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ORIGINAL RESEARCH ARTICLE

Effectiveness of *Saccharomyces boulardii* CNCM I-745 in Adult Indian Patients with Diarrhoea: A Real-world, Multicentre, Retrospective, Comparative Study

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Abstract

Background Multiple clinical studies have described the benefits of probiotic *Saccharomyces boulardii* (*S. boulardii*) CNCM I-745 against diarrhoea, but the real-world evidence supporting its use is lacking.

Objective To evaluate effectiveness of the *S. boulardii* CNCM I-745 group in a real-world setting.

Methods This was an electronic medical record (EMR)-based, retrospective, multicentre, comparative study in Indian adult patients presenting with diarrhoea managed between January 2020 and January 2022. Data of patients at the baseline visit, with a follow-up visit within 15 days, and who were administered *S. boulardii* CNCM I-745 (for the test group) or any other treatment modality excluding probiotics (for the control group) were considered. Effectiveness was evaluated on the basis of number of patients who did not complain of diarrhoea at follow-up.

Results Of 30,385 adult patients with diarrhoea, 270 patients prescribed *S. boulardii* CNCM I-745 were included, while the control group comprised 1457 patients. The baseline median age of the test group was 47 years (range 19–86 years), while it was 44 years (range 19–100 years) for the control group. The majority of patients in both study groups were females (56.7% in the test and 51.5% in the control group). Median duration between visits was 5 days (range 1–15 days) in both study groups. In all, 77.8% patients (95% CI 72.34–82.59) in the test group did not complain of diarrhoea at follow-up, while the proportion was 15.8% (95% CI 13.95–17.76) in the control group ($p < 0.05$). Odds ratio (OR) for absence of diarrhoea in the *S. boulardii* CNCM I-745 group versus the control group was 18.7 (95% CI 13.6–25.7, $p < 0.05$). For subgroups on concomitant antibiotics, a significant advantage was noted again for the test versus the control group (76.8% versus 18.4%; $p < 0.05$; OR: 14.7 with 95% CI 8.8–24.4; $p < 0.05$).

Conclusion The effect of *S. boulardii* CNCM I-745 probiotic in controlling diarrhoea was better than anti-diarrhoeal and/or oral rehydration therapy in real-world clinical practice. The effect was similar even with concomitant antibiotic usage.

1 Introduction

Diarrhoea is defined by the World Health Organization (WHO) as the passage of three or more loose or watery stools per day [1]. The etiological factors related to diarrhoea include infections from bacterial, viral or protozoal organisms, and other causes such as medications (antibiotics, non-steroidal anti-inflammatory drugs and chemotherapeutic agents) [2]. Based on the symptoms and duration, diarrhoea could be acute or chronic and infectious or non-infectious. Acute diarrhoea lasts less than 2 weeks and is commonly due to infections, while chronic lasts longer (> 2 weeks) and is generally non-infectious. According to the global burden of disease study on the burden of diarrhoea in India from 1990 to 2019, the mortality rate per 100,000 population for all ages was 45.46, under 5 years was 47.24; 5–14 years was 6.31, 15–49 years was 6.65, 50–69 years was 62.76, and > 70 years was 682.21 [3]. The prevalence of diarrhoea is highly heterogeneous across Indian states, and it ranged from 0.1 to 33.8% in the period between 2007 and 2008 and 0.6–29.1% in the period between 2015 and 2016

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Key Points

Real-world and observational studies are important to understand whether the benefits and efficacy of *S. boulardii* CNCM I-745 seen in clinical trials are replicated in clinical practice.

There is a scarcity of Indian studies which have evaluated the effectiveness of *S. boulardii* CNCM I-745 in diarrhoea, which may reduce the duration as well as frequency of loose motions.

In this study it was found that there was a significant improvement noted in adult patients of diarrhoea managed with *S. boulardii* CNCM I-745. The effect of *S. boulardii* CNCM I-745 probiotic in controlling diarrhoea was better than other anti-diarrhoeal and/or oral rehydration therapy in the real-world practice, irrespective of concomitant administration of antibiotics.

[4]. A recently published Indian study by Shrivastava et al. evaluated the prevalence of diarrhoea among older Indian adults between 2017 and 2018 [5]. About 15% of older adults reported to the physician with complaints of diarrhoeal episodes over the preceding 2 years. Every year, over 10 million patients suffer from diarrhoea in India, and over 1000 deaths are reported consequently [6]. Of these cases, 90% are attributed to unsafe drinking water, inadequate sanitation and poor hygiene [7]. The mainstay of managing diarrhoea involves maintenance of hydration by oral rehydration or intravenous fluids. Oral rehydration solution is intended to decrease the mortality and morbidity due to diarrhoea by restoring hydration and electrolyte balance [8].

Apart from rehydration strategies, probiotics are also used in the management of diarrhoea [9]. A retrospective, multicentre, electronic medical record (EMR) study by Ragavan et al. evaluated the effects of *Saccharomyces boulardii* against acute diarrhoea in children. A significant reduction in the frequency of stools and duration of diarrhoea was noted in the *Saccharomyces boulardii* group versus the control group [9]. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [10]. The seven core genera of microbial organisms most often used in probiotic products are *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia*, and *Bacillus* [11]. Yeast probiotics differ from bacterial probiotics in size, cell wall composition, antibiotic resistance and metabolic properties [12, 13]. Compared with bacterial probiotics, yeast cells are naturally resistant to antibiotics, as they are fungi, and there is no observed DNA exchange pertaining to antimicrobial resistance genes [14]. The only yeast genus that has been proven effective as probiotic in humans in double-blind studies is *Saccharomyces* [15]. Existing evidence strongly suggests that the efficacy of probiotics is both strain-specific and disease-specific [16]. The probiotic actions demonstrated by a particular strain of yeast are not extrapolatable to other strains. *Saccharomyces boulardii* (*S. boulardii*) CNCM I-745 is the first identified yeast strain that has been studied for use as a probiotic in human medicine. A study by Dinleyici et al. established that *S. boulardii* significantly diminished the duration of diarrhoea by about 24 h in the Western world, in both adults and children [17]. Multiple clinical studies have discussed the benefit of *S. boulardii* in the management of both adult and paediatric diarrhoea associated with various causes, whether it be antibiotics or *Clostridium difficile* (*C. difficile*) infection [18, 19]. A systematic review and meta-analysis by McFarland et al. noted that *S. boulardii* CNCM I-745 showed the strongest effect on decreasing the diarrhoea duration, as well as hospital stay in paediatric acute gastroenteritis cases [20]. There is a lack of Indian studies which have assessed the effectiveness of *S. boulardii* CNCM I-745 in adult diarrhoea, showing reduction in duration as well as the frequency of loose motions. We aimed to evaluate the effectiveness of *S. boulardii* CNCM I-745 in adult Indian patients with diarrhoea with the help of a retrospective, multicentre, comparative study. The study also evaluated the effectiveness of *S. boulardii* CNCM I-745 in comparison to non-probiotic treatment (control group) in adult diarrhoea patients. Diarrhoea is a major concern in India, with high morbidity and mortality related to it. In a study by Joseph et al.[6] the monthly prevalence rate of diarrhoea in India was reported as 12%, which was more than the monthly prevalence rate of 5.1 % reported from the USA [21]. Unsatisfactory living conditions and poor sanitation as a consequence of the population explosion in the country are significantly associated with presence of diarrhoea in Indian households.[6] If the diarrhoea is not controlled in time, malabsorption can affect the individual, leading to malnutrition and unintentional weight loss. Dehydration and severe renal damage from the dehydration are potential complications as well. Abnormalities in serum electrolytes can also be problematic and necessitate monitoring for replenishment requirements [22]. Hence, there is an urgent need for effective treatment modalities to control diarrhoeal episodes. Numerous clinical studies have noted the benefit of *S. boulardii* in the management of diarrhoea, but there remains a dearth in published real-world experience with the probiotic. Usually, the quality of the evidence produced in a randomized controlled clinical trial (RCT) holds greater credibility than that produced in the real world. However, the inference of results from an RCT can be restricted only to the kind of patients who were eligible for the RCT. In the real world, the clinician cannot exclude any patient from receiving treatment. Therefore, RCT results can

have generalizability restrictions [23, 24]. Real-world and observational studies are important to understand whether the benefits and efficacy of *S. boulardii* CNCM I-745 seen in clinical trials are replicated in clinical practice. This real-world study, which was planned to evaluate the effectiveness of *S. boulardii* CNCM I-745 in adult patients with diarrhoea, can help in bridging the gap between the clinical trial results and real-world practice.

2 Materials and Methods

Analysis was performed from an Indian electronic software, owned and administered by HealthPlix. HealthPlix is an Indian-origin-based EMR platform that operates from outpatient clinics and captures longitudinal information including demographics, diagnoses, medications, investigations, procedures conducted, functional status and other data elements.

This retrospective observational study assessed the data of adult patients presenting with diarrhoea at baseline visit, with at least one follow-up visit to the physician within 15 days and administered *S. boulardii* CNCM I-745 (for the test group) or any other treatment modality excluding probiotics (for the control group) between the period of January 2020–January 2022. In the control group, other treatment modalities are encompassed but not limited to rifaxamin, loperamide, racecadotril, ofloxacin, metronidazole and oral electrolytes. Patients whose relevant data were absent from the database due to any reason were not considered for study inclusion.

Ethics committee approval for the study was obtained on 8 August 2022 from the Suraksha Ethics Committee with the protocol number DRL-IND-GGI08-AAD/2022. Informed consent waiver was acquired, as this is a non-experimental, retrospective data analysis study. Patient confidentiality was maintained throughout the time, as the study was performed using anonymized data. The study was conducted in accordance with the applicable national regulatory laws and guidelines.

2.1 Outcome Measures

The primary outcome measure was to calculate the number of patients who complained of diarrhoea versus those who stopped to complain of diarrhoea or loose movements in the test group at follow-up visit. The key secondary outcome measure was comparing the effectiveness between the test group and the control group (non-probiotic treatment) on the basis of the number of patients who did not complain of diarrhoea or loose movements at follow-up visits to physician. Additionally, a subset analysis evaluating the effectiveness in patients who had received concomitant antibiotics was also conducted in both study groups.

2.2 Statistical Analysis

Descriptive statistics were used to summarize demographic and baseline characteristics. The continuous data was summarized using descriptive statistics [number of patients (n), mean, standard deviation (SD), median, minimum and maximum]. Categorical data (such as gender) were summarized using frequency count (n) and percentages (%). Odds ratio was calculated to compare the absence of diarrhoea between the test group and the control group in the study. A p-value of less than 0.05 was considered significant wherever applicable.

3 Results

3.1 Patient Disposition

The EMR records (January 2020–January 2022) comprised data of a total of 11,316,984 patients. Of these patients, the number of adult patients with diarrhoea, having at least one follow-up visit with physician within 15 days was 30,385. The total number of patients prescribed *S. boulardii* CNCM I-745 was 270, while the control group comprised 1457 patients who were not prescribed probiotics but were administered anti-diarrhoeal and/or oral rehydration therapy for managing diarrhoea (Fig. 1). In the control group, 21% of patients received ofloxacin, 10% of patients with rifaxamin, 8% with racecadotril, 5% with loperamide, 5% with metronidazole and 25% with oral electrolytes. Some patients were prescribed with more than one treatment option. Interestingly, it was observed that 376 (25.80%) patients in the control group had zinc as part of their prescription.

3.2 Demographic and Follow-Up Details

For the test group, the mean age was calculated to be 48.54 ± 16 years. The mean age in the control group was 45.84 ± 16.08 years. The majority of patients in both the study groups were females [$n = 153$ (56.7%) in the test group; $n = 750$ (51.5%) in the control group] (Table 1).

The duration between visits was similar in both groups, with the mean duration (SD) between visits in the test group noted as 5.97 days (3.71) and for the control group it was 5.95 days (4.02).

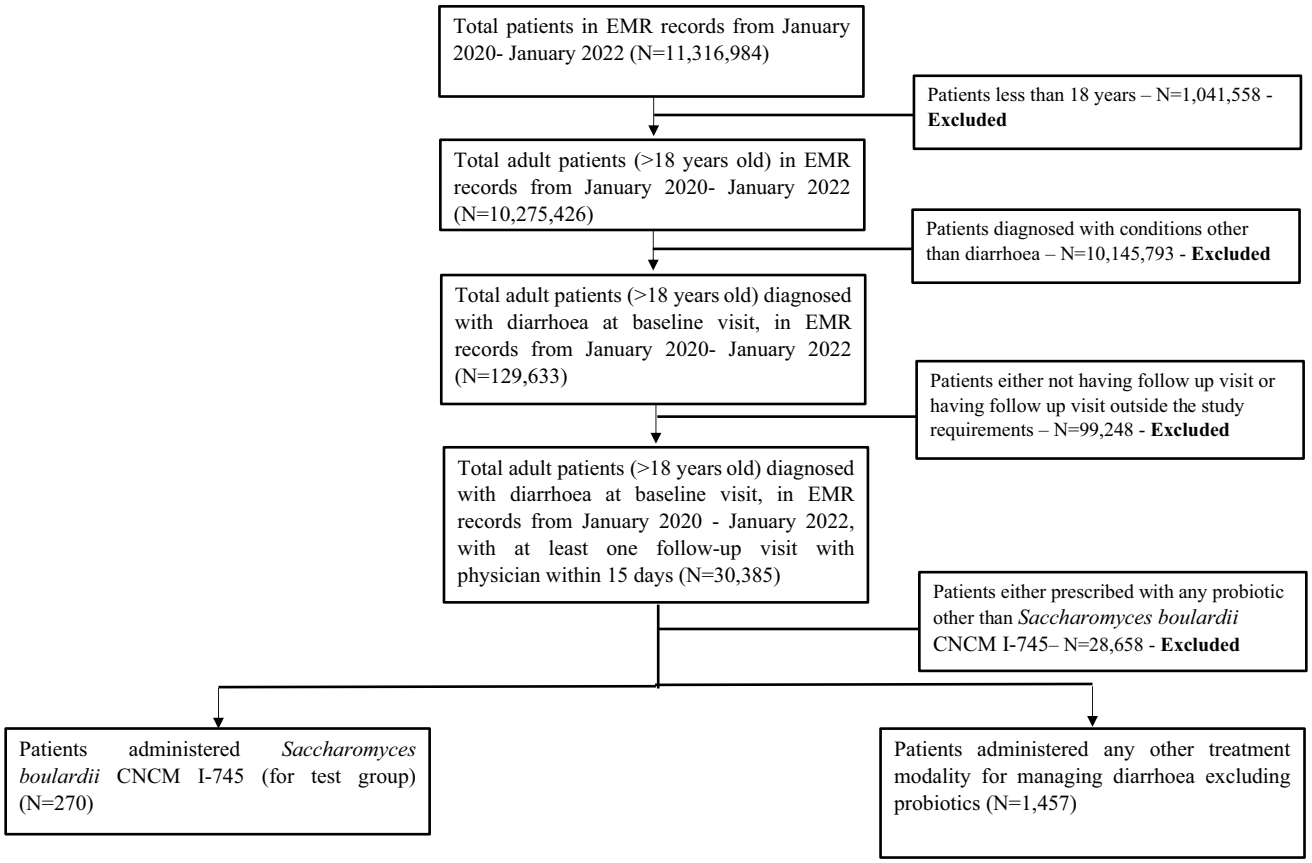

Fig. 1 Patient disposition in the study represented by CONSORT diagram. *EMR* electronic medical records, *N* number, *EMR* electronic medical records, *N* number

3.3 Study Outcome Assessment

In all, 77.8% patients (95% CI 72.34–82.59) in the test group did not complain of diarrhoea at follow-up, while 15.8% (95% CI 13.95–17.76) in the control group did not report diarrhoea complaint at follow-up. The proportion of patients with continued diarrhoea at follow-up was significantly lower in the test group versus the control group ($p < 0.05$) (Fig. 2). The odds ratio for noting absence of diarrhoea in the test group versus the control group was 18.7, with 95% confidence interval of 13.6–25.7 ($p < 0.05$). In total, 77.8% patients (95% CI 72.34–82.59) in the test group did not complain of diarrhoea at follow-up, while 15.8% (95% CI 13.95–17.76) in the control group did not report diarrhoea complaint at follow-up. The proportion of patients with continued diarrhoea at follow-up was significantly lower in the test group versus the control group ($p < 0.05$).

3.4 Concomitant Antibiotic Administration and Subset Outcome Analysis

A total of 112 patients with diarrhoea at baseline in the test group, and 392 patients with diarrhoea in the control group, were noted to have been administered concomitant antibiotics such as clarithromycin, amoxicillin plus clavulanic acid, azithromycin, cefpodoxime, doxycycline, ciprofloxacin, cefixime, metronidazole and cefuroxime. Doxycycline and metronidazole were the most frequently prescribed antibiotics in the study group.

On subset analysis involving patients who received concomitant antibiotics, it was noted that 76.8% patients (95% CI 67.86–84.24) in the test group did not complain of diarrhoea at follow-up compared with 18.4% (95% CI 14.66–22.56) in the control group, and this difference in proportion was statistically significant ($p < 0.05$; Fig. 3).

Table 1 Demographic characteristics

Characteristic	Test group ($N = 270$)	Control group ($N = 1457$)
Age (years)		
Mean ± SD (median)	48.54 ± 16 (47)	45.84 ± 16.08 (44)
Gender		
Males, *n* (%)	117 (43.3%)	706 (48.5%)
Females, *n* (%)	153 (56.7%)	750 (51.5%)

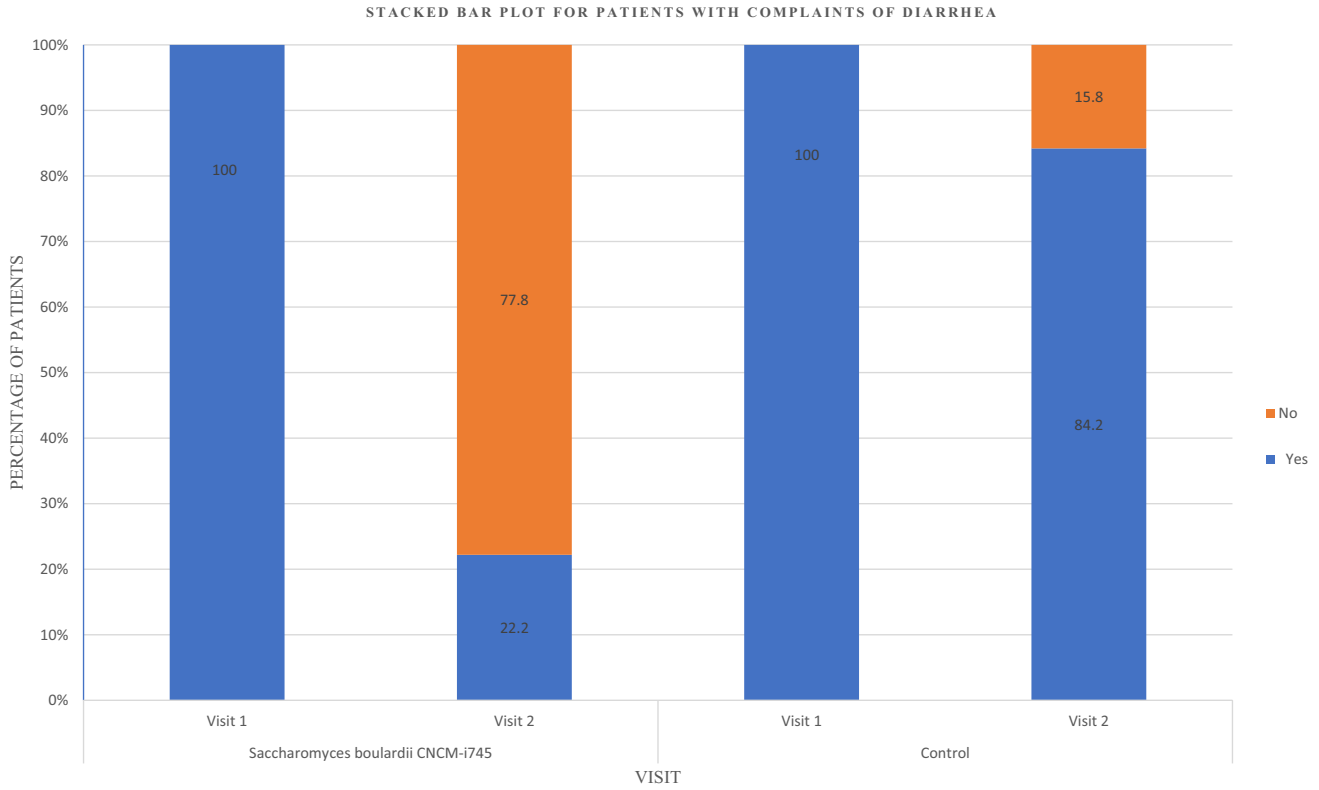

Fig. 2 Percentage of patients who had complaints of diarrhoea in study groups at baseline (visit 1) and follow-up visit (visit 2)

For patients who received concomitant antibiotics, the odds ratio for noting absence of diarrhoeal episodes at follow-up in the test group versus the control group was 14.7, with 95% confidence interval of 8.8–24.4 ($p < 0.05$). In total, 76.8% patients (95% CI 67.86–84.24) in the test group did not complain of diarrhoea at follow-up compared with 18.4% (95% CI 14.66–22.56) in the control group, and this difference in proportion was statistically significant ($p < 0.05$).

A comparison of the number of patients who complained of diarrhoea for patients ≥ 60 years between the test and control groups is presented in the supplementary tables.

4 Discussion

Of the total patients on EMR from January 2020 to January 2022, 129,633 patients had reported diarrhoea. Of these, 270 patients received *S. boulardii* CNCM I-745. After assessing the completeness of data, a comparative assessment was done between adult patients who received *S. boulardii* CNCM I-745 (test group) and other non-probiotic treatment modalities (control group). The age range of patients included in the test group was 19–86 years, which led to the assessment of *S. boulardii* CNCM I-745 effectiveness across all adult age groups. The majority of patients were females in both groups. Though the gender predilection of diarrhoea is not observed in scientific literature, some diseases such as irritable bowel syndrome (IBS) are found to be more common in women [25, 26]. Hence, some of the included patients may be suffering from irritable bowel syndrome, leading to female predilection in the current study.

On outcome assessment at follow-up, 77.8% patients in the test group did not complain of diarrhoea at follow-up, versus 15.8% in the control group. Thus, the proportion of patients experiencing cessation of diarrhoea at follow-up was almost five times in the test group versus the control group, signifying a decrease in the prevalence of diarrhoea in the test group, and the odds ratio was also significantly higher on similar lines. An outcome assessment in the subset of patients who received concomitant antibiotics was also conducted to understand the influence of antibiotic administration on the effectiveness. A similar trend was noted when the patients on concomitant antibiotics were assessed. In all, 76.8% patients in the test group did not complain of diarrhoea at follow-up, versus 18.4% in the control group for subgroups on concomitant antibiotics, which was in line with the overall analysis. Hence, the effectiveness of *S. boulardii* CNCM I-745 persisted even with concomitant antibiotic usage.

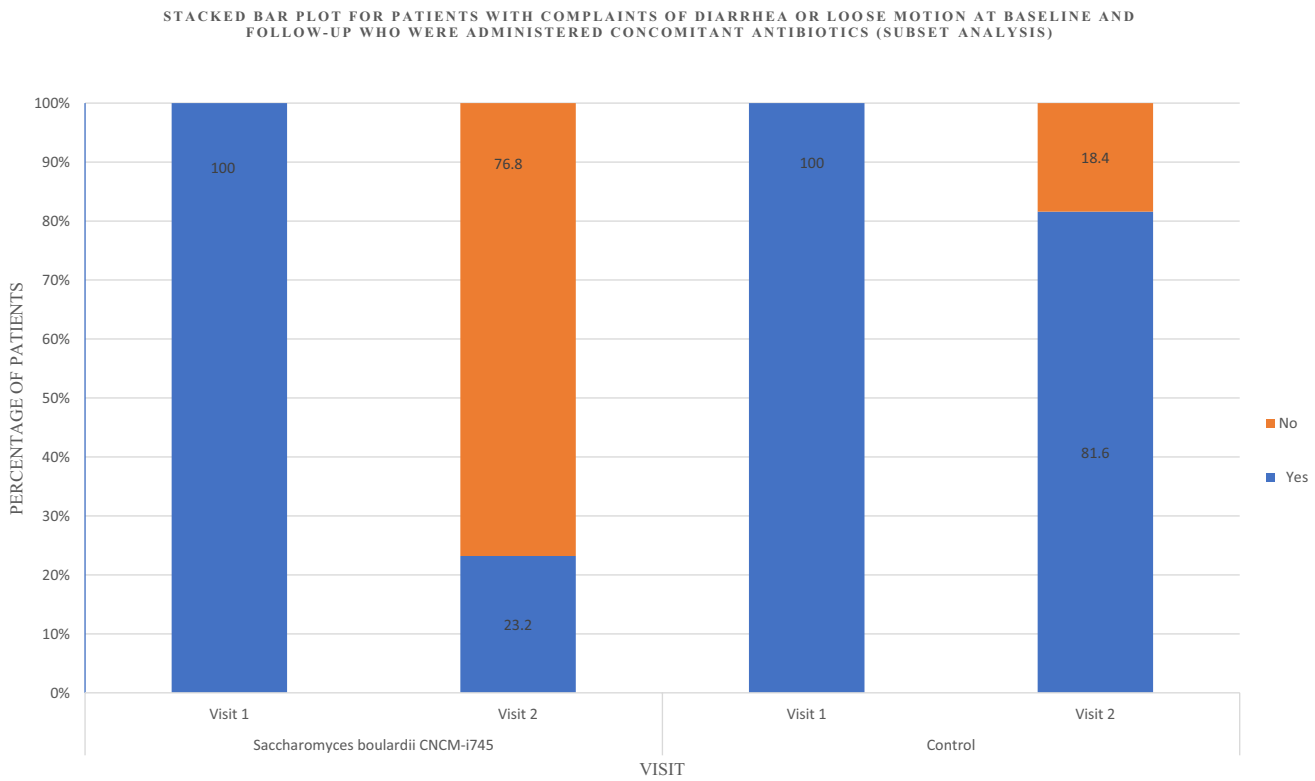

Fig. 3 Percentage of patients who had complaints of diarrhoea in study sub-groups (who received concomitant antibiotics) at baseline (visit 1) and follow-up visit (visit 2)

The clinical guideline update by Szajewska et al. was published in 2020, on behalf of the Working Group of Probiotics and Prebiotics of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. This update made weak recommendations for *S. boulardii* usage in the management of children with acute gastroenteritis [27]. A systematic review and meta-analysis by McFarland et al. noted that *S. boulardii* CNCM I-745 had the strongest effect on reducing the duration of diarrhoea and hospital stay in paediatric acute gastroenteritis cases [20]. Our present study mentions the effect of *S. boulardii* CNCM I-745 in specifically adult population, a distinct objective from other similar studies which have assessed *S. boulardii* CNCM I-745 mainly in paediatric population only.

As per the World Gastroenterology Organization Global Guidelines for recommendation of probiotics in adults, there is evidence supporting the use of *S. boulardii* in the treatment of acute diarrhoea in adults, antibiotic-associated diarrhoea, prevention of *C. difficile*-associated diarrhoea (or prevention of recurrence) [28]. One of the key findings related to diarrhoea in the general population is intestinal dysbiosis. Intestinal dysbiosis can be defined as any alteration to the composition of resident commensal microbiota relative to the commensals found in healthy individuals [29]. Microscopic examinations have revealed a disruption of the protective mucus layer for different diarrheic dysbiotic situations such as inflammatory bowel disease (IBD; either Crohn's disease or ulcerative colitis), IBS, human immunodeficiency virus (HIV) enteropathy and other intestinal conditions. This disruption leads to the attachment of bacteria directly to the exposed mucosa and elicits a polymicrobial infection [30–32]. There are certain risk factors causing dysbiosis, such as malnutrition, old age, diabetes/metabolic syndrome and stress, which can destabilize the microbiota [33, 34].

Numerous clinical studies performed with lyophilized *S. boulardii* CNCM I-745 demonstrated efficacy and safety in a variety of gastrointestinal conditions associated with diarrhoea. In contrast to other probiotics, *S. boulardii* achieved broad clinical efficacy with significant positive outcomes in many different dysbiotic situations [35]. Some of the conditions where *S. boulardii* CNCN I-745 has strong evidence is in tackling antibiotic-associated diarrhoea, [36] preventing or reducing *C. difficile*-associated colitis or traveller's diarrhoea, significantly shortening duration of infectious diarrhoea and reducing the incidence of tube-feeding-associated diarrhoea in enterally fed patients [17]. The review article by Micklefield et al. [36] mentioned that 14 studies evaluating the effectiveness of *S. boulardii* demonstrated its protective effect against diarrhoea, ranging between 43.7% and 87.3%.

The meta-analysis by Szajewska et al. [18] used data from 21 studies, 15 of which were clinical studies done in adult population, with the objective of understanding the effectiveness of *S. boulardii* in preventing antibiotic-associated diarrhoea. In 15 randomized controlled studies with 3114 participants, *S. boulardii* decreased the incidence of diarrhoea from 17.4% and 8.2% (RR: 0.49, 95% CI 0.38–0.63).

S. boulardii and its protein are known to inhibit proinflammatory cytokine production by interfering with the nuclear factor κB and modifying the activity of mitogen-activated protein kinases extracellular signal-regulated kinase (ERK1/2). This prevents gastrointestinal inflammation by upregulating the expression of peroxisome proliferator-activated receptor-gamma (PPAR-γ). Additionally, it inhibits the growth of bacteria, and the adhesion of host cells releases a protease that breaks down *C. difficile* toxin A and its intestinal receptor, and increases the generation of antibodies that fight toxin A [37]. The current study has strengthened and reinforced the existing evidence, showing the effectiveness of *S. boulardii*.

This is a real-world study which evaluated a large database of adult diarrhoea patients across India. However, the study had a few limitations. Lack of quality control in data collection and vulnerability to many sources of bias for outcome comparison are two potential drawbacks of the real-world evidence (RWE) study design used in the present study. Additionally, doses and dose effects of *S. boulardii* was not captured, and details of the pre-existing medical conditions were not recorded as part of the study. There was no specific definition for diarrhoea and the data of patients having a mention of diarrhoea or related terms in diagnosis section of the EMR were included. Data on the duration of diarrhoea were not available. Also, the study included cases with at least one follow-up visit, which might have excluded patients who recovered early and did not follow-up with the physician.

5 Conclusion

There was significant improvement noted in adult patients of diarrhoea managed with *S. boulardii* CNCM I-745. The effect of *S. boulardii* CNCM I-745 probiotic in controlling diarrhoea was better than other anti-diarrhoeal and/or oral rehydration therapy in the real-world practice, irrespective of concomitant administration of antibiotics.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-024-00424-3.

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Declarations

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Conflict of interest Dr Bhaskar Bikash Pal and Snehal Shah declare no conflicts of interest. Dr Rupali Vinodchandra Bandagi, Dr Kranthi Kiran Pebbili, Dr Rahul Rathod, Dr Bhavesh Kotak and Gauri Dhanaki are employees of Dr Reddy's Laboratories Ltd.

Availability of data and material All the data presented in the manuscript are in anonymized and aggregated format.

Ethics approval statement Ethics committee approval for the study was obtained on 8 August 2022 from the Suraksha Ethics Committee with the protocol number DRL-IND-GGI08-AAD/2022.

Patient consent statement Informed consent waiver was acquired, as this is a non-experimental, retrospective data analysis study.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions Dr Bhaskar Bikash Pal, Dr Rupali Vinodchandra Bandagi, Dr Kranthi Kiran Pebbili, Dr Rahul Rathod, Dr Bhavesh Kotak and Gauri Dhanaki contributed to conception, design, manuscript preparation, editing and review. Snehal Shah contributed to literature search, data acquisition, data analysis and manuscript review. All authors have read and approved the final version of manuscript.

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