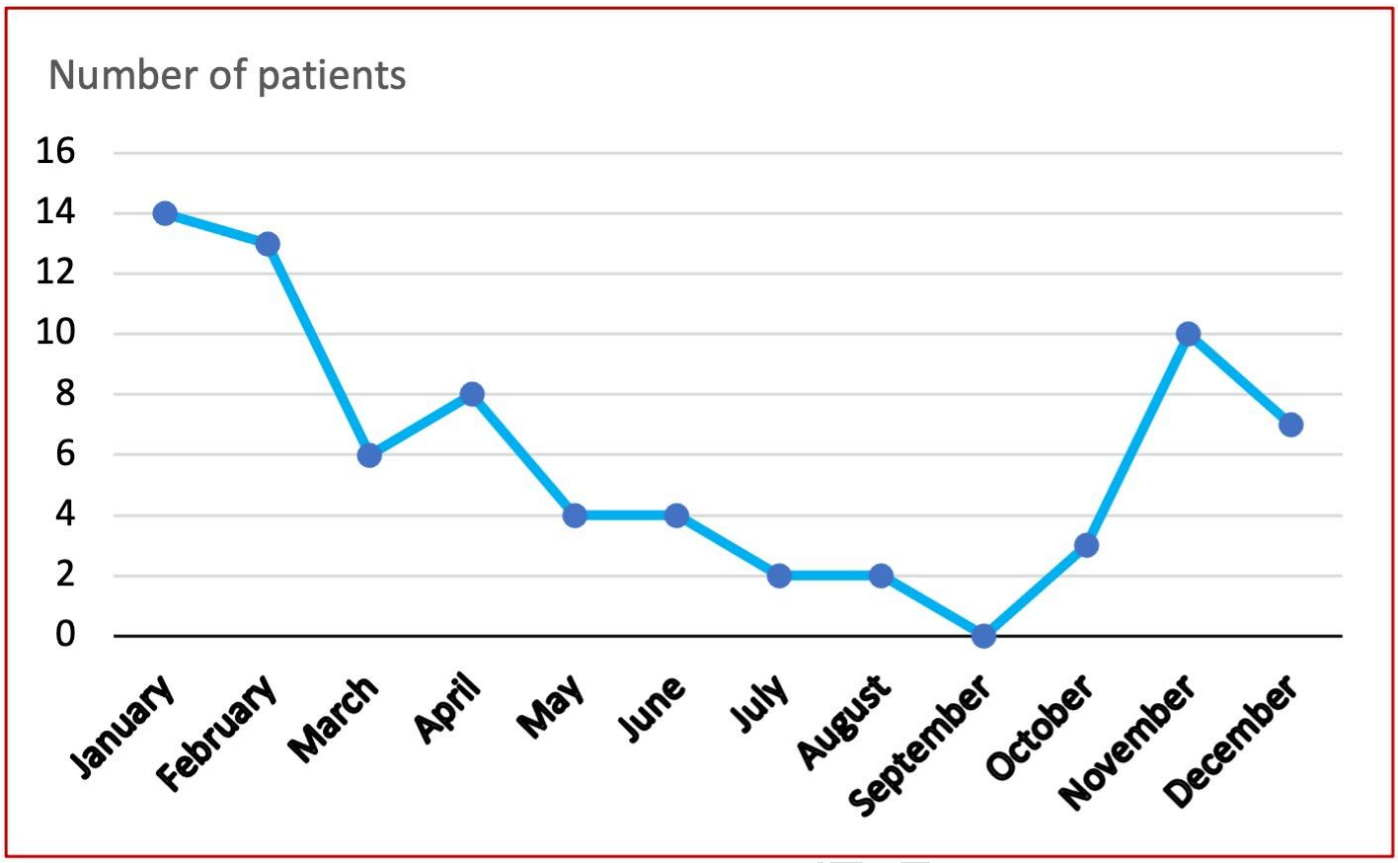
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Table 4. Clinical diagnosis of patients in two groups

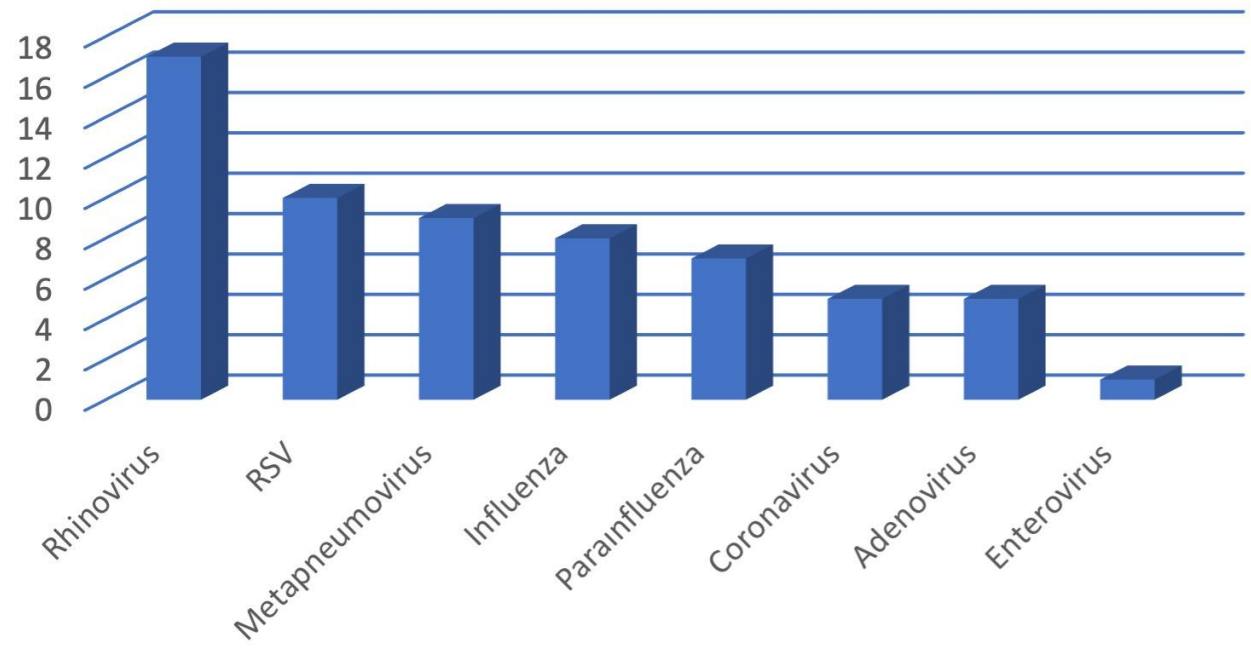
Clinical Diagnosis	Bocavirus mono-infection (n=32)	Bocavirus co-infection (n=41)
Bronchiolitis-viral pneumonia	27	31
Lobar pneumonia	1	-
Necrotizing pneumonia	1	1
Acute otitis media	1	2
Gastroenteritis	1	2
Myocarditis	1	-
Fever without a focus	1	1
Febrile convulsions	-	1
Lymphadenitis with URTI	-	1
Submandibular abscess with URTI	-	1

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