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Seasonal variation of HbA1c levels in diabetic and non-diabetic patients

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A R T I C L E I N F O

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A B S T R A C T

Background: Hemoglobin A1c (HbA1c) serves as a pivotal marker for long-term glycemic control. The Diabetes Control and Complications Trial (DCCT) established its relevance, yet gaps exist in understanding potential seasonal variations in HbA1c levels among diabetic patients. The study highlights the need to explore potential seasonal variations in HbA1c levels and their impact on diabetic patients.
Materials and methods: This is an observational study conducted in a tertiary care hospital from January to December 2019, the study analyzed HbA1c levels in 8138 patients. Blood samples were collected using Potassium EDTA-containing vials and processed with an automated analyzer. Seasonal variations were explored using time series analysis.
Results: Mean HbA1c levels peaked during the monsoon (June to September) and were lowest in autumn (October to November). Subgroup analysis revealed differences in patients with HbA1c values below and above 6.5 %. Those with controlled blood sugar showed higher levels in winter (December to February) and monsoon (June to September), while patients with HbA1c values ≥ 6.5 % exhibited significantly lower levels in monsoon (June to September) and autumn (October to November) compared to summer (March to May).
Conclusion: In contrast to global trends, Indian patients demonstrated distinct seasonal variations in HbA1c levels. The highest levels during the monsoon (June to September) may be linked to reduced outdoor activity and dietary changes. The study emphasizes the need for tailored diabetes management considering seasonal influences. Further extensive, longitudinal studies across diverse Indian regions are recommended to comprehensively grasp the impact of seasonal changes on diabetes outcomes.

1. Introduction

Hemoglobin A1c (HbA1c) also referred to as glycated hemoglobin signifies a minor subtype of Hemoglobin A that has been altered by the addition of glucose to the *N*-terminal amino acid of its beta globin chain. As erythrocytes are easily permeable to glucose, the attachment of glucose to hemoglobin happens constantly throughout the lifecycle of RBC. It is dependent on glucose concentration and the period of exposure of the erythrocyte to blood glucose [1].

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HbA1c is usually believed to mirror the assimilated average glucose level over the previous 4–8 weeks. Diabetes Control and Complications Trial (DCCT), brought its use to common practice by establishing the fact that it can be used to evaluate glycemic control over a prolonged period which plays a dominant part in the pathogenesis of longstanding complications [2].

In a study by Trivelli et al. it was observed that HbA1c levels in diabetics are approximately two to three times more than those found in normal individuals. Hence, HbA1c acts as a marker of metabolic control in diabetics [3]. Clinicians use it for deciding the treatment and may intensify glucose-lowering treatment if the HbA1c targets recommended by various guidelines are not met.

Increasingly suggestions have been made that glycemic control in diabetics, as shown by the HbA1c levels, exhibits a seasonal pattern in both type 1 and type 2 diabetic patients [4–13]. Though the matter of seasonal change in HbA1c levels appears to be of clinical significance it has still not been focused upon, signifying that additional pertinent substantiation is needed. Although this matter of seasonal variation in HbA1c levels appears to be of great importance it has not been addressed by clinical practice guidelines, suggesting that further relevant evidence is needed. One of the imperative issues that requires to be tackled is whether and to what intensity the seasonal variation of glycemic control affects all diabetic people from different geographical regions. Thus, the present study strives to observe seasonal variations in HbA1c levels in both diabetic and non-diabetic patients, attending a tertiary care centre in North India for the period between January 2019 and December 2019. It also scrutinized the relationship between mean HbA1c values and the month of the year in which the samples were collected.

In Indian literature, there are no published data regarding this matter. The present study aimed to assess HbA1c variation across various months for a year and to corroborate the presence of any seasonal effect.

2. Materials and Methods

This study was conducted in a tertiary care hospital in North India over twelve months starting from January 2019 to December 2019. The HbA1c levels of all patients visiting the outpatient department were noted. Samples received from wards during this period were also included in the study.

Samples for HbA1c testing were collected in Potassium EDTA (K2E) containing vials by trained phlebotomists under aseptic conditions. Samples were transported and stored according to established guidelines. Samples were tested within 4 h of collection. The blood samples were run into the automated analyzer ISE S. r.l. HbA1c (100 test) [ISE, Rome, Italy]. The automated analyzer worked on the principle of interaction of antigen and antibody to determine HbA1c levels. When the test samples were run in the automated analyzer it absorbed the HbA1c onto the surface of latex particles, which then interacted with *Anti*-HbA1c using antigen-antibody reaction and agglutination took place. The amount of this agglutination was then measured by calculating the absorbance, using subjecting the agglutinant to a wavelength of 578 nm [6].

Blood samples which were inadequate in quantity or degenerated due to improper storage conditions were excluded from the study. Pediatric blood samples and samples drawn from patients with Type 1 diabetes were also excluded from the study.

The values calculated in our laboratory were considered normal when they were less than 6.5 % and in the diabetic range when they were greater than (or equal to) 6.5 % respectively. To sustain consistent results, quality control was performed using commercially available human control serum and calibration was done every fortnight. The analyzer can measure the glycemic values up to 16 % only [6]. Further, external quality assurance testing was done every month. The quality control and external proficiency testing data for the last year are included in Supplementary file 1.

Meteorological seasons over India defined in India by the Indian Meteorological Department are namely: Winter, occurring from December to February; Summer or pre-monsoon season, lasting from March to May; Monsoon or rainy season, lasting from June to September and Post-monsoon or autumn season lasting from October to November [14].

The samples collected were coded for the seasons as Winter: December to February; Summer or pre-monsoon season: March to May; Monsoon or rainy season: June to September and Post-monsoon or autumn season: October to November. The data were then subjected to time series analysis. Time series analysis is a statistical technique used to examine patterns and trends over time by analyzing sequential data points. In this study, the time series analysis involved categorizing the data into distinct time intervals corresponding to meteorological seasons defined by the Indian Meteorological Department: Winter (December to February), Summer (March to May), Monsoon (June to September), and Post-monsoon or Autumn (October to November).

After categorization, the HbA1c values of patients in different seasons were compared with each other using statistical methods. Specifically, post hoc tests, such as the Turkey HSD test, were employed to compare HbA1c values between various seasons and determine statistical significance. Additionally, individuals with HbA1c values less than 6.5 % and those with values greater than or equal to 6.5 % were analyzed separately to assess any variations within these subgroups.

3. Results

A total of 8138 samples were analyzed in the department. The samples received belonged to patients ranging from 3 to 98 years. The 100 patients in <18-year age group were excluded from analysis. Among the **adult** patients, there were 4338 samples from males and 3700 from female individuals. A total of 1633 samples were received in the winter season in December, January and February. Two thousand three hundred and forty-five samples were received in the summer season extending from March till May; 2698 samples were collected in the monsoon season starting in June and lasting till September. Only 1362 samples were included in the autumn or post-monsoon season extending from October till November.

It was observed that mean values of HbA1c were highest in monsoon (June to September) (6.862 ± 1.997 %) and least in autumn (October to November) (6.771 ± 1.890 %) [Tables 1 and 2]. The quality control and external proficiency testing data attached in

Supplementary file 1 were at minimum, able to confirm the seasonal fluctuations are not attributed to variations in calibrations, reagent lot changes, and day-to-day fluctuations observable by QC means ± SD. The annual mean, standard deviation and coefficient of variation for the QC levels were 5.61 %, 0.27 and 4.7 % respectively.

Post Hoc tests were applied to compare the HbA1c values in these 8038 individuals over different seasons to look for any seasonal variation. However, the difference was not statistically significant.

The individuals with HbA1c values less than 6.5 % and those with values greater than 6.5 % were analyzed separately. It was observed that in the group with values < 6.5 % HbA1c values were highest in the winters (December to February) followed by monsoon (June to September) and were least in summers (March to May). [Tables 3–6].

Post hoc tests (Turkey HSD test) were used to compare the HbA1c values between the various seasons and it was found that values in winter (December to February), monsoon (June to September) and autumn (October to November) were significantly higher than those in summer (March to May) (p-value <0.05).

The post hoc tests (Turkey HSD test) to compare the HbA1c values between the various seasons showed that values in monsoon (June to September) and autumn (October to November) were significantly lower than those in summer (March to May) (p-value <0.05). However, the difference between the months of winter (December to February) and summer (March to May) was not statistically significant.

4. Discussion

Worldwide the number of people diagnosed with diabetes mellitus is likely to increase from the present 415 million people to 642 million by 2040. Approximately three-fourths of these people with diabetes mellitus reside in developing countries [15]. In 2010, the World Health Organization (WHO) stated that diabetic patients in India would soar to 190 % across the next two decades [16].

Fasting blood glucose (FBG), post-prandial blood glucose (PPBG) and glycated hemoglobin (HbA1c) are most commonly used for assessing glycemic control. HbA1c is a very good indicator of the long-term metabolic control of diabetes and is widely used to monitor patients and decide on treatment for Type 2 diabetes mellitus. The seasonal variations in HbA1c have been studied in a few countries. However, there is a paucity of similar large studies from Northern India. The current study evaluated the seasonal variation of HbA1c in 8038 (excluding pediatric cases) patients over one year from January 2019 to December 2019 in a tertiary care hospital in North India. This is the first large-scale study conducted in India on this topic to the best of our knowledge.

It was observed that the mean HbA1c values calculated for different seasons were highest for the monsoon (June to September) season i.e., the period between June to September. However, on comparing the mean values of all seasons, there was no statistical significance. These results are in contradiction with previous reports from other countries showing maximum values of HbA1c in cooler seasons and minimum values in warmer seasons. This had been attributed to high caloric intake and low physical activity during the winter (December to February) season [2,6,7,11–13,17–24]. In the present study, the higher levels observed during the monsoon (June to September) could be due to reduced outdoor activity in the form of morning walks and exercises as individuals face problems like puddles and muddy & slippery surfaces. Moreover, there is increased consumption of high-caloric fried food items in monsoon (June to September) season which further aggravates the loss of glycemic control. The monsoon (June to September) season in India coincides with various cultural festivals and celebrations, such as Raksha Bandhan, Teej, and Janmashtami. During these festivities, there is a tradition of preparing and consuming elaborate meals and sweet treats, which are often calorie-rich and indulgent. Families come together to enjoy these special dishes, contributing to the increased uptake of calorie-rich food during the season.

The current study further studied the individuals with HbA1c values of <6.5 % i.e., patients with no diabetes, pre-diabetics and individuals with controlled blood sugar. A total of 4538 results were evaluated. It was observed that HbA1c values in this group were significantly high in the winters (December to February) followed by monsoon (June to September) compared to the values observed in summer (March to May). This could be because, winters are often associated with the intake of calorie-rich foods along with an increase in the incidence of cold, flu and infections which may further cause the average glucose levels to be high. This group showed results which are similar to the results of studies in Singapore, Korea, Portugal and the UK [12,13,24,25].

Individuals with HbA1c values ≥ 6.5 % were separately assessed; HbA1c values in monsoon (June to September) and autumn (October to November) were significantly lower than those in summer (March to May) (p-value <0.05). These results were contradictory to the results of studies conducted in most other countries, except an Australian study which reports similar results [17]. This could be possibly attributed to diabetic patients being more cautious regarding sugar intake in the winter (December to February) and monsoon (June to September) months due to lesser physical activity in those seasons. The authors could address the apparent discrepancy between statistical significance (p-value <0.05) and the wide overlapping of mean ± SD between seasons by discussing

Table 1
Demographic data of HbA1c samples from adult patients seen in different seasons.

Season	No. Of samples	Male	Female	Avg age (in years)
Winter	1633	904	729	46.6
Summer	2345	1289	1056	46.8
Monsoon	2698	1397	1301	49.6
Autumn	1362	748	614	46.7

*(Winter: December to February; Summer or pre-monsoon season: March to May; Monsoon or rainy season: June to September and Post-monsoon or autumn season: October to November).

Table 2
Mean HbA1c values (in %) seen in different seasons in adults.

Season	Mean ± SD
Winter	6.810 ± 1.994
Summer	6.775 ± 2.154
Monsoon	6.862 ± 1.997
Autumn	6.771 ± 1.890
Overall	6.810 ± 2.026

*(Winter: December to February; Summer or pre-monsoon season: March to May; Monsoon or rainy season: June to September and Post-monsoon or autumn season: October to November).

Table 3
Mean HbA1c values seen in different seasons in adult individuals with **HbA1c values < 6.5 %.**

Season	No of samples	Mean ± SD
Winter	946	5.493 ± 0.568
Summer	1392	5.381 ± 0.617
Monsoon	1488	5.487 ± 0.604
Autumn	752	5.453 ± 0.595
Overall	4538	5.451 ± 0.595

*(Winter: December to February; Summer or pre-monsoon season: March to May; Monsoon or rainy season: June to September and Post-monsoon or autumn season: October to November; CI: Confidence interval).

Table 4
The multiple comparisons between HbA1c values in different seasons on applying Post Hoc tests (Turkey HSD) in individuals with HbA1c values < 6.5 % in adults.

Multiple Comparisons (Turkey HSD)						
Dependent Variable: HbA1c variation						
(I) Season of Year	(J) Season of Year	Mean Difference (I-J)	Std. Error	Sig. (p value)	95 % Confidence Interval	
					Lower Bound	Upper Bound
Mar–May	Dec–Feb	−0.11,212*	0.02502	0.000	−0.1764	−0.0478
	June–Sep	−0.10,608*	0.02214	0.000	−0.1630	−0.0492
	Oct–Nov	−0.07184*	0.02687	0.038	−0.1409	−0.0028

Table 5
Shows mean HbA1c values seen in different seasons in adult individuals with **HbA1c values ≥ 6.5 %.**

Season	No of samples	Mean ± SD
Winter	687	8.623 ± 1.827
Summer	953	8.810 ± 1.972
Monsoon	1210	8.552 ± 1.807
Autumn	610	8.396 ± 1.677
Overall	3460	8.610 ± 1.841

*(Winter: December to February; Summer or pre-monsoon season: March to May; Monsoon or rainy season: June to September and Post-monsoon or autumn season: October to November).

Table 6
Shows the multiple comparisons between HbA1c values in different seasons on applying Post Hoc tests (Turkey HSD) for adult individuals with Hba1c values ≥ 6.5 %.

Multiple Comparisons						
Dependent Variable: HbA1c variation						
(I) season	(J) season	Mean Difference (I-J)	Std. Error	Sig. (p value)	95 % Confidence Interval	
					Lower Bound	Upper Bound
Mar–May	Dec–Feb	0.18,674	0.09193	0.177	−0.0495	0.4230
	June–Sept	0.25,762*	0.07955	0.007	0.0532	0.4621
	Oct–Nov	0.41,378*	0.09524	0.000	0.1690	0.6586

factors like the large sample size. Although the mean ± SD may overlap, the statistical significance could be driven by the large sample size. Even small differences, when applied to a large sample, could result in statistical significance. Further, the wide variability in HbA1c levels between seasons may be influenced by other factors not considered in the analysis which is one of the limitations of the present study. For example, variations in patient behaviours, dietary patterns, medication adherence, or comorbidities could contribute to fluctuations in HbA1c levels across seasons.

Understanding seasonal variations in HbA1c levels can have implications for the diagnosis of diabetes and prediabetes. Clinicians often use HbA1c levels as one of the diagnostic criteria for diabetes. Seasonal variations in HbA1c levels may also have prognostic implications for diabetic patients. Fluctuations in HbA1c levels could impact the prediction of future complications and the overall prognosis of the disease. Understanding these seasonal trends could help clinicians better anticipate and manage long-term outcomes for their patients. The knowledge of seasonal variations in HbA1c levels can inform treatment strategies for diabetic patients. Clinicians may need to adjust medication regimens or lifestyle interventions based on the time of year to optimize glycemic control. For example, if HbA1c levels tend to increase during certain seasons, clinicians may need to intensify treatment during those times to prevent hyperglycemia and its associated complications.

Educating patients about seasonal variations in HbA1c levels can empower them to better manage their diabetes. Patients may need to be more vigilant about monitoring their blood glucose levels and adhering to treatment regimens during certain times of the year. By understanding how their HbA1c levels fluctuate throughout the year, patients can take proactive steps to maintain optimal glycemic control. Recognizing seasonal variations in HbA1c levels can also have broader public health implications. Health authorities and policymakers may need to consider seasonal factors when designing diabetes prevention and management programs. Targeted interventions that address seasonal challenges, such as changes in diet and physical activity patterns, could help mitigate the impact of seasonal fluctuations on diabetes outcomes at the population level.

Additionally, it is pertinent to consider the quality control (QC) measures implemented in the study, which provide further context to the reliability of the HbA1c measurements. The mean value of QC was determined to be 5.61, with a standard deviation (SD) of 0.27, resulting in a coefficient of variation (CV) of 4.7 %. These QC measures indicate the consistency and accuracy of the laboratory testing procedures throughout the study period.

The mean QC value of 5.61, along with the low SD and CV, reflects the stability and precision of the HbA1c measurements performed in the laboratory. This information underscores the reliability of the data obtained and strengthens the validity of the study findings. By maintaining stringent QC protocols and ensuring consistency in measurement techniques, the study enhances the credibility of its results and reinforces the robustness of the observed seasonal variations in HbA1c levels among diabetic patients in North India.

Furthermore, incorporating QC data into the discussion emphasizes the methodological rigor employed in the study and provides assurance regarding the accuracy of the reported HbA1c values. Clinicians and researchers can have confidence in the reliability of the study findings, thereby facilitating informed decision-making in clinical practice and advancing scientific knowledge in the field of diabetes management.

Numerous studies have been done in different countries and subcontinents to evaluate the seasonal variation of HbA1c including Germany and Austria, Singapore, Korea, Beijing, United Kingdom, Portugal, Sweden, Japan, United States, Poland, Israel [6,7,9, 11–13,18,20,21,23–28,30]. The results of these studies are illustrated in Table 7. In most of the studies, the peak HbA1c values were observed in winter. The plausible reason for this difference was increased caloric intake and decreased physical activity during those months.

The equilibrium between food intake and routine physical activities is the most dominant factor in the metabolic control of diabetic patients. The dietary recommendation made for a diabetic patient is usually determined by taking into consideration the expected physical activity, associated complications, duration of disease and age. This recommendation is based on the assumption that eating habits and physical activity remain the same throughout the year [27].

The biological functions of all life forms have been known to be influenced greatly by the environment Remarkably, seasonal variations are often detected in the metabolism of mammals. A very prominent example is the seasonal variation in glucose metabolism seen in Psammomysobesus (sand rat), displaying nutritionally generated insulin resistance and hyperglycemia which is observed in spring and autumn [29].

There are a few limitations in the present study. This was not a longitudinal study of a cohort of diabetic patients; rather we included all samples that were collected; including non-diabetic and pre-diabetes patients with type 2 diabetes making it a heterogenous group. In addition, only the results of one calendar year were analyzed.

Table 7
Findings of previous studies which evaluated effect of seasonal variation on HbA1c.

Author	Country	Number of cases	HbA1c results	Reason attributed
Gerstl et al. [20]	Germany and Austria	338,330 individual HbA1c measurements from 27,035 patients	Seasonal variation was unusually small with the lowest HbA1c values in September (mean: 7.86 %) and peak values in January (8.08 %; $p < 0.0001$)	–
Hawkins et al. [24]	Singapore	40,267	Circannual pattern with a peak in February/March, a minor peak in July/August and a nadir in November/December with an amplitude of 0.5 %	Positive correlation between the number of festive occasions in the preceding 3 months and the monthly mean HbA1c value
Kim et al. [12]	Korea	57,970 HbA1c values from 4191 patients	The highest values were observed during February to March and its lowest values from September to October	Cultural events may influence the seasonal variability in HbA1c. Further, a lower serum level of 25-hydroxyvitamin D during the winter season may aggravate glycemic control
Takai et al. [26]	Beijing	630 cases	Higher HbA1c values in winter and lower values in summer	Temperature, physical activity and dietary changes played a crucial role
Pereira et al. [13]	Portugal	62,384 H b A1c valid measurements	Highest values found in winters (January–February) (7.1 %), a nadir in August–October (6.8 %) and an average peak-to-trough amplitude value of 0.3 %	–
Maguire et al. [25]	United Kingdom	6721 results from 1295 patients	The values were at maximum in the spring (March, April, and May) and an all-time low in the autumn (September, October, November)	Seasonal factors, such as seasonal food availability, the amount of exercise undertaken or the seasonal changes in vitamin D levels, might also be important.
Asplund et al. [6]	Sweden	11,473 adult diabetic patient	The mean HbA1c values in winter (October–April) were higher than in summer (May–September) with a significant difference ($p < 0.0001$)	This may be attributed to different habits of exercise and diet or an improved insulin sensitivity in the summer.
Ishii et al. [27]	Japan	39	The mean HbA1c level was higher in winter compared with the period between spring and autumn.	This was attributed to an increased dietary calorie intake and decreased physical activity during the cold winter months
Tseng et al. [7]	United States of America	285,705 cases with 856,181 HbA1c tests	The HbA1c values were higher in winter and lower in summer with a difference of 0.22	A possible explanation for seasonal fluctuations in A1c levels could stem from the excess food consumed at the time of the winter holidays celebrated in the United States
Gikas et al. [9]	Greece	638 diabetic patients	significantly higher in colder than in warmer months	There were apparent peaks in fasting glucose levels after the Christmas and Easter months
Higgins et al. [21]	Edmonton and Calgary, Canada; Singapore; Melbourne, Australia; Marshfield and Wisconsin	–	HbA1c was higher in cooler months and lower in the warmer months. Singapore, which has minimal temperature variation, shows minimal variation.	–
Hill et al. [18]	United Kingdom	5140 measurements	A seasonal variation in HbA1c of 0.3 % with values lower in the summer (July–September) than in the winter (January–March)	Attributed to differences in exercise, carbohydrate consumption, and the number of illness episodes between the summer and winter months
Mianowska et al. [11]	Poland	3935 HbA1c measurements in 677 cases	The minimum HbA1c levels were observed in late summer and the maximum in winter months	Attributed to temperature change
Sohmiya et al. [28]	Japan	11 cases	HbA_{1c} levels were increased in winter and decreased in summer	seasonal variations in HbA_{1c} could be the increases in insulin resistance in winter
Baba et al. [30]	Middle East	105 cases	HbA1c was also lower (but not significantly so) in the early summer season (cloudy months).	–
Raphael et al. [23]	Israel	2860 patients with 61,187 HbA1c measures	Sinusoidal seasonal pattern with statistically significant HbA1c levels gaps between the spring peak and the autumn trough	A possible explanation is that during hot periods people tend to change their diet and decrease their physical activity, effecting indirectly diabetic imbalance
Present study	India	8038 samples	It was observed that the mean HbA1c values calculated for different seasons were highest for the monsoon (June to September) season i.e., the period between June to September.	This could be attributed to reduced outdoor activity in the form of morning walks and exercises as individuals face problems like puddles and muddy & slippery surfaces. Moreover, there is increased consumption of high-caloric

(*continued on next page*)

Table 7 (*continued*)

Author	Country	Number of cases	HbA1c results	Reason attributed
				fried food items in monsoon (June to September) season as in India it coincides with various cultural festivals.

5. Conclusion

To summarize, a trend in seasonal variation in HbA1c in Indian patients was observed. Although the mechanism underlying this manifestation is yet to be explained, lifestyle modification and frequent assessment of glucose control seem indispensable during the monsoons to prevent such fluctuations of glycemic control in diabetic patients. In addition, clinicians need to be aware of the possibility of seasons causing a minor variation in HbA1c before proceeding to make changes in the pharmacologic treatment.

It is further concluded that similar studies should be conducted in various parts of India on a large cohort of diabetic patients followed longitudinally as the weather conditions in our country are starkly different in various regions and the impact of temperature and other factors that vary with seasons should be studied.

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Informed patient consent was taken. The study was done in accordance with the Declaration of Helsinki of 1975.

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Availability of data and material

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Sana Ahuja: Writing – review & editing, Validation, Formal analysis, Data curation. **Sugandha Sugandha:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Rohit Kumar:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Sufian Zaheer:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Mukul Singh:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2024.e00396.

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