JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2024-078
http://journal-arc.jp

Review Article

Gastroenterological Surgery and Management of *Clostridioides difficile* Infection: A Review

Tomonori Takano, Hiroyuki Aiba, Mitsuo Kaku and Hiroyuki Kunishima

Department of Infectious Diseases, St. Marianna University School of Medicine, Kawasaki, Japan

Abstract

Fever and diarrhea are the common symptoms of *Clostridioides difficile* infection (CDI); however, pseudomembranous enteritis, megacolonization, and paralytic ileus have been observed in severe cases. *C. difficile* spores are resistant to several types of disinfectants. Thus, they are often the causative pathogens of healthcare-associated infections. Rapid diagnostic tests based on glutamate dehydrogenase and toxins are the mainstay of CDI laboratory diagnosis owing to their simplicity. CDI can be diagnosed with high specificity using the nucleic acid amplification test, a genetic test for *C. difficile* toxins. The risk factors for CDI include age ≥65 years; history of antimicrobial use; previous hospitalization; history of gastrointestinal surgery, chronic kidney disease, or inflammatory bowel disease; nasal tube feeding; and use of proton pump inhibitors and histamine H2 receptor antagonists. The risk of CDI development persists even 1 year after discontinuation of proton pump inhibitor use. Furthermore, colorectal surgery and radical cystectomy with urinary diversion are associated with high incidences of postoperative CDI. The choice of therapeutic agent depends on the severity of the disease and recurrence. However, a combination of oral or nasogastric vancomycin, intracolonic vancomycin, and intravenous metronidazole can be considered in patients with toxic megacolonization and paralytic ileus. In January 2024, the European Committee on Antimicrobial Susceptibility Testing established a breakpoint for fidaxomicin (minimum inhibitory concentration breakpoint > 2 mg/L) against *C. difficile*. Rapid progress has been achieved in CDI treatment. Thus, multidisciplinary teams must collaborate to diagnose, treat, and control CDI.

Keywords

Clostridioides difficile infection, risk factor, severity, recurrence, nucleic acid amplification test

J Anus Rectum Colon 2025; 9(1): 25-32

Introduction

Discovered by Hall and O'Toole in healthy neonates in 1935, *Clostridioides difficile* was named *Bacillus difficile* from the Latin term "difficile," which means difficult due to the difficulty in its culture and isolation. *B. difficile* is a gram-positive biased anaerobic rod[1] with a peritrichous flagella that forms subterminal spores. The colonies of *C. difficile*, (3-5 mm in size) exhibit a ground-glass appearance on cycloserine cefoxitin fructose agar (CCFA) medium and give off a characteristic odor known as horse barn odor. In 2016, *C. difficile* was renamed as *C. difficile*[2].

C. difficile has been isolated from diverse environments, such as livestock, companion animals, rivers, and humans. Screening tests have detected *C. difficile*, which causes cecitis in rabbits and hares, in approximately 10% of inpatients[3]. Bacterial load and toxins, dysbiosis of the gut microbiota, and the presence of anti-toxin antibodies and receptors have been implicated in the pathogenesis of *C. difficile* infection (CDI)[1].

Corresponding author: Hiroyuki Kunishima, h2kuni@marianna-u.ac.jp
Received: July 22, 2024, Accepted: August 8, 2024

C. difficile is a major cause of antibiotic-associated diarrhea and was first isolated from a patient with clindamycin-induced pseudomembranous enteritis in 1977[1]. Notably, a highly virulent mutant strain (type B1/NAP1/027) of *C. difficile* caused an outbreak of enteritis in Canada in 2003[4]. In a previous study, a 20-fold increase in the production of toxins A and B as well as ADP-ribosylating binary toxin was observed after the deletion of the tcdC (negative regulator) gene in the type B1/NAP1/027 strain[4]. *C. difficile* has been identified as the cause of several healthcare-associated infections owing to its ability to form spores and resistance to disinfectants.

CDI

Fever and diarrhea are the common symptoms of *C. difficile* infections; however, pseudomembranous enteritis, megacolonization, paralytic ileus, and, very rarely, bacteremia and wound infections have been observed in severe cases. In Japan, patients aged ≥2 years who present with diarrhea, a Bristol Stool Scale score ≥ 5 (Table 1), and positive stool toxin/toxin-producing *C. difficile* isolated on CDI testing/pseudomembranous enteritis on lower gastrointestinal endoscopy or colon pathology are diagnosed with CDI[5]. Diarrhea is defined as passing muddy or watery stools ≥3 times in a 24-h period or passing a greater than normal number of stools. Objective assessment of the symptoms using the Bristol Stool Scale is the first step in CDI diagnosis. The solid part of the diarrheal stool is obtained during specimen collection. Thus, nurses must have knowledge regarding CDI and appropriately assess symptoms to make an accurate diagnosis. Patients with a history of laxative use, inflammatory bowel disease, and nasotracheal tube feeding can also present with diarrhea. Therefore, differentiating between conditions other than CDI and considering concurrent symptoms, such as fever, as well as inflammatory findings and the posttreatment course are important in CDI diagnosis[5].

Table 1. Bristol Stool Scale.

Score	Types of stool
1	Separate hard lumps
2	Sausage-shaped but lumpy
3	Sausage-shaped but with cracks on its surface
4	Sausage- or snake-shaped, smooth and soft
5	Soft blobs with clear-cut edges
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces, entirely liquid

Cited from Table 1 of Reference 48, 49.

CDIs can be classified as healthcare facility-onset; city-community-onset, healthcare facility-associated (CO-HCFA), and community-associated (CA) CDI based on the time of infection and disease onset (Table 2)[6]. CDI encountered in the outpatient setting is classified as CO-HCFA-CDI for up to 28 days following discharge; CA-CDI is also common abroad.

Dysbiosis, defined as the breakdown of the microbiota, is associated with CDI onset. Dysbiosis continues after CDI onset[7,8], and continued dysbiosis can lead to the recurrence of CDI. Such a recurrence has been reported in approximately 20%-30% of cases, making it the most recurrent infectious diseases[9,10].

Several studies have evaluated the risk of CDI development. Age ≥65 years; history of antimicrobial use, hospitalization, gastrointestinal surgery, chronic kidney disease, or inflammatory bowel disease; nasal tube feeding; and history of receiving proton pump inhibitors (PPI) and histamine H2 receptor antagonists have been identified as risk factors[11]. Notably, patients are at risk of developing CDI even 1 year after PPI discontinuation[12]. In addition, a previous study evaluated the risk of CDI development for the following PPIs: dexlansoprazole (adjusted hazard ratio [aHR], 0.86; 95% confidence interval [CI], 0.28-0.72), lansoprazole (aHR, 1.32; 95% CI, 0.77-2.25), pantoprazole (aHR, 2.02; 95% CI, 0.77-2.25), and esomeprazole (aHR, 1.98; 95% CI, 1.44-2.21)[13]. Older age, emergency surgery, prolonged duration of surgery, surgical site infection, deep/organ-space infection, use of steroids, metastatic cancer, smoking, and lower body mass index increase the risk of CDI development in surgical patients[14]. Sadik et al. and Alizadeh et al. reported that the incidence of CDI varies depending on the surgical site[15,16]. In previous studies, the incidence rates

Table 2. Definition Used for CDI Surveillance.

Classification	Definition
Healthcare facility-onset (HO) CDI	Symptom onset > 3 days after admission to a healthcare facility (reported as the number of cases per 10,000 patient-days).
Community-onset, healthcare facility-associated (CO-HCFA) CDI	Symptom onset in the community < 28 days after discharge from a healthcare facility (reported as the number of cases per 1,000 patient admissions).
Community-associated (CA) CDI	Symptom onset in the community > 12 weeks after last discharge from a healthcare facility.

CDI, *Clostridioides difficile infection*

Cited from Table 2 of Reference 48, 49.

of CDI following surgery, colorectal surgery, and radical cystectomy with urinary diversion were reported to be 0.3%, 1.0%, and 2.7%, respectively[15,16]. In Japan, the incidence of CDI following cardiac surgery ranges from 2.64 to 8.66. Notably, a trend toward a shorter time to the postoperative development of CDI has been observed with the use of external circulation[17].

Recurrent CDI is defined as recurrence of CDI within 8 weeks of the its onset despite receiving appropriate medical care[6]. Recurrence leads to delayed treatment of the underlying disease, reduced quality of life, and increased healthcare costs[18,19]. Older age; history of antimicrobial use after the diagnosis of CDI; presence of underlying medical conditions, such as chronic kidney disease or inflammatory bowel disease; history of CDI; and use of PPIs are risk factors for CDI recurrence[6].

Screening and Diagnosis of CDI

Culture, rapid diagnostic tests using glutamate dehydrogenase (GDH) and toxins, *C. difficile* toxin gene test, nucleic acid amplification test (NAAT), and *C. difficile* toxin gene test have been employed for the screening and diagnosis of CDI. Rapid tests that combine toxins and GDH, a *C. difficile* antigen, are the most commonly conducted tests. The sensitivity of the GDH test conducted using stool samples ranges from 70% to 98%, whereas that of the toxin test ranges from 60% to 80%[20,21]. The sensitivity of the stool toxin test is insufficient; consequently, GDH-positive and GDH-negative results could indicate toxin-producing or non-toxin-producing *C. difficile*. The NAAT test or a two-step method (wherein strains are isolated and cultured to evaluate their toxin-producing potential) are performed to diagnose CDI in cases with GDH-positive and toxin-negative results[6].

Isolated cultures of *C. difficile* have been used for molecular epidemiological analysis. However, bacteria must be cultured in an anaerobic environment using selective media, such as CCFA, to isolate *C. difficile* from stool samples[22]. Notably, nontoxigenic strains of *C. difficile* can also be cultured via 48-72 h of incubation in CCFA under these conditions. Molecular epidemiological identification methods include polymerase chain reaction (PCR) ribotyping, PCR-based open-reading frame typing, restriction endonuclease analysis, toxin typing, multilocus sequence typing, surface layer protein A, multilocus variable number tandem repeat analysis, and whole genome sequencing[23].

NAAT for the Detection of CDI

In recent years, various genetic devices have been introduced in healthcare facilities for the detection of infectious diseases, particularly during the coronavirus disease 2019 (COVID-19) pandemic. This has facilitated NAAT testing at an early stage. NAAT has sensitivity and specificity of 87%-91% and 94%-96%, respectively, which are higher than those of antigen tests[24-26]. NAAT facilitates a more accurate and rapid diagnosis of CDI; however, it has certain limitations, such as false positives, high cost, and insurance coverage restrictions[27]. In a previous study, NAAT exhibited superior cost-effectiveness, as measured by the incremental cost-effectiveness ratio in the USA[28]. NAAT is a sensitive and useful test that can be employed for the exclusion of CDI diagnosis. It reduces the duration of CDI treatment, number of additional tests, and length of hospital stay, thereby lowering healthcare costs[29-31]. The characteristics of rapid diagnostic kits, NAAT, and culture tests play a pivotal role in CDI diagnosis (Figure 1). Multidisciplinary collaboration is required for appropriate laboratory diagnosis and management.

Drug Susceptibility

In a previous study, enhanced biofilm production and increased adherence to intestinal epithelial cells were exhibited by *C. difficile* strains with low susceptibility to metronidazole (MTZ) under sub-MIC MTZ conditions, suggesting an association with the risk of CDI recurrence[32]. In a study conducted in Houston, USA, vancomycin (VCM)- and MTZ-susceptible strains were detected in 26% and 29% of 438 patients with CDI, respectively. Another study reported that VCM- and MTZ-susceptible strains were detected in 67% and 85% of 98 patients, respectively, in Nairobi[33]. An animal study using a mouse model of CDI demonstrated that CDI could not be cured in mice infected with a strain that is nonsusceptible to VCM[33].

Drug-resistant strains of *C. difficile* are rare in Japan[34-36]. A surveillance performed from 2014 to 2016 in Japan showed that *C. difficile* did not exhibit resistance to fidaxomicin, VCM, or MTZ; however, *C. difficile* with reduced susceptibility to fidaxomicin was observed after treatment with fidaxomicin. These trends should be monitored[37]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) evaluated the susceptibility of *C. difficile* to drugs and established different breakpoints: the EUCAST (resistance > 2) for MTZ and the CLSI (resistance ≥ 32) for MTZ[6]. No CLSI or EUCAST breakpoints for fidaxomicin were previously established; however, a MIC breakpoint >2 mg/L was set in the EUCAST in January 2024[38].

Treatment

The European Society of Clinical Microbiology and Infectious Diseases states that severe CDI is characterized by

Japanese Society of Chemotherapy, The Japanese Association for Infectious Diseases. CDI diagnosis guidelines 2022

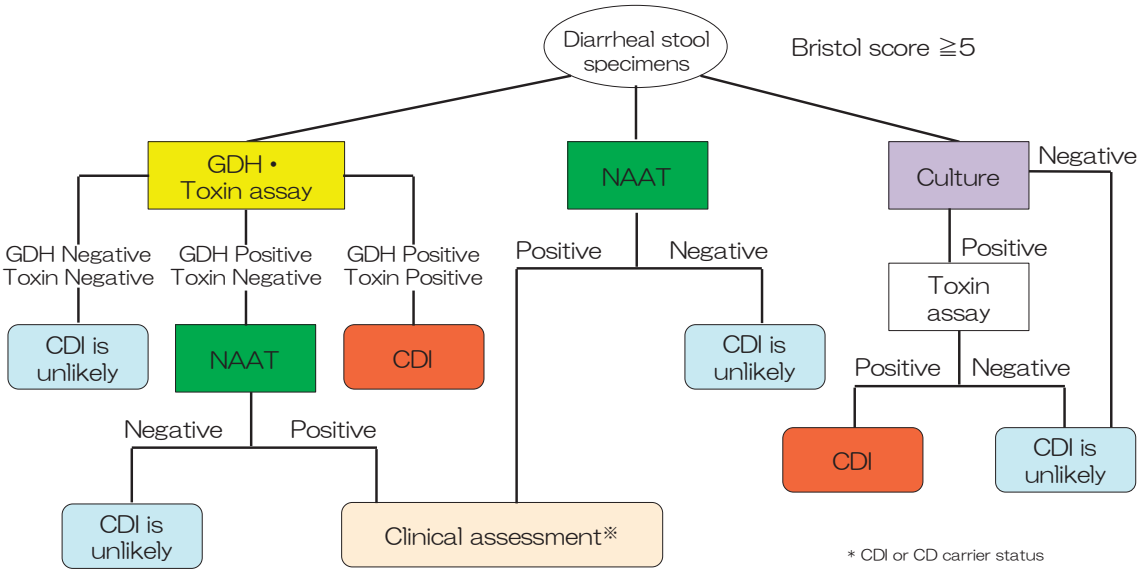

Figure 1. NAAT is performed without waiting for the GDH and toxin assay results. It is also performed based on the GDH and toxin assay results.
GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; CDI, *Clostridioides difficile infection*
Cited from Algorithm in Reference 48, 49.

Table 3. MN Criteria for CDI.

Category/Point	0	1	2	3
Age	<65	≥65	-	-
Abdominal distension or pain	No	Yes	-	-
Fever (°C)	37<	37≥, <37.5	37.5≥, <38.5	38.5≥
Diarrhea (frequency/day)*	0-2	3-9	10≥	-
Leukocyte count (/μL)	12,000<	12,000≥, <15,000	15,000≥, <20,000	20,000≥
eGFR (mL/min/1.73 m^2)	80≥	50≥, 80<	30≧ , 50<	30< or Hemodialysis
Serum albumin (g/mL)	3.0≥	2.5≥, 3.0<	2.0≥, <2.5	2.0<
Imaging findings (intestinal Dilation, wall thickening, adipose tissue consolidation around the intestine, ascites of unknown origin other than CDI, presence of the pseudomembrane)	No	-	Yes	-

*1 point added for each condition in the case of bloody stool.
Interpretation: ≤4 points, mild; 5-9 points, moderate; 10-13 points, severe; ≥14 points, extremely severe.

the presence of fever (temperature > 38.5°C), marked leukemia (white blood cell count > 15 × 10^9/L), and elevated serum creatinine levels (>50% above the reference value)[38]. Intestinal dilation, wall thickening, and adipose tissue consolidation around the intestine are also considered as reference findings if severe CDI is suspected. Severely complicated CDI (or fulminant CDI) is characterized by the presence of any of the following CDI-related phenomena: hypotension, septic shock, elevated serum lactate levels, ileus, toxic megacolon, bowel perforation, or a fulminant course (i.e., rapid deterioration)[38].

The MN criteria was developed by Mikamo et al. in Japan (Table 3) to facilitate the classification of CDI severity[6,39]. Meta-analyses have revealed that the cure rate of fidaxomicin was significantly higher than that of VCM, whereas its recurrence rate is lower than that of VCM in the first-episode and nonsevere disease groups[40]. The Japanese guidelines for the treatment of CDI recommend selecting the drug after assessment of the following factors: whether the disease is primary or recurrent, severity, risk of recurrence, and refractoriness. In addition to MTZ and VCM, fidaxomicin is another first-line drug for the treat-

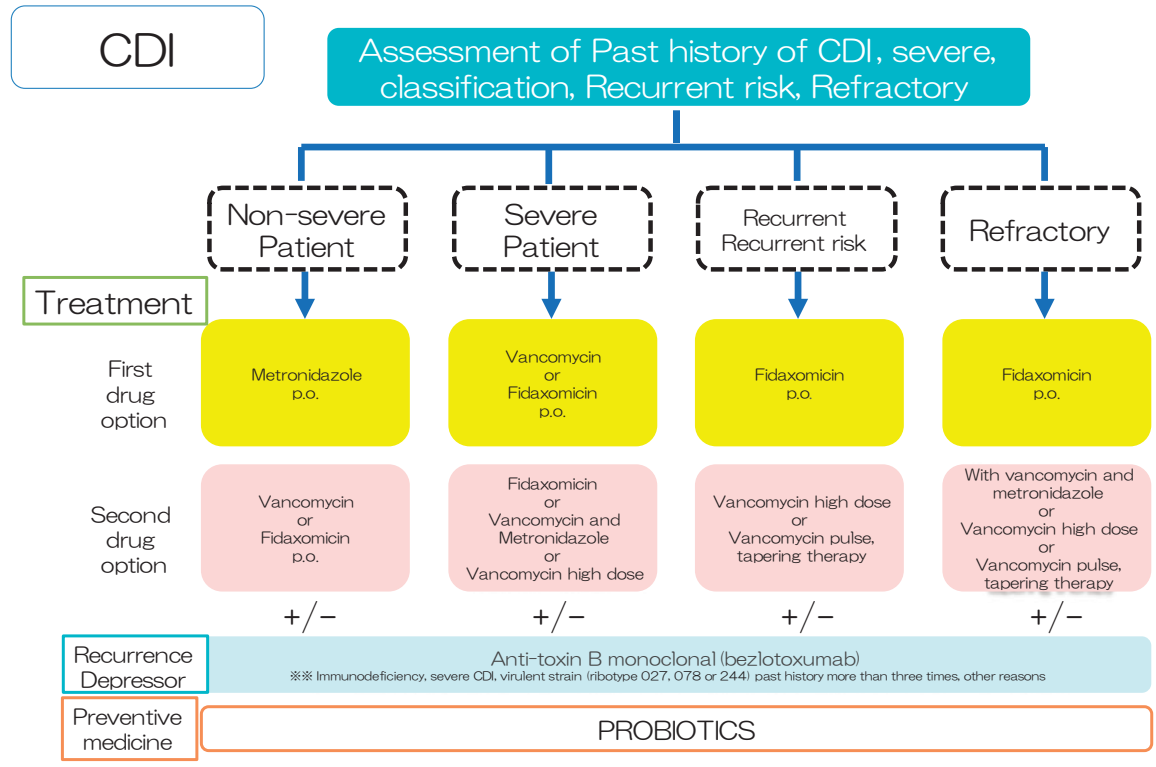

Figure 2. C. difficile treatment algorithm.
CDI: *Clostridioides difficile infection*
Bezlotoxumab has been withdrawn from the market and has no longer been covered by insurance in Japan since 2024.
Cited from Algorithm in Reference 48, 49.

ment of recurrent CDI or risk of recurrence (Figure 2)[5,6]. Notably, fidaxomicin exhibited a superior incremental cost-effectiveness ratio to VCM in cases of treatment failure with MTZ in Japan[41].

VCM (500 mg) is administered four times daily for 10 days via the oral or nasogastric route to patients with shock, hypotension, toxic megacolonization, or paralytic ileus. Alternatively, intravenous MTZ or 500 mg/100 mL of VCM can also be administered four times daily for 10 days via the intracolonic route[5,6]. Kim et al. reported that the intracolonic administration of VCM yielded favorable outcomes in 70% of critically ill patients[42]. Anti-toxin B antibodies (bezlotoxumab) are no longer available in the market (since 2024); however, neutralizing antibodies may protect the intestinal mucosa by neutralizing toxins, promoting a return to healthy microbiota, and protecting the systemic organs from toxin-induced cytokinesis. These approaches can be employed to formulate new treatment strategies for CDI in the future[43]. Live biotherapeutic products and microbiome medicines have exhibited efficacy. The use of these agents has been approved for the treatment of recurrent CDI overseas[44,45].

C. difficile Testing in Asymptomatic Patients

C. difficile is widely detected in humans and in the environment. Notably, *C. difficile* is detected in approximately 10% of hospitalized patients[3]. Fidaxomicin exerts an anti-spore effect and reduces the time period during which *C. difficile* can be detected in stool samples; however, treatment with MTZ or VCM enables the detection *C. difficile* in the stool samples[46]. According to the CDI guidelines from the Japanese Society for Infection Prevention and Control, patients with CDI may continue to shed *C. difficile* in their stools and contaminate the environment even after the resolution of diarrhea. Furthermore, the risk of recurrence after the end of treatment is high. Therefore, contact precautions should be implemented for at least 48 h after the resolution of diarrhea, if possible[5]. Carriers of *C. difficile* are at risk of developing and transmitting CDI; however, implementing contact precautions, including the isolation of carriers in private rooms and administration of anti-*C. difficile* agents, is not recommended in this population[7]. Patients continue to test positive following CDI treatment. Thus, confirmation of negative test results after CDI treatment is unnecessary. Moreover, carriers should not necessarily be subject to isolation. Environmental disinfection is effective in the preven-

tion of CDI. Thus, environmental disinfection using UV-C or hydrogen peroxide spraying equipment should be considered[47]. *C. difficile* testing of asymptomatic individuals can be conducted in consultation with local experts in the event of CDI outbreaks or the emergence of highly virulent strains, such as ribotype 027[48,49].

Environmental Sampling for *C. difficile*

Tests for culturing pathogens in hospital environments have been employed to evaluate the adequacy of environmental cleaning and disinfection. Environmental sampling during CDI outbreaks ensures that adequate cleaning and disinfection have been performed; this helps lift restrictions on admission to hospital wards and rooms[48,49].

Direct observation and environmental sampling have been employed to objectively evaluate the adequacy of environmental cleaning and disinfection. Environmental sampling is subdivided into simple, rapid, and inexpensive observations of wipe adequacy, such as fluorescent wipe tests, adenosine triphosphate (ATP) wipe tests, and microbiological methods, to detect toxigenic *C. difficile* using culture and NAAT[48,49].

Environmental sampling can confirm environmental contamination. Thus, environmental sampling, with the use of molecular epidemiological analysis, can contribute to epidemiological studies. The sampling method has a low detection rate for *C. difficile* when swabs are utilized for sample collection, even when using the flocculent type. However, a good detection rate can be achieved by using the sponge or contact plate method[50-52]. The ATP wipe test, a simple, quick, and easy-to-understand indicator of cleaning, has been widely employed in infection control team activities. The ATP levels in ATP swab tests exhibit a significant correlation with culture positivity, with 3% of cultures from the same site being positive when the ATP levels are <250 relative light unit compared with 19% when the ATP levels are higher[53].

Conclusion

CDI is a common anaerobic infection occurring in healthcare facilities. Appropriate clinical assessment using the Bristol Stool Scale and diagnosis using appropriate laboratory methods play a pivotal role in treatment and infection control. Therefore, multiprofessional understanding and collaboration are integral in enabling appropriate testing, diagnosis, and treatment of CDI. In recent years, NAAT has played an important role in the rapid and accurate diagnosis of various infectious diseases. Thus, the active use of NAAT is expected.

Acknowledgements

We thank the staff working on CDI treatment and infection control.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Conceptualization: T.T. and H.A.; methodology: T.T., H.K., M.K., and H.A.; software: T.T.; validation, T.T., H.K., M.K., and H.A.; formal analysis, H.K.; investigation, H.K. and M.K.; resources, T.T.; and data curation, H.K. and M.K. Writing-original draft preparation, T.T. and H.A.; writing-review and editing, T.T.; visualization, T.T. and H.A.; supervision, H.K. and M.K.; project administration, T.T. All authors have read and agreed to the published version of the manuscript.

Approval by Institutional Review Board (IRB)

Not applicable

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