

# Norovirus infection in children in Romania

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## ABSTRACT

Norovirus represents the most frequent cause of pediatric gastroenteritis requiring medical care. We conducted a prospective study on 276 patients admitted to a tertiary hospital in Romania from January 2017 to December 2019 to estimate the clinic-epidemiological and evolutionary impact of Norovirus infection. Among the 276 patients, the median age was 2.34 years, and 57.61% were male. The frequency of hospitalizations in a year was higher in August, September, and October, and 72.1% of patients were from urban areas. Diarrhea (92.58%), vomiting (83.33%), anorexia (92.03%), and fever (57.61%) predominated, while abdominal pain (46.74%), nausea (30.8%), headache (18.84%), and myalgia (18.12%) were in lower percentages. Dehydration occurred in 99.28% of patients. Using the Pearson correlation coefficient, we formulated two hypotheses: in the 0-4 years category, the number of cases requiring hospitalization is inversely proportional to age (Pearson coefficient age-number of cases - 0.92), and the younger the age, the more it is associated with other infections and the longer the hospitalization duration.

**Conclusions.** The clinic-epidemiological characteristics of patients with Norovirus infection are influenced by age – the younger the age, the longer the hospitalization duration and the higher the presence of associated infections; the average age is 2.34 years, with a predominance of males and children from urban areas. Hospitalization is high in August, September, and October, and diarrhea, vomiting, and anorexia predominate.

**Keywords:** Norovirus, children, clinical features

## INTRODUCTION

Norovirus infection is among the most common causes of diarrheal illness in young children, along with Rotavirus infection. In developed countries where rotavirus vaccination has been introduced into national vaccination programs, norovirus surpasses rotavirus as the most frequent cause of gastroenteritis in children.

## OBJECTIVES

We aimed to analyze the multi-year clinical-epidemiological evolution pattern of norovirus infection in children. To our knowledge, this is the first study of its kind in our country. The general objectives were defined as follows: defining the typical characteristics of Norovirus infection cases in pediatric patients requiring hospitalization for this diagnosis at the "Prof. Dr. Matei Bals" National Institute

of Infectious Diseases, a reference center in Romania; evaluating epidemiological and demographic factors influencing the incidence of norovirus gastroenteritis in Romania; studying the clinical and paraclinical aspects of norovirus infection; establishing correlations between disease determinants and predisposing factors that may influence the course and prognosis of the illness.

## MATERIAL AND METHOD

We conducted a prospective study on 276 pediatric cases hospitalized with Norovirus Gastroenteritis at the "Prof. Dr. Matei Bals" National Institute of Infectious Diseases, Children's Department IX, from January 2017 to December 2019. The data were collected from observation sheets, and all patients included in this research were tested and confirmed for Norovirus infection by the presence of virus an-

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tigens in fecal specimens (positive NADAL Norovirus GI/GII test). Patients hospitalized with diarrheal disease who tested negative for norovirus in the NADAL Norovirus GI/GII test were excluded. For each patient, a series of parameters were recorded. Statistical data processing was performed using IBM SPSS Statistics for Windows, version 22, and Microsoft Excel 2011. We conducted a multivariate analysis of the recorded parameters to find various correlations useful for documenting the research objectives. The study was carried out with the written consent of the patients' guardians and the prior approval of the ethics committee of the "Prof. Dr. Matei Bals" National Institute of Infectious Diseases.

The recorded parameters included demographic data such as admission date, age, gender, and place of origin; clinical symptoms such as diarrhea, vomiting, nausea, abdominal pain, headache, myalgia, anorexia, dehydration; paraclinical indices such as white blood cell count with analysis of the leukocyte formula (number of neutrophils, lymphocytes, monocytes), hemoglobin, platelet count, blood glucose, alanine transaminase (ALT), alkaline reserve, urea, sodium and potassium levels, and stool analysis; duration of hospitalization and antibiotic treatment received during hospitalization.

## RESULTS AND DISCUSSION

Regarding the seasonality of Norovirus infection, the distribution of cases over calendar months in the study revealed a higher incidence during the summer and fall seasons (August, September, October), compared to the winter and spring seasons (cold and wet seasons), where a significant decrease in cases was observed (Figure 1).

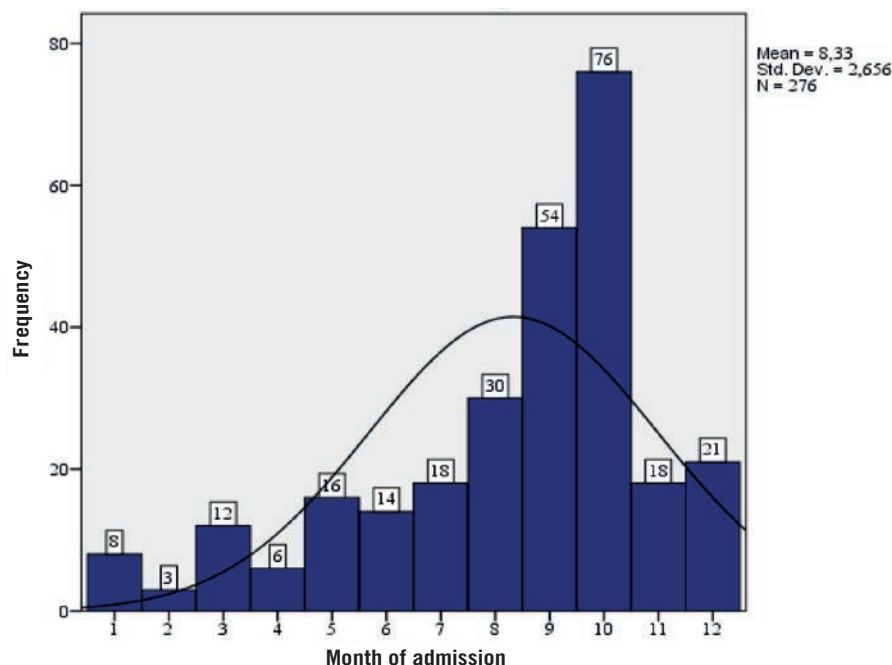


FIGURE 1. The distribution by calendar months of the cases included in the study

This is somewhat surprising for us, as literature data describe a higher incidence of Norovirus enteritis during the cold season. A study conducted in Ghana [1] over a period of 10 years identified two seasonal peaks: a major peak in the cold and dry months from October to January and a minor peak in the wet months from May to July. These differences can be explained, in part, by the geographical positioning of our country with a temperate climate. The presented results can be accurately interpreted as our case series is consecutive, including all patients from a calendar year, following the criteria mentioned earlier.

The cases of diarrhea associated with Norovirus were present in almost all age groups, but according to the statistics, a higher frequency was observed among children aged 1 to 24 months. The average age of patients in our study was 2.34 years. The minimum age recorded was one month, while the maximum age was 13 years (Figure 2).

The distribution by gender of the patients showed a higher frequency of Norovirus infection among male patients (57.61%) compared to female patients (42.39%) (Figure 3).

In our study, there was a predominance of cases from urban areas (72.1%), with a ratio to cases from rural areas (27.9%) being more than 2:1 (Figure 4).

There can be a series of explanations, namely: the level of medical education of patients, the larger population of Bucharest, the presence of family doctor offices and communal hospital units in rural areas and small towns, the "Prof Dr. Matei Bals" National Institute of Infectious Diseases as a reference center for more severe cases, and the total cost of hospitalization per case is much higher.

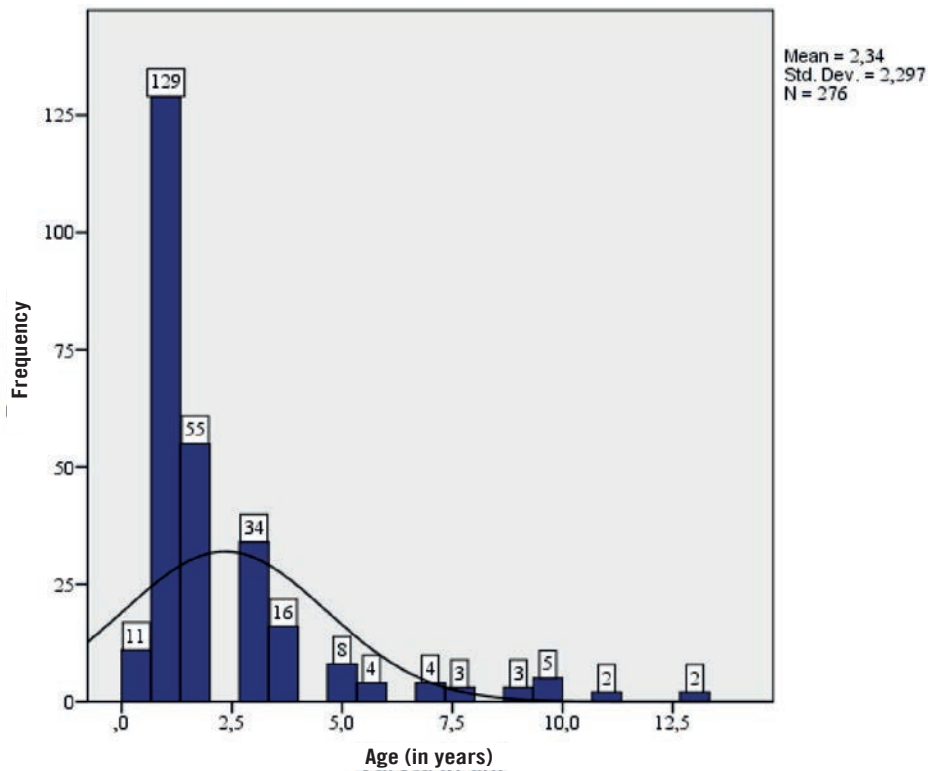


FIGURE 2. The distribution by age groups of patients included in the study

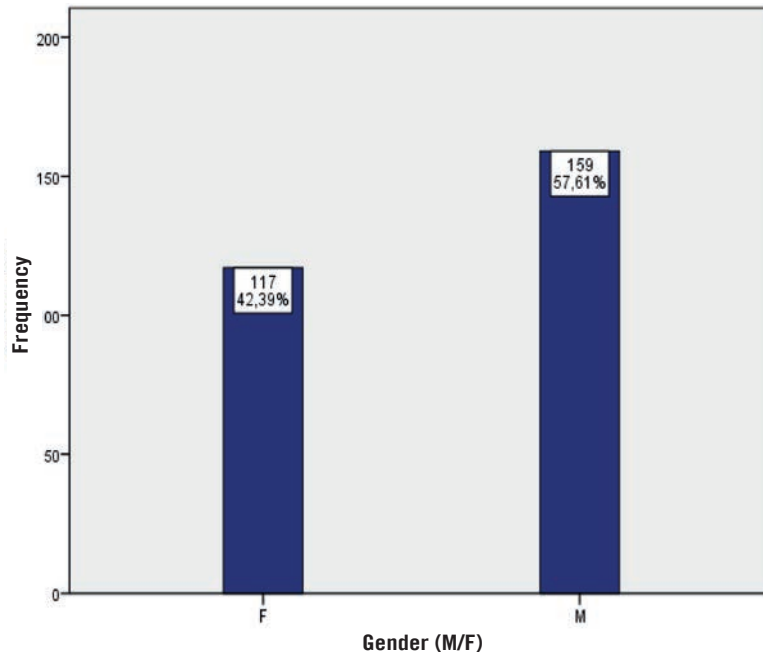


FIGURE 3. The proportion of patients by sex

The symptoms of Norovirus infection generally begin approximately 12-60 hours after exposure to Norovirus particles [2]. These include fever, watery diarrhea, vomiting, nausea, abdominal cramps, headache, and myalgia [3]. Fever is one of the clinical signs present in Norovirus diarrheal disease [4], but it lacks specificity. Observing the fever status of patients reveals two predominant intervals regarding temperature values at admission, namely: an interval between 36.0°C and 37.0°C (normal temper-

ature), with a percentage of 42.39% of patients, and another interval between 38.0°C and 39.0°C (febrile patients), with a percentage of 46.73%. The total percentage of patients with subfebrile, febrile, and high fever was 57.61% (Figure 5).

Diarrhea is one of the predominant signs of Norovirus infection, with a percentage of 90.58% (250 patients) experiencing watery diarrhea and an average duration of 3-4 days. Those who also had pathological elements in their stool (leukocytes and/or

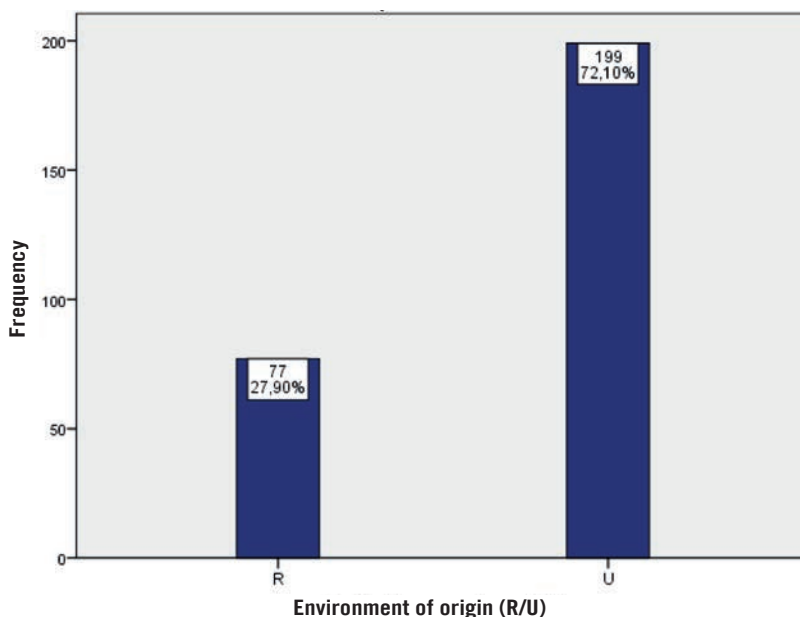


FIGURE 4. The share of patients according to the environment of origin

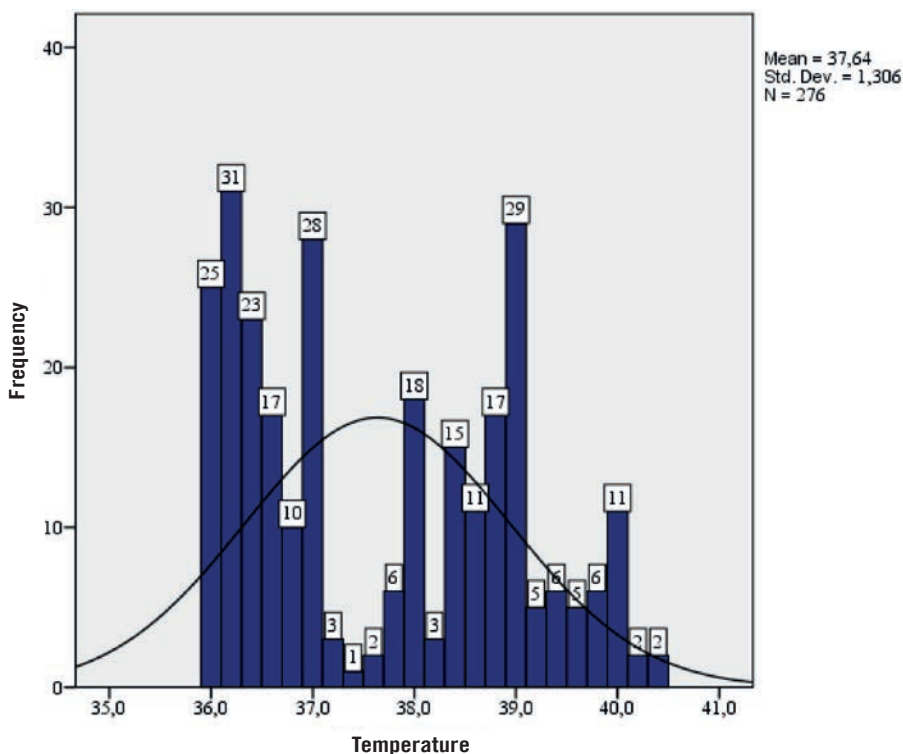
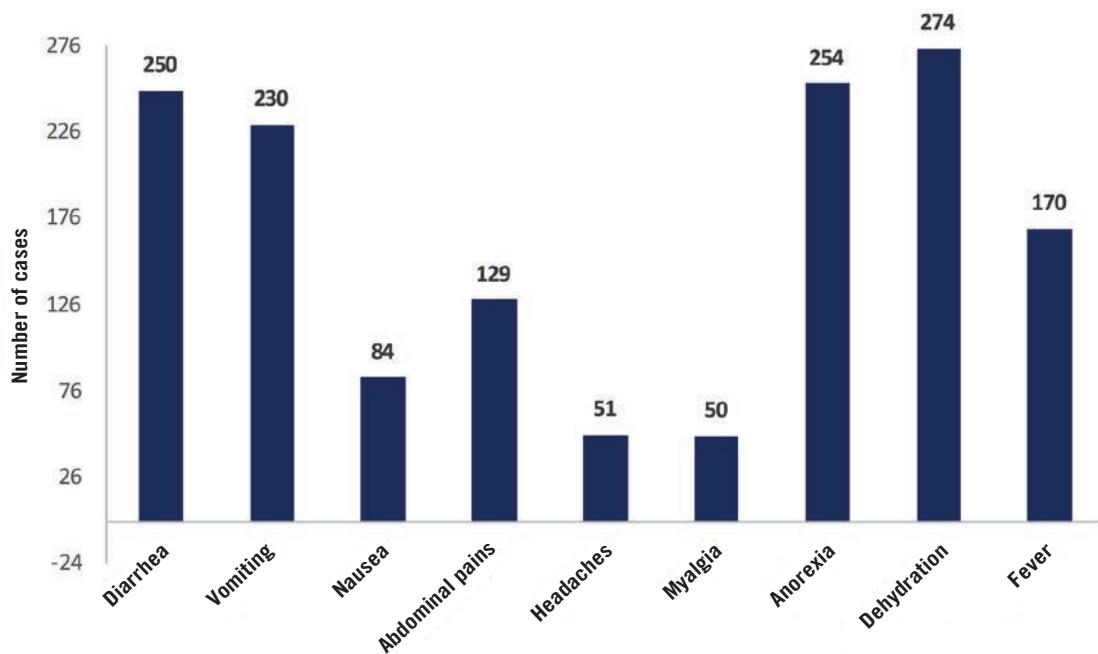


FIGURE 5. Maximum core temperature values recorded in patients

red blood cells) were investigated for associated pathologies. Vomiting is present to a significant extent in our study, with 83.33% of patients exhibiting this symptom (230 patients). Our collected data for this study are approximately consistent with those cited in the specialized literature, with various studies conducted in the USA, UK, Taiwan, Afghanistan mentioning the presence of vomiting in percentages ranging from 25.5% to 80% and diarrhea in percentages ranging from 66% to 100% [5].

Abdominal pains were present in our study at a percentage of 46.74% (129 patients), while nausea

occurred in only 30.8% (85 patients). Although nausea is considered one of the characteristics of this illness, our study did not observe this hypothesis. The explanation could be attributed to the young ages of the patients, as obtaining a medical history is challenging in these age groups compared to adults. Anorexia was described in most patients (92.03%), especially in infants and young children. Dehydration occurred in a very high percentage of patients (99.28%, 274 patients), while headache and myalgia occurred in low percentages (18.84%, 52 patients, and 18.12%, 50 patients, respectively) (Figure 6).



**FIGURE 6.** Symptoms associated with Norovirus

The dehydration parameter can be correlated with other recorded parameters, namely age and alkaline reserve, with the presence of metabolic acidosis observed in many investigated cases. The parameters of metabolic acidosis and dehydration can be reliable markers of Norovirus infection.

By analyzing the paraclinical parameters, we observe the presence of leukocytosis in a percentage of 53.26% (147 patients), compared to the percentage of normal values at 44.93% (124 patients). Given the presence of leukocytosis in more than half of the patients included in the study, we also investigated the leukocyte formula to identify which component could contribute to the total leukocyte count increase. The predominant percentage was that of normal values for lymphocytes and neutrophils (49.28%, 136 patients and 55.8%, 154 patients), while monocytosis (51.45%, 142 patients) was in percentages almost equal to normal monocyte values (48.55%, 134 patients).

68.84% (190 patients) presented normal values of fibrinogen, while for PCR, the percentage is 58.33% (161 patients). It is noteworthy that 41.67% (115 patients) had elevated PCR values. Most of the patient cohort (59.42%, 164 patients) had below-normal hemoglobin values, indicating anemia, while 40.58% (112 patients) had normal hemoglobin values. There is a weak influence of the platelet count component in Norovirus infection, with 68.48% (189 patients) having normal platelet values.

In relation to blood glucose levels, 51.81% (143 patients) of the total patients had normal values, and a percentage of 38.77% of cases (107 patients) had hypoglycemia, a parameter correlated with the presence of anorexia and vomiting at a relatively high rate.

The presence of metabolic acidosis reflected by the low value of alkaline reserve was observed in 94.20% (260 patients), practically indicating a very high percentage in Norovirus infection. The following paraclinical data were also analyzed: ALT, Na<sup>+</sup>, and K<sup>+</sup>, with the predominant percentage of normal values, demonstrating that they are not involved in Norovirus infection. From the statistical analysis, it is observed that 71.01% (196 patients) did not receive antibiotics during hospitalization, and the percentage of 28.99% of those who received antibiotics (80 patients) is explained by the presence of associated diseases. This parameter is somewhat correlated with the parameter of other associated infections, the percentage of which is 28.26% (78 patients) (Figure 7).

Analyzing the histogram conducted to observe the number of days of hospitalization for patients admitted to the “Prof Dr Matei Bals” National Institute of Infectious Diseases during the study period, we observe an average hospitalization of 3.93 days, with a peak occurring during the 2-4 days of admission (Figure 8).

Starting from the observation that in the 5-13 age category, there were not many cases requiring hospitalization, but those associated with other infections required more days of hospitalization and antibiotic therapy, we limited the study's conclusions to the 0-4 age category. Here, we created four age groups to test the following hypotheses with statistical coefficients: the number of cases requiring hospitalization is inversely proportional to age; in the 0-4 age category, the younger the age, the more it is associated with other infections, and the duration of hospitalization is longer. In the 0-4 age category, the number of cases requiring hospitalization is in-

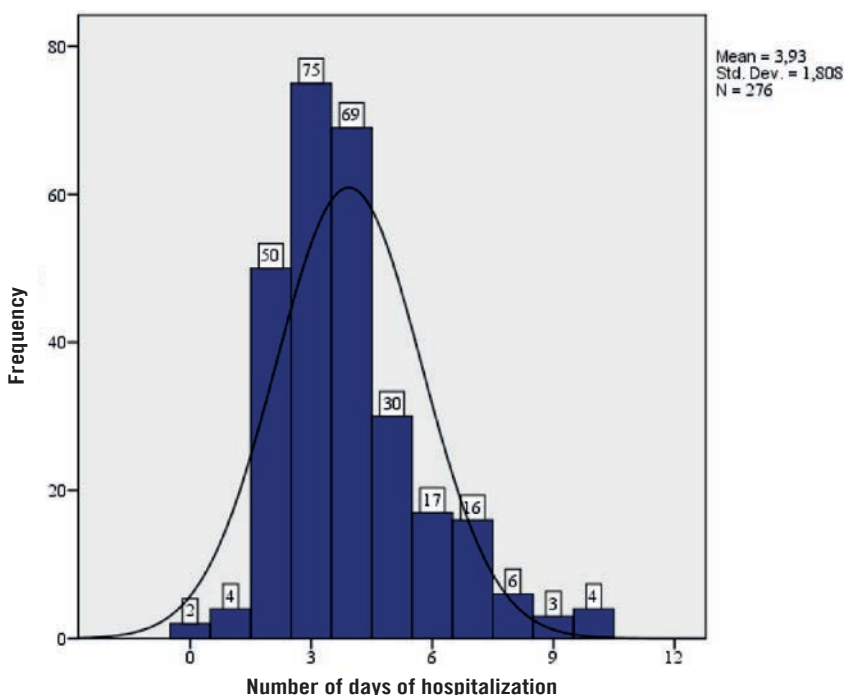


FIGURE 7. Distribution of patients according to the number of days of hospitalization

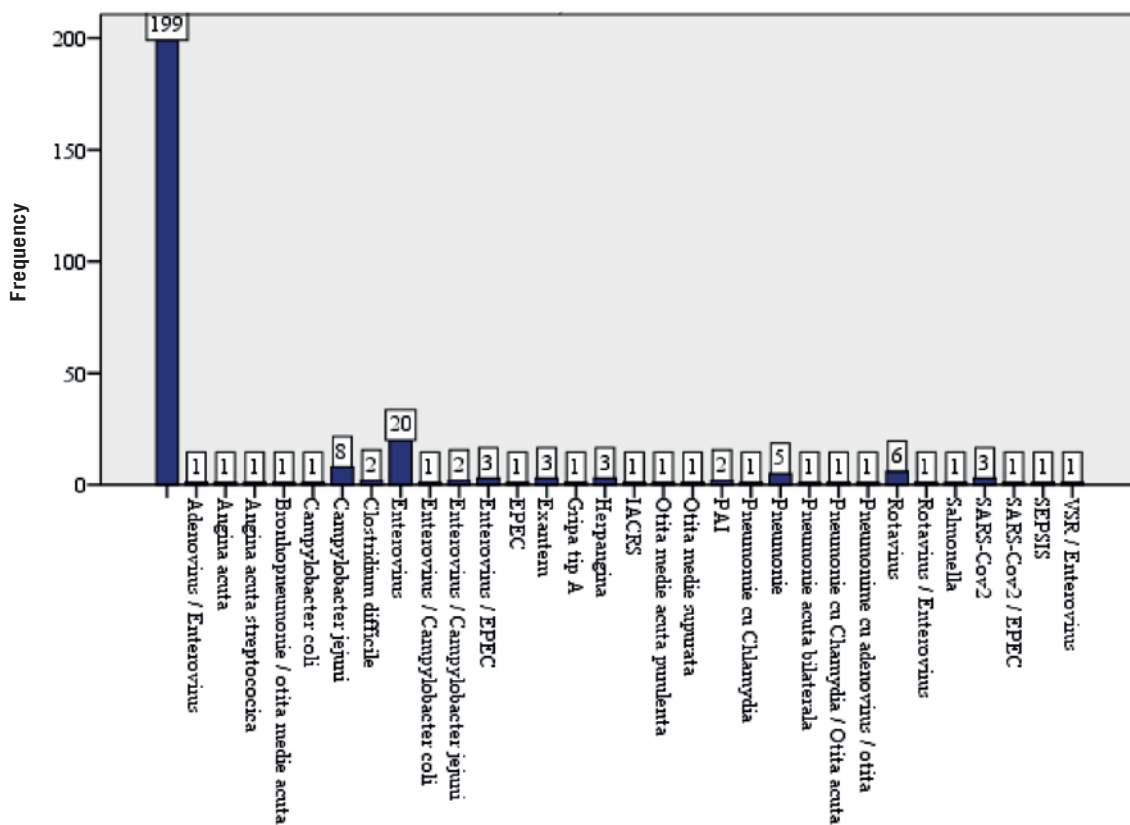


FIGURE 8. Other infections associated with Norovirus infection

versely proportional to age (Pearson correlation coefficient age - number of cases being -0.92, Pearson correlation coefficient age - duration of hospitalization -0.92, Pearson correlation coefficient age - number of cases without other associated infections -0.94). In the 0-4 age category, the younger the age, the more it is associated with other infections, and

the duration of hospitalization is longer (Pearson correlation coefficient age - number of cases with other associated infections -0.88; Pearson correlation coefficient age - duration of hospitalization with other associated infections -0.93; however, the Pearson correlation coefficient age - duration of hospitalization without other associated infections

is -0.42 (indicating a weak correlation - thus, the longer duration of hospitalization is due to the presence of associated infections).

## CONCLUSIONS

Following the conducted study, the following observations were made: there is a higher seasonality in the summer and autumn months (August, September, October). Norovirus infection predominantly affects males, with the highest incidence occurring in the age group of 0-2 years, with an average age of 2.34 years. A significantly higher number of patients from urban areas were hospitalized compared to those from rural areas. The typical duration of hospitalization was 2-4 days, with an average of 3.93 days. Fever was present in more than half of the patients at admission (57.61%), and the most

common clinical manifestations were diarrhea, vomiting, and anorexia. Patients were presented with leukocytosis, normal values of lymphocytes and neutrophils, monocytosis, intra-infectious anemia (possibly also nutritional), and a prevalence of metabolic acidosis. After narrowing down the study conclusions to the 0-4 age category (excluding the 5-13 age categories with fewer recorded cases), the following additional findings were noted: The number of cases requiring hospitalization is inversely proportional to age. In the 0-4 age category, the younger the age, the more it is associated with other infections, and the duration of hospitalization is longer.

*Conflict of interest:* none declared

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