Low body mass index has minimal impact on plasma levels of cytokines and chemokines in tuberculous lymphadenitis

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ARTICLE INFO

ABSTRACT

Malnutrition, due to low body mass index (LBMI), is considered to be one of the key risk factors for tuberculosis (TB) development. The link between pro and anti-inflammatory cytokines and BMI has been studied in active pulmonary TB. However, the association of BMI with cytokines and chemokines in TB lymphadenitis (TBL) has not been examined. Hence, we wanted to examine the plasma levels of different cytokines and chemokines in TBL individuals with LBMI, normal BMI (NBMI) and high BMI (HBMI). LBMI with TBL disease is associated with enhanced systemic levels of type 1 (tumor necrosis factor alpha [TNFα], interleukin-2 [IL-2]) and type 2 (IL-4, IL-13) cytokines in comparison with NBMI and/or HBMI. However, other pro-inflammatory (IFNγ, IL-1β, IL-17A, IL-6, IL-7, IL-12, G-CSF, and GM-CSF) and anti-inflammatory (IL-5 and IL-10) cytokines were not significantly different among the TBL individuals with different BMI status. Likewise, no significant differences were observed in the CC (CCL-1, CCL-2/MCP-1, CCL3/MIP1α, CCL4/MIP-1β, CCL11/eotaxin) and CXC (CXCL-1/GRO-α, CXCL2/GRO-β, CXCL9/MIG, CXCL10/IP-10, CXCL11/ITAC 1) chemokine profile among the TBL individuals with different BMI. Hence, our data implies that TBL individuals with LBMI are characterized by minimal effects on plasma cytokines and chemokines in TBL.

1. Introduction

Malnutrition is considered to be one among the major threats responsible for the progression of latent to active pulmonary tuberculosis (PTB) [1]. Low body mass index (LBMI) can weaken the host immune system and therefore could enhance the risk of developing active tuberculosis (TB) [2]. The impact of being overweight on the risk of TB development is controversial [3,4]. Previous reports have suggested that malnutrition increases the susceptibility to TB in both high and low endemic settings [5,6]. Also, deficiency in nutrient supplements could impact the cell mediated immunity and this was improved partly upon nutritional replenishment [7–9]. In addition, LBMI significantly increased the risk of mortality among active TB disease patients [6,10,11].

Certainly, pro-inflammatory cytokines (IFNγ, TNFα, IL-1α, IL-β and GM-CSF) mediate host protection and in contrast, anti-inflammatory cytokines elevate the host risk factors in development of active disease [12–14]. Previous studies have shown that latent TB (LTBI) with LBMI individuals are characterised by reduced levels of Type 1, Type 17 and pro inflammatory cytokines as well as increased Type 2 and regulatory cytokines compared to LTBI with normal BMI (NBMI) [15]. Similarly, LTBI with high BMI (HBMI) individuals are characterised by elevated plasma and TB antigen stimulated levels of pro-inflammatory and decreased circulating levels of anti-inflammatory cytokines [16]. Also, coexistent LBMI is known to modulate the systemic and TB antigen stimulated levels of chemokines in LTBI [17]. However, the association of BMI with extrapulmonary form of TB disease, specifically in tuberculous lymphadenitis (TBL) has not been studied completely. TBL is the most common form of extra pulmonary TB. The site of infection for TBL is different from pulmonary TB (PTB, infection occurs in the lungs) and it commonly affects the cervical lymph nodes and is more female biased [18,19].

Therefore, we have examined the plasma levels of a panel of pro- and anti-inflammatory cytokines and chemokines (CC and CXC) in TBL individuals coexistent with different BMI (LBMI, NBMI, HBMI) status.

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2. Materials and methods

2.1. Study population

We examined a group of 152 individuals with TBL disease with 33 LBMI (< 18.5 kg/m^2); 67 NBMI (> 18.5 to < 24.9 kg/m^2) and 52 HBMI (> 24.9 kg/m^2). TBL individuals were diagnosed positive for *Mycobacterium tuberculosis* (Mtb) either in liquid cultures or GeneXpert using the excision biopsied lymph node samples. TBL individuals had normal chest X-ray, did not have any symptoms of pulmonary TB and negative sputum smear. All the study individuals were BCG vaccinated, HIV negative and not administered with steroids. BMI (Low, normal and high) values were categorized on the basis of the 2013 American Heart Association/American College of Cardiology guidelines. This study was approved by the Internal Ethics Committee (IEC) of National Institute of Research in Tuberculosis (NIRT, NIRTIEC2010007). The informed written consent was acquired from all the volunteers involved in this study.

2.2. Samples

Whole blood was collected in heparin vacutainer tubes and centrifuged for 10 min at 2600 revolutions per minute (rpm) in 4 °C. The separated plasma was carefully transferred into 2 ml sterile screw cap tubes and stored at −80 °C until further use.

2.3. Luminex assay

The circulating levels of cytokines (Bio- Rad, Hercules, CA, lot number-64103329) and chemokines were measured using a Bioplex multiplex cytokine assay system. The cytokines measured were IFNγ, TNFα, IL-2, IL-1β, IL-17A, IL-6, IL-7, IL-12, G-CSF, GM-CSF, IL-4, IL-5, IL-13, and IL-10. TGFβ alone was measured using legend max kit (Biolegend). The CC (CCL-1, CCL-2/MCP-1, CCL3/MIP1α, CCL4/MIP-1β, CCL11/eotaxin) and CXC (CXCL-1/GRO-α, CXCL2/GRO-β, CXCL9/MIG, CXCL10/IP-10, CXCL11/ITAC 1) chemokines were measured using Bio-Rad ELISA kit.

2.4. Statistics

All the statistical analyses were performed using GraphPad PRISM Version 8.01 (GraphPad Software, Inc., San Diego, CA, USA). Geometric means (GM) were used to measure the central tendency. Statistically significant differences between groups were analyzed using Kruskal-Wallis test with Dunn's multiple comparisons or chi-square test.

3. Results

3.1. Characteristics of study population

TBL individuals were classified into three groups such as LBMI (< 18.5 kg/m^2), NBMI (> 18.5 to < 24.9 kg/m^2) and HBMI (> 24.9 kg/m^2) based on their BMI status. The demographics (age,

gender) of the study population are given in Table 1. The three BMI groups were significantly different in gender.

3.2. LBMI is associated with elevated plasma levels of TNFα and IL-2

To define the influence of BMI on Type 1 and other pro inflammatory cytokines in TBL individuals, we have examined the plasma levels of these cytokines in LBMI, NBMI and HBMI coexistent TBL individuals (Fig. 1). The plasma levels of Type 1 (TNFα [GM of LBMI 4.542 pg/ml versus (vs) NBMI 4.914 pg/ml vs HBMI 3.703 pg/ml] and IL-2 [GM of LBMI 14.39 pg/ml vs NBMI 12.65 pg/ml vs HBMI 11.64 pg/ml]) cytokines alone were significantly increased in LBMI individuals up on comparison with NBMI and/or HMBI individuals (Fig. 1A). In contrast, the circulating levels of other pro-inflammatory (IFNγ, IL-1β, IL-17A, IL-6, IL-17, IL-12, G-CSF and GM-CSF) cytokines were not significantly different from NBMI and/or HMBI individuals (Fig. 1B & C). Hence, TBL individuals with LBMI are associated with increased plasma levels of TNFα and IL-2.

3.3. LBMI is associated with enhanced plasma levels of IL-4 and IL-13

To examine the role of BMI on Type 2 and regulatory cytokines in TBL individuals, we have measured those plasma cytokine levels in LBMI, NBMI and HBMI coexistent TBL individuals (Fig. 2). As shown in Fig. 2A, Type 2 (IL-4 [GM of LBMI 9.524 pg/ml vs NBMI 9.429 pg/ml vs HBMI 9.039 pg/ml] and IL-13 [GM of LBMI 10.13 pg/ml vs NBMI 9.361 pg/ml vs HBMI 9.103 pg/ml]) cytokines alone were significantly in higher in LBMI individuals compared to NBMI and/or HMBI individuals. Similarly, anti-inflammatory or regulatory (TGFβ [GM of LBMI 103.9 pg/ml vs NBMI 168.8 pg/ml vs HBMI 74.25 pg/ml]) cytokines were significantly increased in NBMI when compared to HBMI individuals (Fig. 2B). The other Type 2 (IL-5) and regulatory (IL-10) cytokines did not exhibit significant differences between the different BMI groups (Fig. 2C). Thus, TBL individuals with LBMI are associated higher circulating levels of Type 2 cytokines.

3.4. LBMI is not associated with alterations in CC and CXC chemokines

Next, we wanted to determine the influence of BMI on CC (CCL-1, CCL-2/MCP-1, CCL3/MIP1α, CCL4/MIP-1β, CCL11/eotaxin) chemokines in LBMI, NBMI and HBMI coexistent TBL individuals (Fig. 3). As shown in Fig. 3, LBMI individuals did not exhibit any significant differences in CC chemokines compared to NBMI/HBMI individuals. Finally, we wanted to determine the influence of BMI on CXC (CXCL-1/GRO-α, CXCL2/GRO-β, CXCL9/MIG, CXCL10/IP-10, CXCL11/ITAC 1) chemokines in LBMI, NBMI and HBMI coexistent TBL individuals (Fig. 4). As shown in Fig. 4, LBMI individuals did not exhibit any significant differences in CXC chemokines compared to NBMI/HBMI individuals. Thus, TBL individuals with LBMI are not associated with altered circulating levels of CC or CXC chemokines.

Table 1
Demographics of the study population.

Study Demographics	LBMI	NBMI	HBMI	P Value*
No. of subjects recruited	33	67	52	–
Gender (Male/Female)	12/21	23/44	5/47	0.0027[a]
Median Age (Range)	27.7 (19–53)	28.2 (18–59)	29.5 (19–51)	NS
Median Height, cm	157.3 (147–178)	154.5 (143–170)	152.1 (136–173)	0.0043
Median Weight, kg	42.4 (34–55)	51.6 (39–64)	65.7 (45–98)	< 0.0001
QuantiFERON-TB Gold	Positive	Positive	Positive	–

* Calculated using Kruskal-Wallis test with Dunn's multiple comparisons.
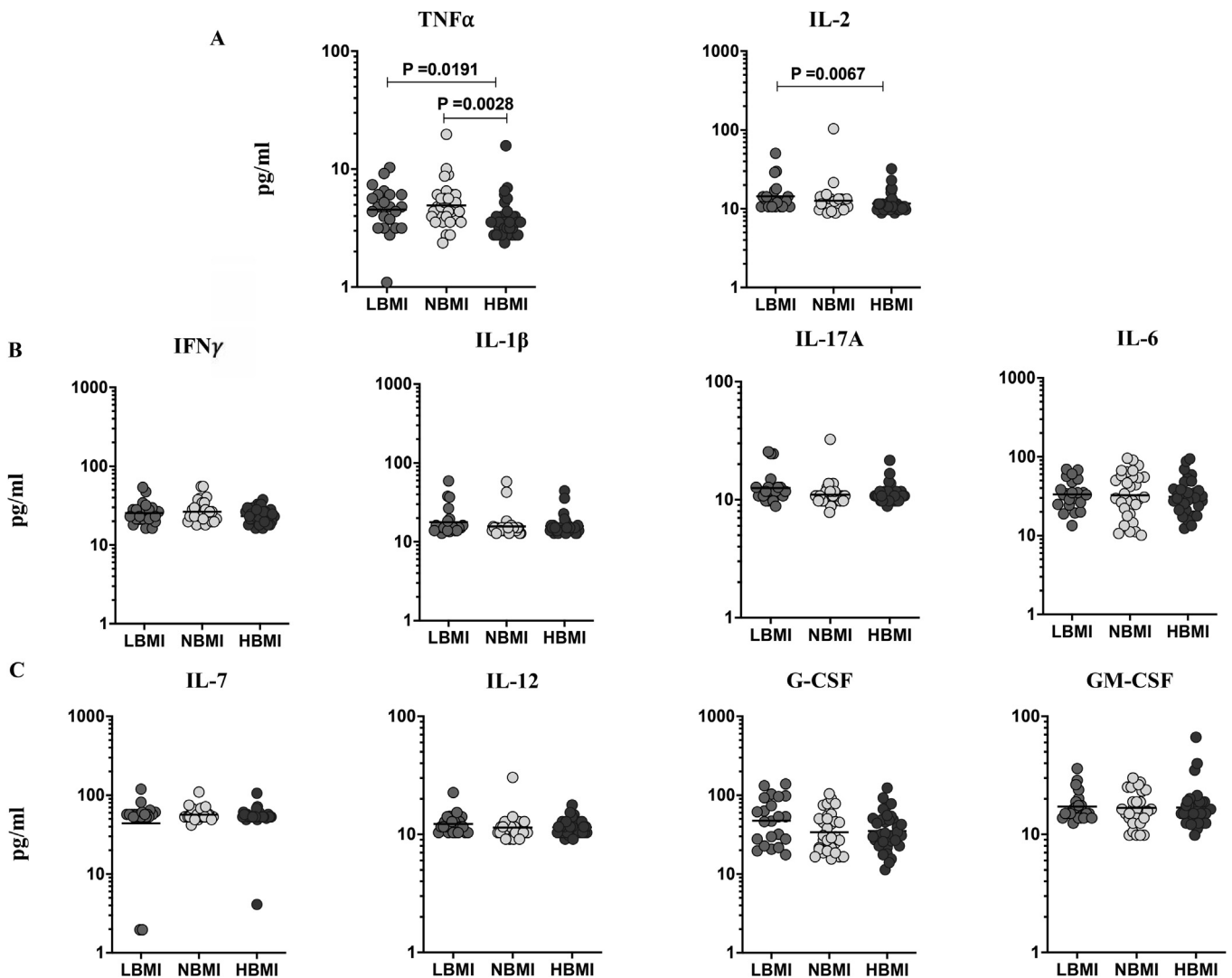[a] Calculated using chi-square test.

Fig. 1. Elevated plasma levels of Type 1 cytokines associated with TBL individuals with LBMI. (A) The plasma levels of Type 1 (TNFα, IL-2) cytokines were analysed by multiplex assay in LBMI (n = 22), NBMI (n = 31) and HBMI (n = 35) coexistent with TBL individuals. (B) The plasma levels of other pro-inflammatory (IFNγ, IL-1β, IL-17A, IL-6), (C) (IL-7, IL-12, G-CSF and GM-CSF) cytokines were measured by multiplex assay in LBMI, NBMI and HBMI coexistent with TBL individuals. Each circle represents a single individual and the bars represent the geometric means. P values were calculated using the Kruskal-Wallis test with Dunn's multiple comparisons. *P < 0.05, **P < 0.01, ***P < 0.001 and ***P < 0.0001.

4. Discussion

Immunity and nutritional status are strongly associated; this has been a topic of investigation for many years. One among them is malnutrition which promotes secondary immune deficiency, affects both innate and cell mediated immune responses and confers susceptibility to an array of infections [2,20–22]. In addition, malnutrition directly disturbs the antibody responses, diminishes the CD4 to CD8 ratios and enhances the CD4/CD8 double negative cell populations [23]. LBMI as a result of malnutrition was linked to enhanced disease severity, unfavourable treatment outcome and relapse in active TB [11,24–29]. Besides, BMI have a robust association with active pulmonary TB but it has not been found with extra-pulmonary TB indicating that someway LBMI influences the TB infection in the lungs predominantly [24,30]. The immunological basis of the interaction between TBL infection and BMI, if any, has not been studied. Our data reveals BMI has minimal impact on the cytokine and chemokine profiles in TBL disease.

Cytokines of both innate and adaptive immunity play an important role in host protective immune response against Mtb infection [31–34]. In animal models of pulmonary TB, it was shown that both Type 1 (IFNγ and TNFα) and Type 17 (IL-17A) cytokines were correlated to provide host defense against Mtb disease. Similarly, pro-inflammatory (IL-1β, IL-6, IL-12, IL-18 and GM-CSF) cytokines provide resistance to TB infection [10,35]. In our study, plasma levels of Type 1 (TNFα, IL-2) cytokines were significantly elevated in LBMI coexistent individuals upon comparison with NBMI and HBMI individuals. TNFα is the major cytokine responsible for early inflammation against Mtb disease [33]. Experimental studies have described TNFα as not only critical in mediating host immune response, but it is also critically involved in immunopathology against Mtb disease [36]. It is also crucial for the establishment and maintenance of the granuloma architecture and generates effector molecules through macrophage activation upon synergistically mediate with IFNγ [37].

The plasma levels of IL-2 cytokine was also significantly increased in LBMI coexistent TBL individuals. Active TB patients tend to show elevated IL-2 levels in response to Mtb-specific antigens, indicating that this cytokine might be a potential biomarker for TB disease [35,38]. Thus, it could be the reason that LBMI-TBL coexistent individuals have higher plasma levels. In contrast to our data, earlier studies have shown decreased Type 1 cytokines in coexistent LBMI with LTB individuals compared to NBMI or HBMI LTB coexistent individuals [15,16].

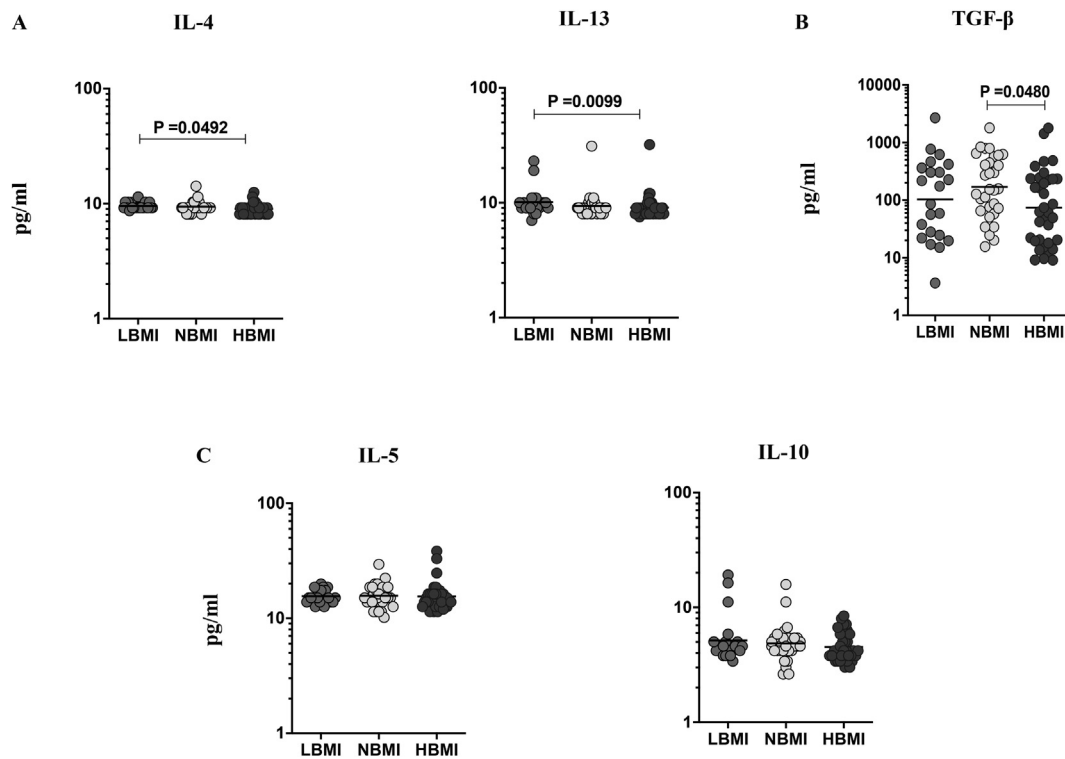Type 2 and regulatory cytokines involved are well known to induce

Fig. 2. Elevated plasma levels of Type 2 cytokines associated with TBL individuals with LBMI. (A) The plasma levels of Type 2 (IL-4, IL-13), (B) regulatory (TGF β) and (C) IL-5, IL-10 cytokines were analysed by multiplex ELISA in LBMI (n = 22), NBMI (n = 31) and HBMI (n = 35) coexistent with TBL individuals. Each circle represents a single individual and the bars represent the geometric means. P values were calculated using the Kruskal-Wallis test with Dunn's multiple comparisons.
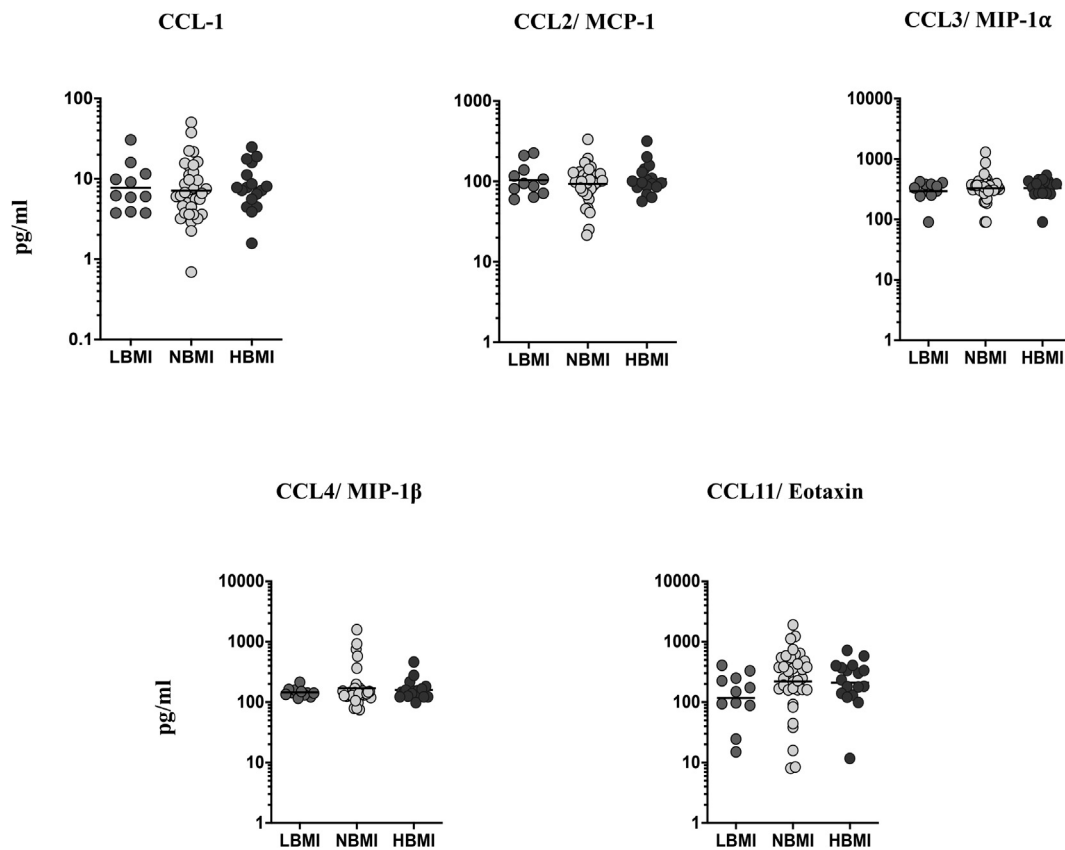

Fig. 3. No difference in CC chemokine levels in TBL individuals with different BMI. The plasma levels of CC (CCL-1, CCL-2/MCP-1, CCL3/MIP1α, CCL4/MIP-1β, CCL11/eotaxin) chemokines were analysed by multiplex assay in LBMI (n = 11), NBMI (n = 36) and HBMI (n = 17) coexistent with TBL individuals. Each circle represents a single individual and the bars represent the geometric means. P values were calculated using the Kruskal-Wallis test with Dunn's multiple comparisons.
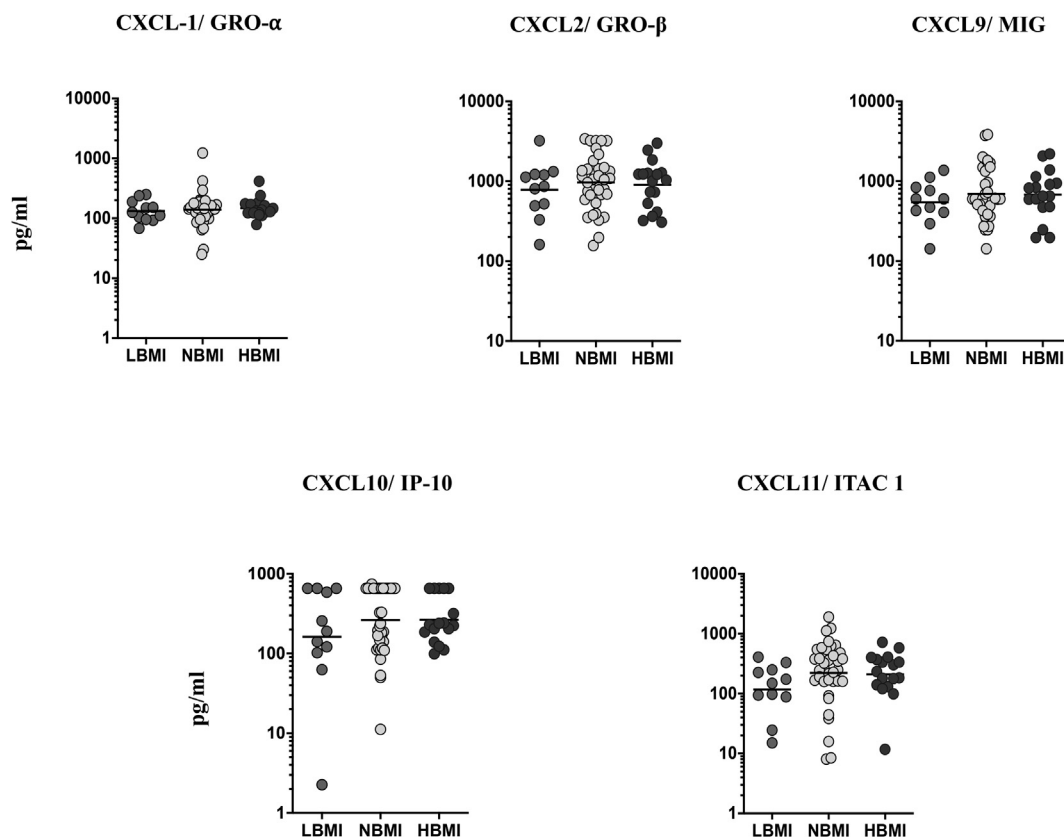
Fig. 4. No difference in CXC chemokine levels in TBL individuals with different BMI. The plasma levels of CXC (CXCL-1/GRO-α, CXCL2/GRO-β, CXCL9/MIG, CXCL10/IP-10, CXCL11/ITAC1) chemokines were analysed by multiplex assay in LBMI (n = 11), NBMI (n = 36) and HBMI (n = 17) coexistent with TBL individuals. Each circle represents a single individual and the bars represent the geometric means. P values were calculated using the Kruskal-Wallis test with Dunn's multiple comparisons.

susceptibility to TB infection [39]. Both IL-4 and IL-13 play an important role in modifying the Th1 mediated immune responses and often result in alternative macrophage activation [39–41]. Indeed, our data also reveals that individuals with LBMI actually demonstrate higher circulating levels of Type 2 (IL-4, IL-13) cytokines compared to NBMI and HBMI coexistent TBL individuals. It is possible that higher cytokine response might increase the disease severity in LBMI individuals. Apart from the above cytokines, other cytokines might be crucial in protecting and inhibiting the host immunity, especially, pro-inflammatory (IL-1β, GM-CSF, IFNγ, IL-6, IL-17A, IL-12) and regulatory (IL-10 and TGFβ) cytokines [42–44]. However, based on our data with LBMI, no significant differences could be discerned among the regulatory and other inflammatory cytokines analysed in this study. This is perhaps owing to the lesser severity of antigen load in the circulation. The implication of higher levels of certain Type 1 and Type 2 cytokines in LBMI individuals with TBL needs to be examined further. The higher levels of Type 1 cytokines (TNFα, IL-2) could possibly be associated with enhanced bacterial loads in TBL. In contrast, elevated levels of Type 2 or regulatory cytokines might antagonize or suppresses the protective immune response and help in establishing chronic infection in LBMI individuals. Thus, improving BMI in those disease individuals might improve the boosting of protective immune responses.

Like cytokines, different chemokines and their cognate receptors play an important role in TB disease specifically in migration of T cells to the lungs, naïve, effector and memory T cell differentiation and regulatory T cell function. Chemokines also mediate the trafficking of dendritic cells (DC) to the lymph nodes, T cell localization and recruitment of activated T cells [45–47]. In addition, the plasma levels of chemokines have the capacity to influence host immunity to sustain the protective immune response [45]. However, our data on chemokines did not demonstrate any significant difference between the LBMI, NBMI and HBMI groups. In contrast, a previous study revealed that LBMI coexistent LTB individuals were associated with decreased baseline and Mtb antigen-stimulated chemokine responses [2]. Overall, our data suggests LBMI coexistent TBL individuals have minimal changes in plasma cytokine and chemokine profiles. Our study has certain limitations by not measuring the cytokines at the affected lymph nodes and relying only on systemic association. Further, we do not have the data on other co-morbidities (diabetes, hypertension and alcohol) to study their relationship and we do not have sample groups without TB to measure cytokines and chemokine levels. Thus, measuring the above cytokines either using lymph nodes or antigen stimulated samples could provide a better knowledge of how LBMI influences the poorly studied form of extra pulmonary TB disease.

Ethical statement

This study was approved by the Internal Ethics Committee (IEC) of National Institute of Research in Tuberculosis (NIRT, NIRTIEC2010007). The informed written consent was acquired from all the volunteers involved in this study.

CRediT authorship contribution statement

Gokul Raj Kathamuthu: Conceptualization, Methodology, Writing - review & editing, Writing - original draft, Formal analysis, Investigation. **Rathinam Sridhar:** Resources. **Dhanaraj Baskaran:** Resources. **Subash Babu:** Conceptualization, Methodology, Writing - review & editing, Supervision, Validation, Project administration.

Declaration of Competing Interest

Acknowledgements

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