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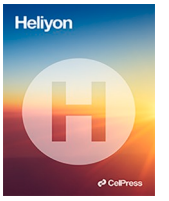

Research article

BCG vaccination is associated with longitudinal changes in systemic eicosanoid levels in elderly individuals: A secondary outcome analysis

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ABSTRACT

We investigated how BCG vaccination affects the levels of certain eicosanoids, namely Leukotriene B4, 15-epimer of LXA4, prostaglandin F2, Lipoxin A4, Prostaglandin E2 and Resolvin D1 in the plasma of healthy elderly individuals (aged 60–80) before vaccination, one month post-vaccination (M1), and six months post-vaccination (M6). This study is part of the clinical trial "BCG Vaccine Study: Reducing COVID-19 Impact on the Elderly in Indian Hotspots," registered in the clinical trial registry (NCT04475302). While some primary outcomes have been previously reported, this analysis delves into the immunological outcomes. Our findings indicate that BCG vaccination leads to reduced plasma levels of 15-*epi*-LXA4, LXA4, PGE2, and Resolvin D1 at both M1 and M6. In contrast, there is a notable increase in circulating levels of LTB4 at these time points following BCG vaccination. This underscores the immunomodulatory effects of BCG vaccination and hints at its potential to modulate immune responses by dampening inflammatory reactions.

1. Introduction

The Bacille Calmette Guérin (BCG) vaccine wasintroduced over a 100 years ago and it is the single most widely used vaccine around the world. BCG has protected many individuals by preventing the disseminated form of TB (miliary TB) in childhood [1,2]. Moreover, BCG demonstrates off-target and non-specific, or heterologous, effects against various infectious diseases [3]. Previous studies have shown that BCG vaccination offers defense against human experimental models of yellow fever and malaria infection in individuals without underlying health conditions [4,5]. Recent studies focusing on innate immunity suggest that BCG vaccination might offer protection against viral respiratory diseases, potentially including Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6]. Likewise, BCG has also been effective in treating bladder cancer [7]. This varied choice of cross-protection implies that BCG augments the immune response independently of specific adaptive immunity.

Host immune responses to infectious disease are coordinated by several classes of signaling mediators, including a class of largely

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Abbreviations

15-*epi*-LXA4 15-epimer of LXA4
BCG Bacille Calmette Guérin
CCA: Canonical Correlation Analysis
CCL: Conical correlation
GM Geometric Mean
IL: Interleukin
LTB4: Leukotriene B4
LXA4 Lipoxin A4
M1: Month 1
M6: Month 6
Mtb: *Mycobacterium tuberculosis*
PGE2 Prostaglandin E2
PGF2 prostaglandin F2
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

bioactive lipids termed eicosanoids [8]. Eicosanoids, originating from arachidonic acid, are lipid molecules that elicit both inflammatory and anti-inflammatory reactions. They include prostaglandins, lipoxins, leukotrienes, and resolvins [9]. The critical roles eicosanoids play in immune function have been well-established. A diverse array of eicosanoids contributes to the maintenance of tissue homeostasis, with certain families exhibiting either pro-inflammatory or anti-inflammatory properties [10]. Given their ability to modulate immune responses, eicosanoids can also influence the host's defense against viral infections and the replication of viruses [11].

Due to BCG's capacity for nonspecific cross-protection against pathogens, our objective was to assess the correlation between eicosanoids and BCG vaccination. This entailed examining various circulating anti-inflammatory and pro-inflammatory eicosanoids in elderly individuals before and after BCG vaccination.

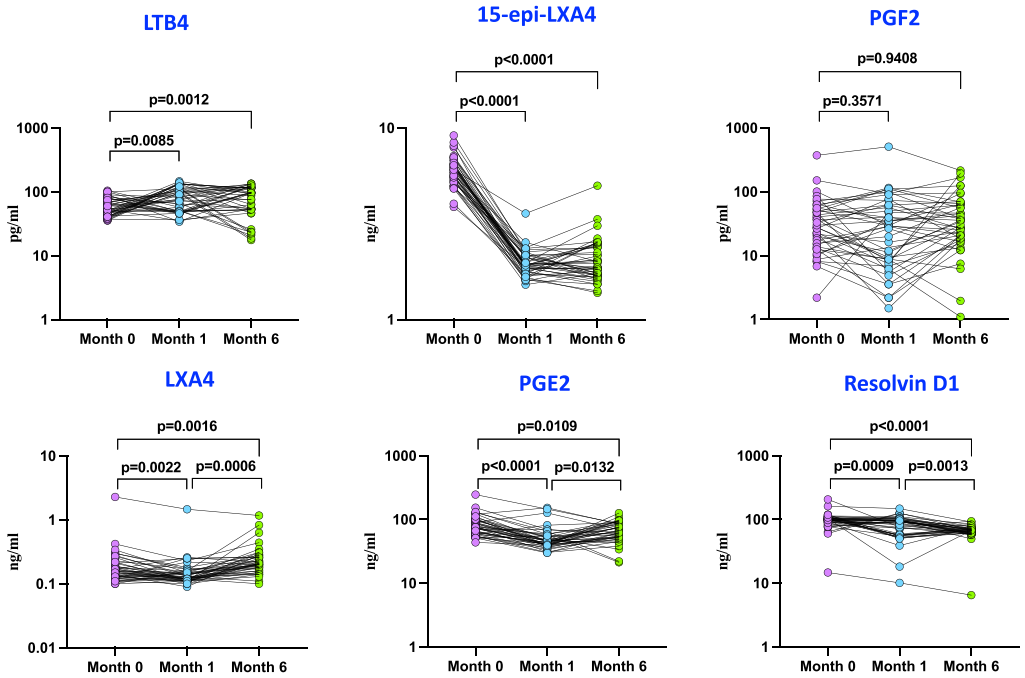

Fig. 1. BCG vaccination leads to decreased levels of eicosanoids compared to baseline. The circulating levels of eicosanoids in BCG pre-vaccinated [M0] (n = 44), month 1 post vaccinated [M1] and month 6 post vaccinated [M6] (n = 44) individuals are shown. The data are depicted through line diagrams, with each line representing an individual participant. To analyze M0, M1, and M6, p-values were computed using Wilcoxon matched-pair tests, with Holm's correction applied for multiple comparisons.

2. Results

2.1. BCG vaccination leads to reduced plasma concentrations of eicosanoids

We compared plasma eicosanoid levels at three different time points: before BCG vaccination (baseline, M0), one month post-vaccination (M1), and six months post-vaccination (M6). As shown in Fig. 1, eicosanoids such as 15-epimer of LXA4 (15-*epi*-LXA4) (M1 $p < 0.0001$ and M6 $p < 0.0001$), Lipoxin A4 (LXA4) (M1 $p = 0.0022$ and M6 $p = 0.0016$), prostaglandin F2 (PGE2) (M1 $p < 0.0001$ and M6 $p = 0.0109$) and Resolvin D1 (M1 $p = 0.0009$ and M6 $p < 0.0001$), all exhibited significantly diminished levels compared to M0. In contrast, Leukotriene B4 (LTB4) (M1 $p = 0.0085$ and M6 $p = 0.0012$) levels were increased at M1 and M6 compared to M0.

2.2. Canonical correlation analysis reveals eicosanoids as important discriminators of BCG vaccine responses

Canonical Correlation Analysis (CCA) is a statistical technique utilized to examine linear relationships between two sets of variables, one designated as independent and the other as dependent, yielding composite scores for each set [12]. CCA generates a canonical function that maximizes the correlation between the two composite variables. As shown in Fig. 2, the use of Canonical correlation 1(CCL1) of 15-*epi*-LXA4, PGE2 and Resolvin D1 and Canonical correlation 2 (CCL2) of LTB4, PGF2 and LXA4 is sufficient to allow significant discrimination between the responses at baseline versus M1 and M6 post vaccination. Therefore, this set of eicosanoids exhibit significant power to delineate the evolution of immune responses before and after BCG vaccination in the elderly population.

2.3. Associations between the circulating levels of eicosanoids at baseline one month and six months post BCG vaccination

We aimed to establish correlations between eicosanoid responses at baseline, M1, and M6 in individuals who received BCG vaccination. As shown in Fig. 3, we utilized Spearman's correlation coefficients to assess correlation effects, and the data were visually represented using heat map color intensity, with variables organized through hierarchical clustering. A multiparametric matrix correlation plot illustrated notable correlations among circulating levels of LXA4 and 15-Epi-LXA4 at the onset of BCG vaccination (month 0). Similarly, multiparametric matrix correlation plot showed significant correlations between circulating levels of LXA4 vs 15-Epi-LXA4 and LXA4 vs PGE2 at month 1 of post BCG vaccination and finally significant correlations between circulating levels of resolvin D1 vs 15-Epi-LXA4 at month 6 of post BCG vaccination.

2.4. The relationship between circulating levels of eicosanoids and inflammatory cytokines at baseline, one month, and six months after BCG vaccination

We aimed to explore the associations between circulating levels of eicosanoids and inflammatory cytokines at baseline, one month (M1), and six months (M6) post BCG vaccination in individuals. The correlation analysis, depicted in Fig. 4, utilized Spearman's correlation coefficients, and the data were visually represented by heat map color intensity, with variables organized through hierarchical clustering. The multiparametric matrix correlation plot revealed notable associations at different time points. Particularly, at the outset of BCG vaccination (month 0), notable correlations were detected, such as the association between circulating levels of LTB4 and IL-2, PGF2 and IL-6, as well as PGE2 and IFNγ, IL-1α, IL-1β, IL-4, and IL-10. Moving to one month post BCG vaccination, the correlation plot highlighted significant associations, including those between circulating levels of PGE2 and IL-6, as well as IL-17A. Finally, at six months post BCG, resolving D1 demonstrated significant correlations, particularly with IL-5. P values and correlation values are provided in the Supplementary Table 2. This comprehensive analysis provides insights into the dynamic interactions

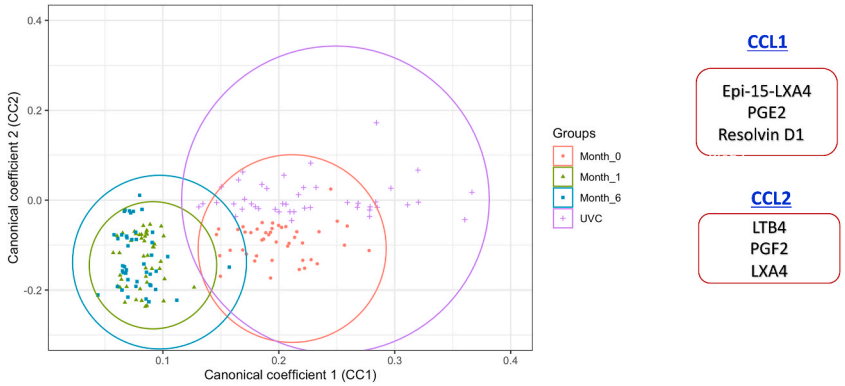

Fig. 2. Eicosanoid pathways are engaged in BCG vaccinated elderly individuals during baseline and post-vaccination. Canonical correlation analysis (CCA) was utilized to evaluate whether a combination of eicosanoids can differentiate between baseline (M0) and Month 1 (M1) compared to Month six (M6), as well as unvaccinated control (UVC). The data are presented in dot plots, where each dot symbolizes an individual participant.

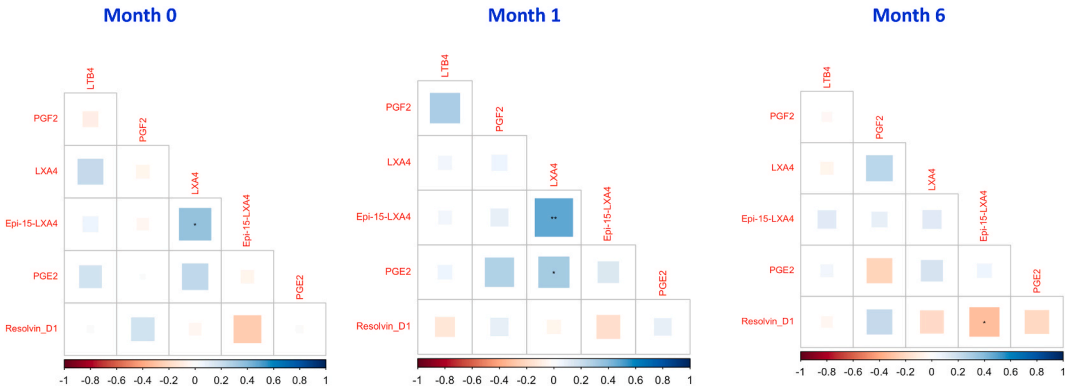

Fig. 3. Relationship between eicosanoids. Multiparametric matrix correlation plot of eicosanoids in all individuals at baseline (M0), Month six (M1) and Month six (M6) post BCG vaccination. Spearman's correlation coefficients are displayed with differing color intensities, while P values and Spearman r values are arranged using hierarchical clustering. In the correlation plot, box sizes reflect correlation values ranging from −1 to +1; larger boxes denote stronger correlations. Blue color signifies positive correlations, whereas red color indicates negative correlations. p-value is statistically significant * represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

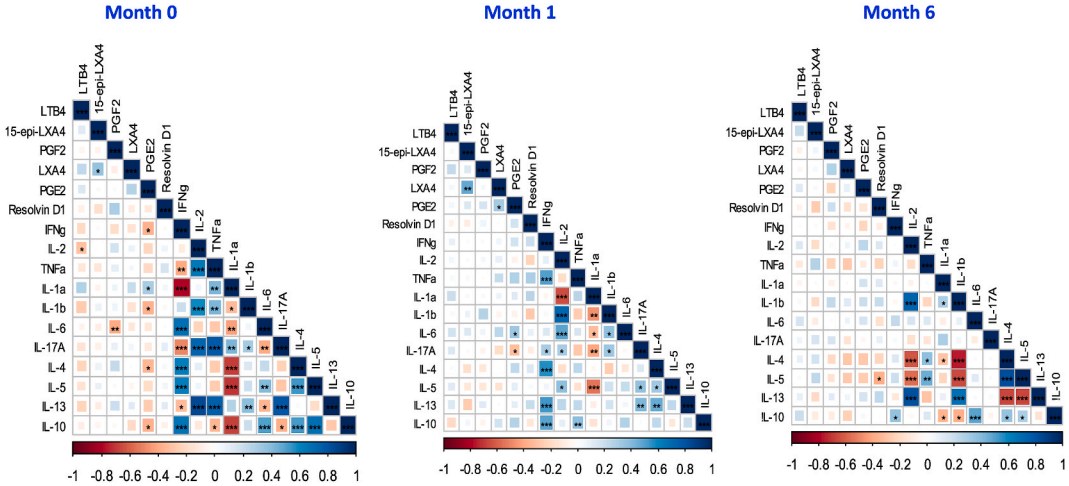

Fig. 4. Relationship between eicosanoids and inflammatory cytokines. Multiparametric matrix correlation plot of eicosanoids and inflammatory cytokines in all individuals of baseline (M0), Month six (M1) and Month six (M6) post BCG vaccination. Spearman's correlation coefficients are depicted using varying color intensities. P values and Spearman r values are organized through hierarchical clustering. Within the correlation plot, the size of each box corresponds to the correlation value, ranging from −1 to +1; larger boxes indicate stronger correlations. Blue color signifies positive correlations, while red color indicates negative correlations. Significant p-values are denoted.* represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

between eicosanoids and inflammatory cytokines across different time points following BCG vaccination.

3. Discussion

The utility of BCG vaccine has been substantiated in various epidemiological findings and randomized clinical trials and the findings revealed that BCG vaccination led to reduced mortality and defense against neonatal sepsis and respiratory infections [13,14]. Furthermore, prior research has indicated that BCG vaccination may provide protection against viral infections, with evidence demonstrating a reduction in the incidence of respiratory syncytial virus infection [15]. Studies conducted in Indonesia and Japan have documented the protective benefits of BCG vaccination against respiratory tract infections in elderly individuals [16,17]. Also, studies on human experimental viral infection have reported that BCG can decrease the viral load and viral replication [4]. Drawing from existing literature, it has been suggested that BCG vaccination might hold potential benefits in mitigating SARS-CoV-2 infection [18]. In earlier findings, we demonstrated that BCG reduces the plasma concentrations of pro-inflammatory cytokines, chemokines, and other mediators in elderly individuals from India [19]. In our research, we focused on the elderly demographic residing in areas heavily affected by COVID-19, recognizing their increased vulnerability to infection. Our aim was to assess prospectively the impact of

BCG vaccination on lipid mediators within this population group.

Eicosanoids have vital roles in disease homeostasis as well as the resolution of inflammation [10,20]. The role of prostaglandin E2 (PGE2) in conferring resistance to *Mycobacterium tuberculosis* (Mtb) infection has been demonstrated in susceptibility tests using murine infection models. Conversely, products of the 5-lipoxygenase (5-LO) axis, such as LXA4, have been associated with increased bacterial growth and impediment of bacterial control [21–23]. The ability of these lipid mediators, either directly or indirectly, to modulate the outcomes of infected macrophage cell death represents a mechanism through which eicosanoids mediate protection against or susceptibility to Mtb [24, 25, 26]. This intricate interplay highlights the diverse and context-dependent roles of eicosanoids in the immune response to Mtb infection. Detailed information regarding the protective and inflammatory effects of eicosanoids is provided in Supplementary Table 1.

Our cohort of BCG vaccinated elderly individuals showed diminished levels of 15-*epi*-LXA4, LXA4, PGE2 and Resolvin D1 and elevated levels of LTB4 at M1 and M6 after BCG vaccination indicating an effect of BCG on the profile of lipid mediators in host immunity. Studies on other respiratory viral infections have suggested that PGE2 modulates immune function in various ways that might impact viral pathogenesis [27]. Moreover, it has been observed that PGE2 can induce inflammation through vasodilatory mechanisms, resulting in edema and passive recruitment of leukocytes [28]. PGE2 is generated by the COX-1 and COX-2 enzymes and is observed as an important mediator of immunopathology during chronic infections [29]. On the other hand, the lipid mediator LTB4 has a protective role by promoting T cell recruitment to sites of inflammation [30]. LTB4 also supports the neutrophil chemotaxis, ROS generation, and survival [31]. A recent study showed that resolvin D1 can reduce SARS-CoV-2-induced inflammation [32]. The present results illustrate that BCG vaccination results in the reduction of inflammatory eicosanoids and the increase of protective eicosanoids, with the sole elevation observed in LTB4. In addition, our data by canonical plots revealed that there was a clear discrimination of these lipid mediators between pre and post BCG vaccination.

The initiation, progression, and resolution of inflammation involve a complex network of interactions between eicosanoids and cytokines [33]. Findings from the zebrafish model of *Mycobacterium marinum* infection have underscored the close connection between cytokines and eicosanoid lipid mediators in the host's defense against mycobacteria [34].In this scenario, decreased levels of LTA4H and leukotriene B4 (LTB4) led to a proportional rise in lipoxin A4 (LXA4), resulting in reduced tumor necrosis factor (TNF) levels and subsequent cell death due to compromised bacterial control. Conversely, heightened LTB4 synthesis worsened TNF-dependent macrophage cell death, weakening host resistance. This underscores the importance of precisely regulating the inflammatory response to Mtb and the necessity for intricate networks that govern cytokines-cytokines and cytokines-lipid mediators [35]. In the presented cohort, significant negative correlations between prostaglandin F2 (PGF2) and interleukin-6 (IL-6), as well as between prostaglandin E2 (PGE2) and IFNγ, IL-1α, IL-4, and IL-10, were observed before BCG vaccination. However, these correlations were resolved after either one or six months post BCG vaccination, indicating a protective effect of these lipid mediators following vaccination.

Given that the elderly population, particularly those with comorbidities such as diabetes, heart disease, or hypertension, face an increased risk of experiencing severe COVID-19. [10,15,36], timely control of the inflammatory lipid mediators at the initial stage is important. Indeed, managing the infection while decreasing the lung infiltration by inflammatory cells is crucial for enhancing the immune status of the elderly. Additionally, one study reported that the plasma lipidome might play a role in the immunogenicity of BCG vaccination in infants [37]. Also gender and age differences may contribute to the altered immunological responses upon vaccination [38, 39]. Inflammation comprises immune cells and serves as a protective immune response, the eicosanoid pathway catalyzes the production of prostaglandins, prostacyclins, and thromboxanes, which are crucial for the resolution of inflammation [40]. Our study suggests that BCG by its propensity to modulate heterologous immunity and balance inflammation could potentially be a key tool in combating inflammatory processes afflicting the elderly population. We have previously shown that BCG can boost T cell, B cell and dendritic cell responses in a non-specific manner [41, 42, 43]. This together with the present finding that BCG can boost LTB4 while simultaneously diminishing LXA4 and 15-*epi*-LXA4 responses, suggest that BCG can modulate heterologous immunity without boosting inhibitory innate responses. It should be noted that the various licensed BCG vaccines vary significantly in the number of active mycobacteria they contain, which may be responsible for the formulation-dependent activation of innate and adaptive immunity as well as the varied protective effects [44]. Finding from a recent randomized, controlled trial revealed that single dose of BCG protects against Covid-19 infection [45]. However they also report that there is some variability across trials and this may be due to the sex differences, BCG strain and dose, and other vaccines [46].

Our research demonstrates how the BCG vaccine affects the levels of eicosanoids in the blood, demonstrating that the vaccine is safe and does not cause elderly population to become more prone to inflammation. One limitation of the study is that while eicosanoids like 15-*epi*-LXA4, PGE2, and resolvin show a downward trend after vaccination, particularly at months 1 and 6, other eicosanoids such as LXA4 and PGF2α only show a decrease at month 1 and then stabilize by month 6. This observation, despite being statistically significant from the baseline (M0), may be influenced by outliers. Additionally, the study faced limitations due to insufficient data on the vaccination status of participants for other vaccines during the follow-up period. Our study does not include a placebo control group and features unvaccinated controls only at baseline. Additionally, for control individuals, samples were collected solely during the baseline visit, with no follow-up samples. Though more efficient T cell mediated COVID-19 vaccines are currently available, targeting trained immunity using BCG vaccine might offer an alternative immune protection in the elderly population. Our results also provide a mechanistic explanation by which BCG protects against or improves the outcomes in inflammatory, allergic, or autoimmune diseases.

4. Materials and methods

4.1. Ethics statement

The research obtained approval from the Ethics Committees of the National Institute for Research in Tuberculosis (NIRT-INo: 2020010). Written informed consent was obtained from all participants, and all experiments followed relevant guidelines and regulations.

4.2. Study population

To investigate the immunological impacts of BCG vaccination, 44 elderly individuals aged between 60 and 80 years, residing in SARS-CoV-2 infection hotspots (areas with significant spread of COVID-19 outbreaks or clusters as identified by the Ministry of Health and Family Welfare). The screening process for samples began towards the end of June, however, the enrolment of the first sample occurred on July 1st, 2020 and the study enrolment was between July 2020 and October 2020 in Chennai, India**.** This research is part of a clinical trial titled "Assessment of BCG vaccine effectiveness in reducing morbidity and mortality among elderly individuals in COVID-19 hotspots in India." Additionally, the study was registered in the clinical trial registry (NCT04475302). After obtaining written informed consent from the study participants, 44 individuals were administered a single dose of BCG vaccine (Freeze-dried) produced by the Serum Institute of India, Pune. The adult dose of the BCG vaccine, 0.1 mL, was injected intradermally over the distal insertion of the deltoid muscle on the left humerus (approximately one-third down the left upper arm). Furthermore, 44 elderly individuals from the same hotspot area, who did not receive vaccination, were enrolled as control subjects. The demographic profile of the study population is detailed in Table 1. Blood samples were obtained during both the screening and enrollment phase (within two days of screening) of the study. During the screening phase, samples were collected to screen for SARS-CoV-2 IgG antibodies and HIV. In the enrollment phase, blood samples were collected at various intervals: baseline (the day before BCG vaccination), at 1 month (M1), and at 6 months (M6) post-vaccination. Major exclusion criteria included elderly individuals who tested positive for SARS-CoV-2 infection through either antibody (serology) or PCR testing; those with confirmed HIV, malignancy, or undergoing transplantation or dialysis; individuals recently diagnosed with TB or currently undergoing anti-TB treatment or taking anti-psychiatric medications within the last 6 months; and those with any contraindication to BCG vaccine, such as allergy or hypersensitivity. This study population of baseline and M1 was reported previously [19,42]. The most common adverse events after BCG vaccination were erythema/redness at the site of injection followed by soft swelling at the injection site. Both of them resolved within a few days.

4.3. ELISA

The quantitative measurement kit sourced from MyBioSource.com was used to assess plasma concentrations of LXA4, 15-*epi*-LXA4, PGE2, PGF2, LTB4, and Resolvin D1. The minimum detectable limits were as follows: LXA4, 0.156 ng/mL; 15-*epi*-LXA4, 0.312 ng/mL; PGE2, 7.8 pg/mL; PGF2, 6.25 pg/mL; LTB4, 15.6 pg/mL; and Resolvin D1, 30 pg/mL. Samples below the detection threshold were assigned the lowest standard value.

4.4. Statistical analysis

Geometric means (GM) were employed as the measure of central tendency. In the BCG vaccinated group, levels of inflammatory markers at M0, M1, and M6 were compared using the Wilcoxon signed-rank test. Significant differences between the unvaccinated and BCG vaccinated groups at M6 were assessed using the Mann-Whitney test. All analyses were conducted using GraphPad PRISM Version 9.0. Spearman Correlation was performed to see the correlation between the variables and p-value with (0.001, 0.01,0.05) significance levels were marked in the correlation plot and also canonical correlation analysis was performed. This analysis was performed in RStudio 2021.09.0 + 351 ″Ghost Orchid".

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CRediT authorship contribution statement

Pavan Kumar Nathella: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Chandrasekaran Padmapriyadarsini:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Arul Nancy:** Methodology, Investigation. **Kushiyasri Karunanithi:** Methodology, Data curation. **Nandhini Selvaraj:** Methodology, Investigation. **Rachel Mariam Renji:** Methodology, Investigation. **B.M. Shrinivasa:** Supervision, Project administration, Methodology, Data curation. **Subash Babu:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Table 1
Demographic profile of the study population.

	BCG Vaccinated	BCG Unvaccinated	pValue
Subjects Enrolled	N = 44	N = 44	
Age (Median)	65 (60–78)	66 (60–80)	p = 0.8977
Gender (M/F)	24/20	27/17	p = 0.7233
Height (Median)	156 cm	155 cm	p = 0.9233
Weight (Median)	62 Kg	63 Kg	p = 0.8634
Pulse rate (Median)	88	88	p = 0.9322
Systolic Blood Pressure (Median)	138	140	p = 0.8322
Diastolic Blood Pressure (Median)	82	82	p = 0.9771
SPOS% (Median)	98	98	p = 0.9232
Interferon gamma release assay (IGRA) – Positive	23 (52 %)	19 (43 %)	p = 0.7233
BCG Scar - Yes	4 (9 %)	3 (7 %)	p = 0.8876
Diabetes Mellitus no. (%)	13 (29 %)	11 (25 %)	p = 0.6342
Smoking, no. (%)	2 (5 %)	2 (5 %)	p = 0.7432
Alcoholism, no. (%)	3 (7 %)	2 (5 %)	p = 0.8977
Cardiovascular Disease, no. (%)	7 (15 %)	3 (7 %)	p = 0.5211
Respiratory Diseases, no. (%)	5 (11 %)	2 (5 %)	p = 0.1922

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32643.

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