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Research Article

Effect of multi-strain probiotics supplementation on chemotherapy-related side effects among patients with breast cancer: A pilot trial

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Abstract

This study aimed to identify the effect of a 7-strain probiotics formulation on chemotherapy-related side effects, complete blood counts, blood biochemistry, and Karnofsky performance scores. All patients diagnosed with breast cancer who received chemotherapy at a hospital in Surabaya, Indonesia, were considered eligible to join the study. Before probiotic supplementation, the baseline values of the tested parameters were obtained and later compared with the values after 21–30 days of probiotic supplementation. Multi-strain probiotics supplementation could alleviate the fatigue and nausea symptoms in our patients. Significant improvements were observed after probiotic supplementation compared to before supplementation in the Karnofsky performance scores (median: 100 versus 90, respectively; $p < 0.001$) and blood urea nitrogen (11.6 mg/dL versus 10.05 mg/dL, respectively; $p = 0.008$). Non-significant differences were found for the complete blood counts, alanine aminotransferase, and serum creatinine. Our findings provide preliminary evidence about the potential role of multi-strain probiotics supplementation to alleviate chemotherapy-related side effects.

Keywords

breast cancer, chemotherapy-related side effects, multi-strain probiotics

Introduction

Breast cancer ranks as the most common cancer globally among women, contributing to 11.5% of new cases and 6.8% of deaths in 2022 (Global Cancer Observatory 2022). The high prevalence demands serious attention due to its impact not only on mortality rates but also on the increasing healthcare burden for patients (Arnold et al. 2022; Franklin et al. 2024). Chemotherapy remains one of the primary therapies for patients with cancer.

While effective, it has both positive and negative impacts (Gennari et al. 2021). However, it should be anticipated that chemotherapy does not only target cancer cells; it also has the potential to harm normal cells, including those in the bone marrow (which produces blood cells), hair follicles, mouth, gastrointestinal tract, and reproductive system (American Cancer Society 2020; National Health Service 2023). These possible harmful effects could put the patients undergoing chemotherapy at a higher risk of experiencing side effects such as fatigue, weakness due to anemia, infections due to immune cell imbalance, bleeding, hair loss, and gastrointestinal disturbances (Di Nardo 2022). As one of the consequences of the side effects, patients could decide to stop receiving chemotherapy, which may lead to decreased survival rates (Krikorian et al. 2019).

In general, symptomatic treatment is considered effective to manage the chemotherapy-related side effects, such as providing the patients with ondansetron at the time patients experience nausea (Palesh et al. 2018). However, providing symptomatic treatment may not always result in an optimal relief of these symptoms, and, hence, efforts to provide complementary alternative therapies to minimize the risks of chemotherapy-related side effects have been globally discussed (Laugsand et al. 2011).

Probiotics are one of the alternative therapies being increasingly researched for their potential benefits in patients with cancer (López-Gómez et al. 2023). Probiotics consist of live microorganisms that, when administered in appropriate doses, can provide benefits for patients receiving chemotherapy (Behzadi et al. 2021). One of the main mechanisms of probiotics that can produce beneficial effects for patients is through the enhancement of the immune system (Chadha et al. 2021; Avtanski et al. 2023). Microorganisms commonly used in probiotics, such as lactic acid bacteria, have demonstrated antiproliferative effects on breast cancer cells (MDA-MB-231) by reducing the expression of cancer-testis antigen genes, which could potentially decrease the severity and improve the prognosis for patients (Abd El-Atti et al. 2009; Kumar et al. 2010; Jirillo et al. 2012).

The efficacy of probiotics to manage chemotherapy-related adverse effects has been documented in the published literature, which mainly focused on identifying the impact of probiotic supplementation on the incidence of oral mucositis and diarrhea (Wang et al. 2016; Shu et al. 2020; Feng et al. 2022). Whether probiotics could potentially be beneficial to manage other chemotherapy-related side effects has not yet been explored. Moreover, recent studies examining the use of probiotics to manage chemotherapy-induced side effects have mainly focused on patients with colorectal cancer and head and neck carcinoma, with fewer investigations involving patients with breast cancer (Dikeocha et al. 2021; Lu et al. 2022). Another important highlight in using probiotics to manage chemotherapy-related side effects is there are numerous mixes of probiotics which make it difficult to suggest one type of probiotic is superior over the others. Previous studies on probiotics have largely focused on single strains to evaluate their effectiveness in tumor growth parameters such as Interleukin-6 (IL-6) and IL-10 (Aragón et al. 2014; Adumuah et al. 2024). Strains supported by evidence in patients with breast cancer include *Lactobacillus acidophilus*, *Lactobacillus crispatus*, *Lactobacillus rhamnosus GG*, *Lactobacillus casei CRL 431*, *Bacteroides fragilis*, and *Bifidobacterium* (Masuda et al. 2023). However, research on multi-strain probiotics (comprising more than two types of microorganisms) and their effects on chemotherapy-related side effects is limited, particularly in patients with breast cancer in Indonesia (Csendes et al. 2022; Thu et al. 2023).

This study aimed to explore the effects of a 7-strain probiotics formulation on chemotherapy-related side effects, which included assessments of Karnofsky performance scores, complete blood counts, and blood biochemistry. The findings are expected to contribute to optimizing therapy for patients with breast cancer.

Methods

Study design

This prospective cohort study was conducted to observe patients with breast cancer undergoing chemotherapy and receiving probiotic supplementation at one hospital in Surabaya, Indonesia. The probiotics used in this study contain *Rhodopseudomonas palustris* EMRO 201 (>2.0 × 10^6 cfu/ml), *Lactobacillus casei* EMRO 002 (>2.0 × 10^6 cfu/ml), *Lactobacillus casei* EMRO 213 (>2.0 × 10^6 cfu/ml), *Lactobacillus plantarum* EMRO 009 (>2.0 × 10^6 cfu/ml), *Lactobacillus fermentum* EMRO 21 (>2.0 × 10^6 cfu/ml), *Lactobacillus rhamnosus* EMRO 014 (>2.0 × 10^6 cfu/ml), and *Lactobacillus bulgaricus* EMRO 212 (>2.0 × 10^6 cfu/ml). According to the product summary leaflet, the antibiotics should be given in doses of 7.5 mL–15 mL three times daily.

Research variables

The independent variables in this study were the patients' sociodemographic data, which included age, gender, treatment history, chemotherapy regimen received, and breast cancer diagnosis at various stages of severity. The dependent variables in this study were the occurrence of side effects after probiotic administration, assessed through the performance score evaluated using the Karnofsky questionnaire, complete blood count, and blood biochemistry tests for alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine.

Population and sample

All patients with breast cancer receiving chemotherapy at a hospital in Surabaya, Indonesia were considered eligible

for this study. However, only patients whose treating physicians allowed the treatment and the patients who agreed to take probiotics were included in this study.

Data collection

In this study, primary data were obtained through the steps described below:

a. Patient identification: Patients with breast cancer undergoing chemotherapy at a hospital in Surabaya, Indonesia, were identified by the research team in collaboration with the attending nurses.
b. Informed consent and sociodemographic data: Patients were explained the purpose of the study and asked to sign an informed consent form. Sociodemographic data were collected by the research team and documented in standardized forms.
c. Outcome observation: Outcomes were assessed using the Karnofsky performance scores to evaluate the patients' ability to perform daily activities. This evaluation was conducted by the research team in collaboration with the attending nurses. In addition, observations also included laboratory results, including complete blood tests and blood biochemistry (ALT, BUN, and creatinine), as reported by the hospital laboratory.
d. Observation points: Two observation points were established to evaluate the study outcomes as described below.
   - Before chemotherapy: Observations were conducted prior to probiotic supplementation administration (pre-probiotics).
   - Before the next chemotherapy cycle: Observations were conducted after 21–30 days of probiotics administration (post-probiotics). Probiotics were administered three times daily in a dose between 7.5 mL and 15 mL per intake for approximately three weeks, spanning from post-chemotherapy until just before the next chemotherapy cycle. One of the research teams contacted the patients regularly to monitor whether the patients developed any symptoms after using the probiotics.

Data analysis

The data obtained in this study are presented descriptively, covering the sociodemographic characteristics of the patients, Karnofsky performance score assessments, and the results of complete blood tests and blood biochemistry (ALT, BUN, and Creatinine) for the patients with breast cancer before and after the administration of the probiotics. Statistical analysis used a difference test to evaluate changes in these parameters. A significant difference was determined if the p-value was < 0.05. The statistical difference was identified using SPSS 29 (IBM Corp., Chicago) with Wilcoxon signed rank tests if the data were not distributed normally and paired t-tests if the data were distributed normally. The effect sizes were also estimated for the analysis.

Results and discussion

There were 28 participants involved in this study. Table 1 describes the demographic data of the participants, and Table 2 describes the chemotherapy data provided to the patients. Tamoxifen was mostly prescribed to the patients. The existing evidence supported the use of tamoxifen for patients with breast cancer owing to its efficacy and safety profile after tamoxifen has been on the market for decades (Buijs et al. 2024). In addition to tamoxifen, letrozole was found as the second most frequently used chemotherapy in our study. Letrozole is recommended as the adjuvant therapy since the existing evidence supported the efficacy of this agent as the adjuvant therapy (Hortobagyi et al. 2018; Ruhstaller et al. 2018).

Table 1. Sociodemographic profile of patients with breast cancer.

Sociodemographic		Frequency	Percentage
Age classification	Elderly	5	17.86%
	Adult	23	82.14%
Gender	Female	28	100.00%
Diagnosis	Ca mamae S	20	71.43%
	Ca mamae D	8	28.57%
Education background	Senior high school	14	50.00%
	Bachelor	12	42.86%
	Master	2	7.14%
Duration of observation	21 days	9	32.14%
	30 days	19	67.86%
Care provision	Outpatient	19	67.86%
	Inpatient	7	25.00%
	One Day Care	2	7.14%

Ca mamae S, carcinoma mammae sinistra; Ca mamae D, carcinoma mammae dextra.

Table 2. Chemotherapy profile of patients with breast cancer.

Class	Chemotherapy	Dosage	Frequency	Route	Total
Alkylating agent	Cyclophosphamide	700 mg	1	IV	3
		750 mg	1		
		850 mg	1		
Anthracycline	Doxorubicin	50 mg	1	IV	2
		80 mg	1		
Taxane	Docetaxel	100 mg	1	IV	4
		110 mg	1		
		120 mg	2		
	Paclitaxel	240 mg	1	IV	
Platinum-based agent	Carboplatin	450 mg	1	IV	1
Monoclonal antibody	Trastuzumab	370 mg	1	IV	3
		400 mg	1		
		720 mg	1		
	Pertuzumab	420 mg	1	IV	1
Aromatase inhibitor	Exemestane	25 mg	1	Oral	10
	Letrozole	2.5 mg	9		
Hormonal therapy	Tamoxifen	10 mg	11	Oral	12
		20 mg	1		

Most of the patients were compliant with the regimens of the probiotics in this study (Table 3), although one patient decreased the frequency of probiotic administration. The reason for decreasing the frequency of the multi-strain probiotics was related to the clinical condition of the patient, who felt fatigue, and the treating physician asked to decrease the frequency of the multi-strain probiotics administration. Even though no post-marketing reports about fatigue were submitted to the Indonesian Food and Drug Supervisory Agency, the research team agreed with the suggestion of the treating physician.

Table 3. Dosing regimens of probiotics.

	Frequency	Percentage
Dosage		
3 × 15 ml	18	64%
3 × 7.5 ml	9	32%
2 × 7.5 ml	1	4%
Compliance with the recommended dosing regimens in the product summary leaflet		
Yes	27	96%
No	1	4%

Fatigue and nausea (60.71%) were the most reported complaints by the patients during chemotherapy and before receiving multi-strain probiotics (Table 4). These most-reported complaints were consistent with the documented side effects of tamoxifen and letrozole in the published literature (Arnold et al. 2001; Bauml et al. 2015; Mao et al. 2018). Two out of 17 patients who complained of fatigue and nausea continued to experience fatigue and nausea after using multi-strain probiotics, which further highlighted the improvement of the symptoms in the majority of the patients (88.23%) after using the probiotics in this study. Inflammation has been identified as a critical biological pathway in cancer-related fatigue (Bower et al. 2014; O'Higgins et al. 2018). In addition, alterations in the intestinal microbiome have been observed in fatigue syndrome among patients with cancer (Hajjar et al. 2021). Understanding the underlying mechanism of fatigue syndrome among patients with cancer would help clarify the rationale of using probiotic supplementation to alleviate the symptoms. Regarding the findings about fewer patients in our study complaining about nausea after receiving probiotics, similar findings were reported in a relatively recently published study by Wei et al. (2024).

One patient complained of having the flu and a cough before receiving the multi-strain probiotics, and after discussion with the treating physicians, it was not considered a chemotherapy-related side effect. A total of 10 patients did not experience any symptoms before and after receiving the multi-strain probiotics supplementation. This finding supports the conclusion that the use of the multi-strain probiotics product in our research did not trigger fatigue and nausea symptoms but, actually, it could alleviate these symptoms as explained in the earlier paragraph. Moreover, our findings were further supported by the post-marketing surveillance reported by the Indonesian Food and Drug Supervisory Agency.

Table 4. Symptoms pre-post probiotics.

No	Symptoms	
	Pre-probiotics	Post-probiotics
1	Fatigue	None
2	Fatigue	Fatigue
3	Nausea	None
4	Nausea	None
5	Fatigue	Fatigue
6	Fatigue	None
7	Fatigue	None
8	Flu and cough	None
9	Fatigue	None
10	Dizziness	None
11	None	None
12	None	None
13	Nausea	None
14	None	None
15	None	None
16	Nausea	None
17	Fatigue	None
18	None	None
19	None	None
20	None	None
21	Dizziness	None
22	Nausea	None
23	Nausea	None
24	None	None
25	Dizziness	None
26	None	None
27	None	None
28	Fatigue	None

Multi-strain probiotics did not improve the complete blood count profile, particularly hemoglobin levels (Table 5). Only small and limited studies investigated the effects of probiotics on thrombocyte count, especially *in vivo*. Our findings are consistent with what has been documented in the published literature (Zhou et al. 2005; Collins et al. 2012; Mansouri-Tehrani et al. 2015). A randomized clinical trial performed on 46 patients with pelvic cancers (colorectal, prostate, endometrial, bladder, ovary, cervical, and bone) undergoing radiotherapy investigated the effect of probiotics on erythrocyte, leucocyte, and thrombocyte counts. The probiotic capsule used in the study contained: *Lactobacillus casei* 1.5×10^9 CFU, *Lactobacillus acidophilus* 1.5×10^{10} CFU, *Lactobacillus rhamnosus* 3.5×10^9 CFU, *Lactobacillus bulgaricus* 2.5×10^8 CFU, *Bifidobacterium breve* 1×10^{10} CFU, *Bifidobacterium longum* 5×10^8 CFU, and *Streptococcus thermophilus* 1.5×10^8 CFU per 500 mg. There were no statistically significant differences in the mean reduction of all blood count parameters (erythrocytes, leucocytes, and thrombocytes) before and after radiotherapy between the probiotic group and the placebo group. The statistically non-significant

Table 5. Profile of hemoglobin, thrombocytes, and leucocytes pre-post probiotics.

No	Hemoglobin (g/dL)		Thrombocytes (10^3/microL)		Leukocytes (10^3/microL)	
	Pre-probiotic	Post-probiotic	Pre-probiotic	Post-probiotic	Pre-probiotic	Post-probiotic
1	12.9	13.2	336	283	12.53	10.84
2	10.9	11.3	436	423	20.8	18.26
3	11.2	12.9	281	379	6.92	7.89
4	11	11.3	445	399	14.82	9.82
5	10.2	10.3	362	344	4.24	5.22
6	11.9	12.2	272	284	10.05	9.8
7	10.2	11.7	223	225	6.24	6.28
8	12.1	11.8	339	326	9.36	9.94
9	14.2	15.7	298	312	9.94	9.8
10	13.4	15.4	322	358	9.11	8.89
11	12.4	12.3	180	202	3.38	4.38
12	12.3	13.2	304	326	7.25	7.23
13	13.6	12.7	231	203	5.66	5.26
14	12.5	13.9	298	312	8.86	7.83
15	15.3	16.5	227	263	7.04	9.21
16	11.3	10.1	193	200	6.61	6.81
17	13.3	13.6	225	245	10.03	9.28
18	12.8	14.8	129	136	4.68	5.02
19	11	11.2	261	226	5.33	4.21
20	12.4	12.3	372	359	7.24	7.62
21	12.1	13.9	254	276	4.85	5.02
22	11.9	12.5	309	300	6.5	6.78
23	13.9	14.7	207	250	3.9	4.5
24	12	13.4	341	315	7.59	8.05
25	11.6	12.3	206	236	3.69	4.89
26	10.3	9.7	282	235	9.59	4.92
27	12.4	12.6	352	275	6.59	5.22
28	13.3	13.7	269	350	10.02	9.87
Mean	12.2286	12.8286	284.0714	287.2143	7.9579	7.6014
St Dev	1.24658	1.66308	74.41671	67.68957	3.70396	2.95697
Median	12.2	12.65	281.5	283.5	7.14	7.425
Minimum	10.2	9.7	129	136	3.38	4.21
Maximum	15.3	16.5	445	423	20.8	18.26
p-value	0.198		0.671		0.699	
Effect sizes	0.259		0.081		0.05	

St Dev, standard deviation.

result was suggested to be attributed to the localized effects produced by probiotics rather than the systemic effects (Mansouri-Tehrani et al. 2015). Similarly, an *in vitro* study of *Lactobacillus rhamnosus* and *Bifidobacterium lactis* demonstrated no effect of these probiotic candidates on spontaneous thrombocyte activation and aggregation. The lack of effect on thrombocytes is one of the expected properties of probiotics. This is because thrombocyte activation and aggregation are important mechanisms that contribute to the development of thrombus. Thrombotic occurrence will lead to certain disorders or diseases. Accordingly, probiotics made from bacterial strains without remarkable effects on thrombocytes have higher safety value for human consumption than the ones compounded from aggregating strains (Zhou et al. 2005). However, another *in vitro* study demonstrated that a certain *Lactobacillus* strain was able to bind to human fibrinogen, hence, increasing its risk for thrombotic complications. Therefore, it is crucial to assess the potential pathogenicity of bacterial strains used for probiotic supplementation in treatment protocols (Collins et al. 2012).

The results of the blood biochemistry tests showed a significant improvement of BUN levels (Table 6) after the use of probiotic supplementation, even though the median BUN values of the patients before receiving probiotics were within the normal range. The median of BUN before and after receiving probiotics was 11.6 mg/dL (5.8–6.1 mg/dL) and 10.05 mg/dL (6.1–16.8 mg/dL), respectively (p = 0.008). Even though the BUN improvement after receiving probiotics in our study occurred among patients with normal BUN levels, our findings could indicate a promising impact of BUN improvement if the probiotics are given to patients with high BUN levels as the baseline. In the study by Firouzi et al. (2015), it is suggested that probiotics have a more significant impact on the improvement of BUN levels among individuals with higher baseline urea levels. The mechanism of probiotics in lowering BUN could be related to the reduction of inflammation and oxidative stress. When inflammation

Table 6. Blood chemistry profile test pre-post probiotics supplementation.

No	ALT (unit/L)		BUN (mg/dL)		Creatinine serum (mg/dL)	
	Pre-probiotic	Post-probiotic	Pre-probiotic	Post-probiotic	Pre-probiotic	Post-probiotic
1	26	29	12	9.6	0.56	0.72
2	16	13	11.6	10.6	0.93	0.89
3	13	12	6.2	7.5	0.6	0.56
4	30	29	9.6	8.8	0.62	0.58
5	9	8	18.2	10.5	0.84	0.75
6	16	12	5.9	6.8	0.78	0.56
7	26	25	12.2	9.4	0.76	0.69
8	27	31	10.3	8.6	0.78	0.82
9	19	16	9.6	8.7	0.58	0.52
10	19	16	9	9.2	0.95	0.9
11	19	14	7.6	6.1	0.46	0.49
12	41	38	17.2	16.7	0.83	0.78
13	17	16	12.4	9.5	0.71	0.73
14	23	21	11.7	10.8	0.65	0.59
15	54	56	11.2	7.6	0.44	0.47
16	17	19	12.8	12.7	0.94	0.86
17	14	11	16.8	12.2	0.92	0.92
18	14	11	12.2	11.8	0.71	0.69
19	6	9	9.5	12.5	0.65	0.74
20	26	30	13.3	11.6	0.86	0.7
21	24	22	5.8	6.97	0.68	0.58
22	15	13	11.6	10.8	0.6	0.57
23	17	14	8.8	8.3	0.69	0.72
24	16	17	8.1	7.82	0.69	0.59
25	14	11	12.6	10.7	0.69	0.57
26	29	23	13.9	10.8	0.81	1.08
27	16	35	9.6	11.6	0.74	0.75
28	15	14	17.5	16.8	0.93	0.91
means	20.6429	20.1786	11.3286	10.1782	0.7286	0.7046
St Dev	9.74	10.82881	3.35138	2.58761	0.14078	0.15186
median	17	16	11.6	10.05	0.71	0.71
minimum	6	8	5.8	6.1	0.44	0.47
maximum	54	56	16.8	16.8	0.95	1.08
p-value	0.119		0.008*		0.192	
effect size	0.21		0.542		0.27	

*$p < 0.05$; ALT, alanine aminotransferase; BUN, blood urea nitrogen; St Dev, standard deviation.

and oxidative stress occur, the protein catabolism increases, which will further lead to the incremental increase of BUN levels (Bulteau et al. 2006; Fukushima et al. 2017).

Significant improvement of Karnofsky performance scale scores after probiotic use was observed in our study (Table 7). To the best of our knowledge, our study is the first to explore the potential benefits of multi-strain probiotics on overall physical function using the Karnofsky performance scale. Improvement in physical function will enable patients to perform daily activities independently and reduce their reliance on others. Knowledge in these cases is limited concerning the mechanism of probiotics in improving the overall physical function. However, it could be suggested that improvement of the symptoms, including fatigue and nausea, would impact the incremental improvement of the patient's physical function.

This study is considered to be limited in size and setting. However, since this is a pilot study, it has fulfilled the exploratory role as one of the first known trials of the effects of multi-strain probiotics supplementation on improving breast cancer patients' performance undergoing chemotherapy. The study's results on the Karnofsky scores seem promising, and the magnitude of the effect needs to be determined in a larger study with more centers. The effects of probiotic supplementation on blood factors and other parameters align with other small studies on patients with other types of cancers and chronic diseases. Overall, the findings of this research show that this field needs to be further explored.

Conclusion

Our findings provide preliminary evidence about the potential role of multi-strain probiotics supplementation to alleviate chemotherapy-related side effects. The supplementation of multi-strain probiotics could significantly improve the Karnofsky performance scores and blood biomarker levels in patients with breast cancer. Future larger studies should be performed to confirm our findings before a multi-strain probiotics supplement treatment could be recommended in clinical practices.

Table 7. Karnofsky performance scale pre-post probiotics.

No	Pre-probiotic	Post-probiotic
1	70	100
2	80	80
3	100	100
4	100	100
5	70	90
6	80	90
7	90	100
8	90	100
9	90	100
10	90	100
11	100	100
12	100	100
13	100	100
14	100	100
15	100	100
16	90	100
17	90	100
18	90	100
19	100	100
20	100	100
21	90	100
22	100	100
23	90	100
24	90	100
25	100	100
26	90	90
27	90	90
28	80	100
Mean	91.4286	97.5
St Dev	8.90871	5.18188
Median	90	100
Minimum	70	80
Maximum	100	100
p-value	<0.001*	
Effect size	0.45	

*$p < 0.05$.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: University of Surabaya (UBAYA).

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the hospital under approval number 31/KEP-RSHU/IX/2024 and Ethics Committee University of Surabaya under approval number 420/KE/VIII/2024. Informed consent was obtained from all participants prior to their involvement in the study.

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Author contributions

AK, HW, TK, BP: Conceptualization and methodology; BP, E: Data analysis; AK: Writing—original draft, editing; VVCMT, GSZ, WD: Data collection; BP, ES: Formal analysis; AK, HW, TK, BP, ES: Writing—review and editing; AK, HW, TJ, BP: Supervision, project administration, funding acquisition, writing—review and editing; All authors have read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available on reasonable request from the corresponding author.

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