Original Research Paper

Prevalence of Diarrhea-Causing Pathogens in South Korea Analyzed Using Molecular Diagnostic Methods

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Abstract: Gastrointestinal inflammation remains a prevalent global health concern. Prompt and accurate diagnosis of the condition is required to mitigate health risks in immunocompromised individuals and alleviate the economic burden linked to treatment and pathogen isolation. Challenges posed by traditional culture tests, such as long detection time and inability to isolate low-abundance organisms, can be overcome using molecular diagnostic methods, which enable rapid and precise identification of pathogens causing water and food-borne infections. To enhance infection response and improve prevention strategies, we aimed to elucidate the prevalence of diarrhea-causing pathogens by analyzing samples from an advanced general hospital, using multiplex real-time reverse transcription polymerase chain reaction. Analysis of 1,711 viral and 1,952 bacterial infection cases from November 2021 to February 2023 revealed 156 and 90 cases positive for bacterial and viral infections, respectively. The highest prevalence of bacterial and viral infections was noted in the summer. Among bacteria, *Salmonella* spp. had the highest co-infection rate (3 cases), followed by *Campylobacter* spp. and STEC/*Shigella dysenteriae* (stx1/stx2) (2 cases) and *Plesiomonas shigelloides* and enterotoxigenic *Escherichia coli* (1 case). Among viruses, rotavirus had the highest co-infection rate (11 cases), followed by adenovirus (9 cases), astrovirus (2 cases), and norovirus (1 case). The highest prevalence of diarrhea-causing bacteria was observed in individuals aged >70 years, followed by those aged 11-20 years and >6 years; however, the highest prevalence of viral infections was observed in individuals aged >70 years, followed by those aged <1 year. Continuous monitoring enables the assessment of age trend changes, aiding in predicting the cause and location of infectious diseases for effective prevention and quarantine measures. Our findings offer novel perspectives on viral and bacterial infections and elucidate the increasing age and concurrent infection trends, advance our comprehension of infection dynamics, and potentially facilitate refinement of clinical management and preventive strategies.

Keywords: Diarrhea-Causing Pathogen, Gastrointestinal Inflammation, Infection Prevalence, Molecular Diagnostic Method

Introduction

Gastrointestinal inflammation is a prevalent global health issue, with billions of cases and a substantial number of deaths annually (Lindsay *et al*., 2011; Park *et al*., 2019). The primary causes of gastroenteritis are water and food-borne infections, which are influenced by complex factors, such as temperature, humidity, residential environment, and public hygiene. Contaminated water and food are the main sources of pathogens, which are often found in communal settings, such as schools and workplaces (Cho *et al*., 2020a-b). Furthermore, diarrhea is the principal symptom of these infections, with fecal pathogen analysis being a critical test for differentiation (Jeong *et al*., 2022; Won *et al*., 2023). Considering the public health significance of infections, a global surveillance system is in place, designating Korea as a fourth-class infectious disease hub (Nan-Ok *et al*., 2019). Additionally, swift and accurate diagnosis is crucial for effective response to infections, prevention of fatal

consequences in immunocompromised patients, and minimization of economic losses from treatment and isolation (Goh *et al.*, 2019).

However, the conventional methods for identifying infection sources, such as culture tests, are hindered by various limitations, as these methods involve separation of the disease-causing microorganisms from other microorganisms, requiring several days for culture and impeding rapid response (Kim *et al.*, 2022). Moreover, previous studies employing these culture methods are limited because of errors or inhibitory factors in the culture methods (Guerrant *et al.*, 2001). In contrast, recent advancements have introduced molecular diagnostic tests in hospitals and laboratories. Such tests offer specific pathogen identification more rapidly than culture tests. Moreover, they excel in identifying multiple pathogens and concurrent infections, providing more accurate results than traditional culture tests (Chi *et al.*, 2018; Kim *et al.*, 2022; Ramakrishnan *et al.*, 2018).

The aim of the present study was to analyze data from an advanced general hospital using multiplex real-time Reverse Transcriptase Polymerase Chain Reaction (RT-qPCR), a molecular diagnostic method. By comparing our findings with those of previous studies, we aimed to elucidate the latest trends in diarrhea-causing pathogens and develop an effective strategy for preventing infectious diseases in light of the evolving trends.

Materials and Methods

Target and Data Collection

From November 2021 to February 2023, fecal specimens from 1,711 virus-infected cases and 1,952 bacterium-infected cases were collected from outpatients, emergency rooms, intensive care units, and hospitalized patients referred to the diagnostic laboratory department of Kyung Hee Medical Center (Seoul, South Korea) and analyzed using multiplex real-time RT-PCR. Among them, 156 cases of bacterial infection and 90 cases of viral infection were compared and analyzed with previous studies, and parameters such as the recent diarrhea-causing virus, seasonality, prevalence, and age of the patient were analyzed. Duplicate patients were not considered.

Ethics Approval and Consent to Participate

The present study was conducted in accordance with the tenets of the Declaration of Helsinki. As this study did not involve collecting any personal information of patients, the informed consent waiver was approved by the Dankook University Institutional Review Board (IRB; IRB number: 2023-11-021).

Detection of Viruses and Bacteria

Five types of diarrhea-causing viruses (adenovirus, astrovirus, norovirus, rotavirus and sapovirus) and eight types of diarrhea-causing bacteria (*Salmonella* spp., *Shigella* spp./EIEC [*ipaH* gene], *Vibrio* spp., *Campylobacter* spp., *Plesiomonas shigelloides, Yersinia enterocolitica*, Enterotoxigenic *Escherichia Coli* [ETEC] and STEC/*S. dysenteriae* [*stx*1/*stx*2 gene]) were detected.

Sample Collection, Analysis, and Interpretation

Mucus and diluted feces collected from patients were stored in clean, dried, sterilized containers, ensuring no contact with water, urine, or tissue to prevent contamination. DNA extraction and multiplex real-time RT-PCR were performed using the BD MAX System, BD MAX Enteric Bacterial Panel, and BD MAX Enteric Viral Panel (Becton, Dickinson and Company, USA). Briefly, fecal samples were rotated and mixed at high speed and 10 µL of the sample was inoculated into the BD MAX Enteric Bacterial Panel and BD MAX Enteric Viral Panel. After the loop was securely locked in the 5-µL inoculation loop, it was placed in a sample buffer tube and the sample was squeezed by twisting. The inoculated tube was then inserted in the appropriate rack in the multi-tube vortex mixer and rotated for 1 min at maximum speed. The prepared sample was examined using the BD MAX System after extracting the unitized reagent strip from the BD MAX Enteric Bacterial Panel and BD MAX Enteric Viral Panel kits. The results were interpreted according to the criteria defined by BD MAX; the positive criterion Ct value was not disclosed owing to the bylaws set by BD. Positivity or negativity was determined based on the interpretation table provided by BD. Enteric Bacterial Panel tests were conducted after storing the samples at 2-8°C for 5 days or 2-25°C for 24 h. All reagents were stored at 2-25°C and used within the expiration date.

Validity

Internal quality control was performed once every 2 months. For negative control of both the bacterial and viral panels, samples previously reported as negative were used. For the positive control of the BD MAX enteric bacterial panel, *Campylobacter* strains isolated and identified in the microbiology laboratory of the Kyung Hee Medical Center were used and for the positive control of the BD max enteric viral panel, samples previously reported as positive were used. In addition, whenever there was a change in the reagent lot number, a parallel test was performed. External quality control was performed once every 6 months by comparing results between hospitals and the control reagents were prepared alternately by each hospital and exchanged with other participating hospitals.

Results

Pathogen Prevalence and Sex-Related Disparities

Of the 1,952 commissioned samples collected, 151 (7.74%) tested positive for bacteria; approximately 156 bacteria were identified. Among the patients tested,

54.41% were male individuals (1,062 cases) and 45.59% were female individuals (890 cases), with positivity rates of 7.34 and 8.76%, respectively. *Shigella* spp. and *Vibrio* spp. were excluded owing to zero positive cases among female individuals.

Regarding virus infections, 1,711 commissioned samples were collected, among which 78 (4.56%) tested positive; 90 viruses were identified. Among the patients tested, 54.76% were male individuals (937 cases) and 45.24% were female individuals (774 cases), with positivity rates of 5.12 and 5.42%, respectively. The ratio of diarrhea-causing bacterial and viral infections was 1.14 and that of positive cases was 1.73, signifying a higher prevalence of bacterial infections. Among the bacterial isolates, *Campylobacter* spp. was the most prevalent (86 cases; 55.13%), followed by *Salmonella* spp. (40 cases; 25.64%). Among the viral isolates, norovirus was the most prevalent (35 cases; 38.89%), followed by rotavirus (21 cases; 23.33%) and adenovirus (18 cases; 20.00%).

Seasonality of Diarrhea-Causing Pathogens

Infections were the most prevalent in summer, followed by autumn, winter, and spring for bacterial infections and in winter, spring, and autumn for viral infections. *Campylobacter* sp. infections peaked in summer, whereas *Salmonella* sp. and *S. dysenteriae* (STEC) infections peaked in autumn. Among viruses, astrovirus, rotavirus, and adenovirus were the most prevalent in summer and norovirus was prevalent in winter. Other bacterial and viral infections exhibited no distinct seasonality, as evidenced by the low number of positive cases.

Co-Infections

Salmonella spp. exhibited the highest co-infection rate in three bacterial infection cases. All cases of co-infection involved viruses, with rotavirus implicated in 11 cases. Rotavirus and adenovirus co-infections were the most common (nine cases), with adenovirus co-infections specifically associated with rotavirus.

Prevalence According to Age

The prevalence of bacterial infections was the highest in individuals over 70 years of age, followed by those aged 11-20 years. Positive cases were observed across all age groups over 6 years (Fig. 1). Additionally, those aged ≥70 years had the highest prevalence of viral infections, followed by those under the age of 1 year (Fig. 2). Notably, individuals under the age of 1 year accounted for 33.33% of the cases, whereas those older than 61 years accounted for 44.87% of the cases (Fig. 2).

The mean and median ages of individuals were also determined (Table 1). The highest mean and median values were observed in *Vibrio* spp. and norovirus-infected individuals, whereas the lowest values were observed in *P. shigelloides*- and rotavirus-infected individuals.
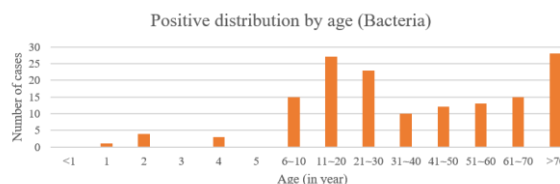

Fig. 1: Age-wise distribution of samples with bacterial infections. Bar plots indicate the age distribution of samples with one or more positive results, categorized accordingly
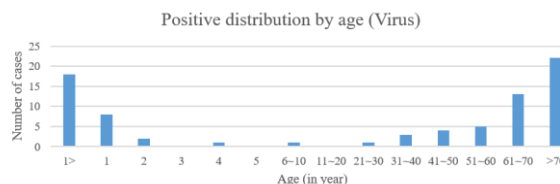

Fig. 2: Age-wise distribution of samples with viral infections. Bar plots indicate the age distribution of samples with one or more positive results, categorized accordingly

Table 1: Mean and median age of patients who tested positive for each pathogen

Bacteria	Mean age of patients (years)	Median age of patients (years)
Salmonella spp.	40.63	33.00
Shigella spp./EIEC (*ipaH* gene)	13.50	13.50
Vibrio spp.	49.50	49.50
Campylobacter spp.	42.10	36.50
Plesiomonas shigelloides	6.00	6.00
Yersinia enterocolitica	42.67	27.00
Enterotoxigenic *E. coli* (ETEC)	26.43	24.00
STEC/*S. dysenteriae* (*stx*1/*stx*2 gene)	37.64	43.00
Virus		
Norovirus	60.17	67.00
Rotavirus	3.81	0.00
Adenovirus	19.11	1.00
Astrovirus	36.58	47.50
Sapovirus	51.00	61.00

For the calculation of average age, values are assigned as 0 for less than 12 months, 1 for more than 12 months and less than 24 months, and 2 for more than 24 months and less than 36 months.

Discussion

Prevalence Based on Sex

For bacterial infection, the prevalence of positive cases did not differ significantly between male (7.34%) and female individuals (8.76%). The trend was consistent across major bacteria, including *Salmonella* spp. and *Campylobacter* spp., with no significant sex-based variations. Meaningful results could not be derived for cases infected with the remaining bacteria owing to the small number of cases. Notably, in cases of infections with *Shigella* spp. and *Vibrio* spp., positivity was observed only in one sex, that is, male and female, respectively and the number of positive cases was limited; therefore, data interpretation from the cases was

inconclusive. Similarly, the prevalence of viral infections revealed no significant sex-based differences, as the ratio of positive cases was 5.12% for male individuals and 5.43% for female individuals. While the prevalence of most viruses did not exhibit significant sex-based differences, the prevalence of astrovirus infection showed a 2.0-fold difference between male and male individuals, albeit with a small number of positive cases. Previous research suggests that diarrhea-causing pathogens primarily cause water and food-borne infections (Mohammed and Tamiru, 2014; GBD 2015). The primary contributors to the infections include education level, residential environment, lifestyle, and climate. Previous studies have consistently demonstrated no significant correlation between sex and the prevalence of these infections, a finding also corroborated by research conducted in Korea (Lindsay et al., 2011; Chi et al., 2018; Kim et al., 2022; Park et al., 2019). Collectively, our findings suggest the lack of significant sex-based differences in the prevalence of bacterial and viral infections.

Positive Isolation Rate by Bacteria and Virus

We examined bacteria and viruses causing intestinal infections, categorized as water- and food-borne infectious diseases and classified as level 4 infectious diseases, specifically sample surveillance infectious diseases. Notably, P. shigelloides is excluded from the Grade 4 epidemic but included in the BD Bacterial Panel as a causative bacterium of diarrhea (Korea Disease Control and Prevention Agency, 2019). Consequently, the Korea Disease Control and Prevention Agency is actively investigating and monitoring infectious diseases through its infectious disease-related website to assess epidemiology and prevent the spread of infectious diseases. According to the data, the most frequently detected bacteria are Campylobacter spp. and Salmonella spp., excluding pathogens not covered in this study (Korea Disease Control and Prevention Agency, 2023). Regarding viruses, norovirus, and rotavirus are predominantly detected, with rotavirus being the most detected in 2018 and adenovirus being the second most detected in 2022 (Korea Disease Control and Prevention Agency, 2023). In addition, when limited to samples from patients with acute diarrhea symptoms, norovirus and rotavirus are detected (Cho et al., 2020a-b). Our findings were comparable with those of the Kyung Hee Medical Center and the trend was almost similar to that observed in Korea (Cho et al., 2020a-b).

Prevalence rates vary globally across countries. Among viruses, norovirus is the primary cause of acute diarrhea in the United States, followed by sapovirus and rotavirus (CDC, 2013; Mattison et al., 2021). Additionally, China and Cape Verde have the highest prevalence of rotavirus and Kenya has the highest prevalence of norovirus (Colito et al., 2022; Shioda et al.,

2016; Wang et al., 2022). With respect to bacteria, Campylobacter spp. had the highest prevalence since 2015, followed by Salmonella spp. and STEC (FoodNet, 2024). In other countries, pathogenic E. coli exhibits the highest prevalence, followed by Vibrio spp. and Campylobacter spp., varying by country (Colito et al., 2022; Wang et al., 2021). Such differences are considered to stem from lifestyle, climate, and regional variations. The positive isolation rate of pathogens causing acute diarrhea in South Korea remains relatively consistent each year (Cho et al., 2020a-b; Korea Disease Control and Prevention Agency 2023). However, with changes in climate and lifestyle, which are key factors related to water- and food-borne infectious diseases, the occurrence pattern may also shift (Cho et al., 2020a-b); therefore, continuous monitoring is required for effective prevention and treatment.

Seasonality of Diarrhea-Causing Pathogens

A comparison of the seasonal prevalence of viruses with that reported by previous studies in Korea revealed that viruses were previously most prevalent in winter when temperatures were low, followed by spring, autumn, and summer (Goh et al., 2019). In contrast, the results of the present study indicate the highest prevalence of viruses in summer, followed by winter, spring, and autumn. Rotavirus, unlike in previous studies where it was rarely detected in summer, astrovirus (Hallowell et al., 2019), as well as adenovirus exhibited the highest prevalence in summer (Thwiny et al., 2022). Bacteria displayed the highest prevalence in summer and fall, consistent with the findings of previous studies in Korea (Goh et al., 2019) and Campylobacter spp. demonstrated the highest prevalence in summer, consistent with previous study findings (Goh et al., 2019). Salmonella spp. exhibited the highest prevalence in the fall in Korea and between August and September in the United States, as per CDC statistics. In the present study, the highest prevalence was observed between September and October, mirroring previous study results in Korea but deviating slightly from the findings of overseas studies (FoodNet, 2024; Korea Disease Control and Prevention Agency, 2023). However, the discrepancy appears to be based on regional characteristics.

For bacteria, our study yielded results similar to those of previous studies (Goh et al., 2019; Hallowell et al., 2019; Thwiny et al., 2022), while the viruses exhibited seasonal patterns distinct from those observed in these studies. However, determining whether the seasonal prevalence of the virus has changed is challenging owing to the use of data collected from a short period in the present study, potentially reflecting temporary results. Therefore, further continuous monitoring is required to identify changes in the

seasonality of diarrhea-causing pathogens and develop prevention and treatment measures.

Co-Infection

Co-infection with bacteria occurred with no specific trend. However, in the case of viruses, co-infection of rotavirus and adenovirus accounted for the largest proportion (9/11 cases; 81.82%), inconsistent with results of previous studies where norovirus-rotavirus or adenovirus-norovirus was the primary co-infection combination (Wang *et al.*, 2021; 2022). Furthermore, rotavirus was detected in all cases of virus co-infections, followed by adenovirus, differing from the findings of previous studies, which reported that norovirus primarily caused co-infections (Ndjangangoye *et al.*, 2021; Park *et al.*, 2019). Our current findings suggest that continuously observing and studying new co-infection trends that are distinct from the observations of previous studies is essential for the identification of emerging trends and minimization of the health burden on patients through the development of effective measures for prevention and treatment.

Prevalence According to Age

Numerous existing studies on diarrhea-causing pathogens have primarily focused on children, who have been identified to be at a high risk of infection (Florez *et al.*, 2020; Lestari *et al.*, 2020; Lu *et al.*, 2021). However, the latest results from Kyung Hee Medical Center indicate a change in the trend. Among viruses, rotavirus was predominantly isolated from patients under the age of 5 years, consistent with previous study findings (Kim *et al.*, 2022; Mohammed and Tamiru, 2014; Park *et al.*, 2019). Conversely, adenovirus was isolated in children as well as older individuals, with most other viruses detected in adults. Contrary to previous study findings, bacteria exhibited varying patterns of infection in the age group of ≥6 years (Colito *et al.*, 2022; FoodNet, 2024; Wang *et al.*, 2021). The prevalence of diarrhea-causing pathogens according to age distribution has not been a focal point in previous studies. However, bacteria and viruses exhibit patterns and results that are different from established trends. Accordingly, minimization of the healthcare burden on patients through prompt diagnosis and treatment could be achieved by establishing the prevalence trends of pathogens causing diarrhea according to age through continuous research.

Our study had several limitations. The retrospective nature of the present study and the limited sample size from a single institution located in Seoul are inadequate for the comprehensive determination of the prevalence and epidemiological characteristics of all causative organisms. Detection of some pathogens was challenging owing to their limited occurrence. Additionally, the study period was short, and patient details, such as the disease name, clinical symptoms, and treatment, were not differentiated.

To address the above limitations, future studies should focus on extensive monitoring of various regions and population groups, identify new infection routes and sources, and strengthen cooperation and data sharing. Furthermore, studying future prevalence trends through continuous monitoring is imperative. In particular, continuous monitoring is essential for assessing various epidemic patterns and changes in concurrent infection trends through lifestyle changes, identifying new infection routes or sources, developing effective measures for prevention and treatment, and detecting and responding to changes in seasonal epidemic patterns. Despite such limitations, our study covers various age groups and utilizes the latest data obtained using the multiplex real-time RT-PCR method, offering insights into recent prevalence trends. Our findings provide novel perspectives on viral and bacterial infections based on age and changes in concurrent infection trends. Furthermore, through additional research, collaboration with various institutions, and continuous monitoring, the primary sources of emerging concurrent infections could be identified according to trends and patient age.

Conclusion

Although this study is limited by the short study period and failure to reflect regional characteristics owing to its single-center design, it contributes to quarantining, prevention, and treatment by highlighting the need for continuous monitoring and identification of diarrhea-causing pathogens in response to lifestyle changes. Future studies should involve more institutions and establish a trend for the prevalence through continuous monitoring.

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Funding Information

Author's Contributions

Both authors have equally contributed to this manuscript.

Ethics

This study was reviewed and approved by the Clinical Trials Ethics Committee of Dankook University (IRB number: 2023-11-021). In this study, we retrospectively analyzed existing test results without including any personal patient information. As patient information was

not included, the need for informed consent from the included patients was waived.

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