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Longitudinal inflammation cytokine trajectories during tuberculosis and their association with lung outcomes

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Post-TB Lung Disease: An emerging global health challenge

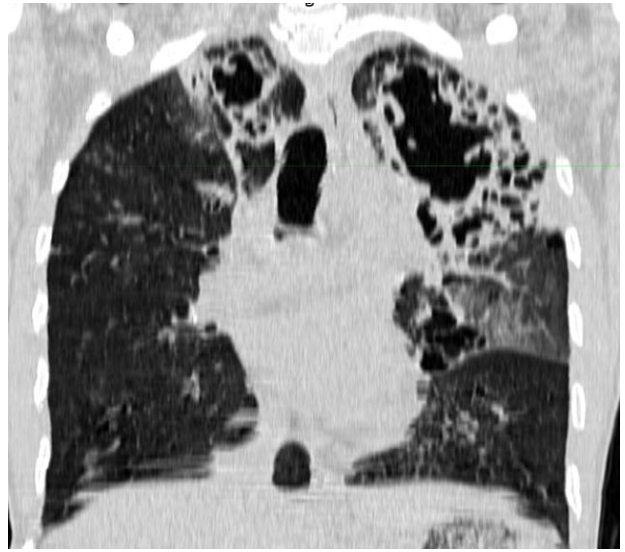
- TB remains a leading cause of infectious mortality globally
  - ~10.7 million new TB cases annually
  - ~1.2 million TB-related deaths per year
- Increasing recognition of long-term morbidity among TB survivors
  - ~155 million people survived TB globally, since the 1980s
  - TB survivors experience excess long-term mortality and chronic respiratory impairment
- Post-TB lung disease (PTLD) affects an estimated 30-50% of TB survivors globally, and
  - Includes persistent airflow obstruction, restriction, fibrosis, and persistent functional limitation
  - Increasingly recognized as a major contributor to long-term morbidity among TB survivors

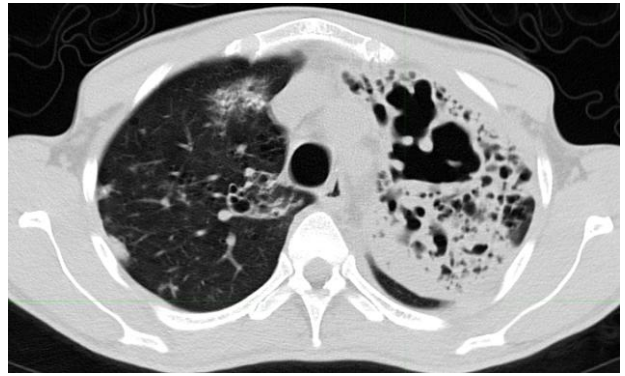
Global TB Report, 2025; Ivanova et al., 2023, Eur Respir

Post-TB Lung Disease (PTLD) is biologically heterogeneous

- PTLD encompasses diverse structural and functional abnormalities
  - Fibrosis and parenchymal destruction
  - Bronchiectasis and cavitation
  - Reduced lung volume and impaired gas exchange
- Lung injury likely reflects multiple biological pathways
  - Persistent inflammation
  - Dysregulated immune responses
  - Matrix remodelling and tissue repair

Inflammatory pathways underlying distinct PTLD phenotypes remain poorly defined





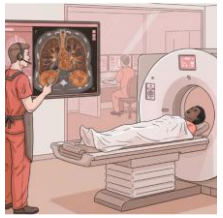
Adult PTB case, Tembisa 4/2022

Allwood et al., 2021, Respiration, Pasipanodya et al. BMC Public

INFIN-TB Study design and cytokine sub-study

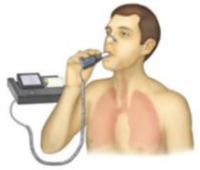
- **Cohort**
  - Parent INFIN-TB cohort included 258 adults with newly diagnosed pulmonary TB
  - By design HIV-positive and HIV-negative participants enrolled in similar numbers
  - Preliminary luminex cytokine sub-study population (n=168)

Sputum collection
- Baseline
- Week 2



HRCT Scan
- Baseline
- Month 12

Baseline 2 Weeks 12 months



PFTs
- Baseline
- Month 12

- **Analyses**
  - Multiplex sputum cytokine profiling
  - Chemokines
  - Remodelling associated mediators (MMPs)
- **Outcomes Examined**
  - Lung function phenotypes
  - Radiographic severity
  - Longitudinal lung function outcomes

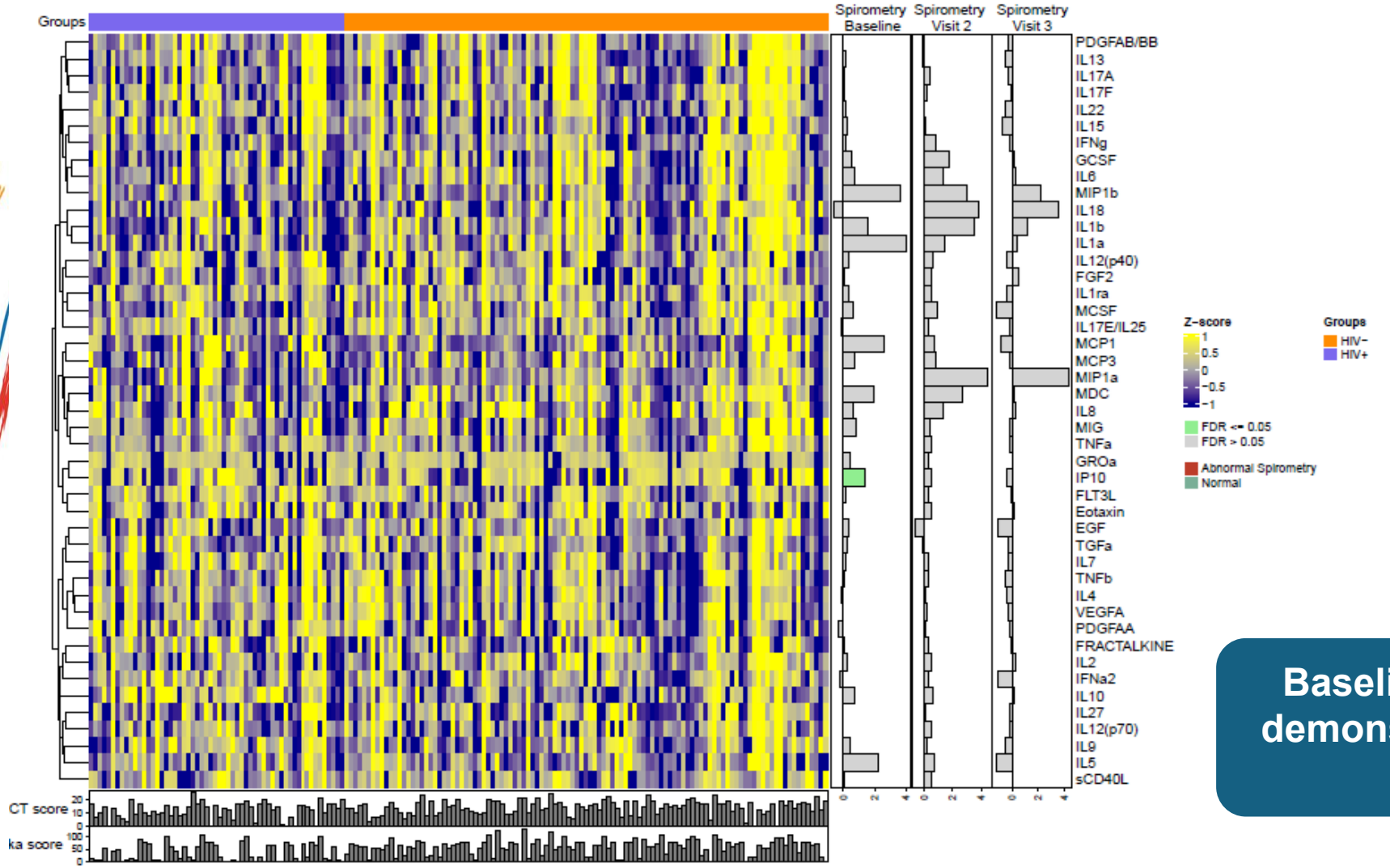
Objective: To identify inflammatory pathways associated with distinct PTLD phenotypes and long-term lung health outcomes

Baseline characteristics by HIV status

Variable	HIV- (N=110)	HIV+ (N=58)	p-value
Age (years)	35.00 (29.00–44.00)	37.00 (34.25–46.75)	0.121
Female sex	20 (18.2%)	18 (31.0%)	0.058
BMI (kg/m²)	19.15 (17.33–20.95)	19.50 (17.43–22.08)	0.399
Smoking status	**77 (70.0%)**	**31 (53.4%)**	**0.033**
FEV_1 Z-score	−1.72 (−2.45–−0.75)	−1.05 (−2.10–−0.06)	0.072
FVC Z-score	−1.47 (−2.16–−0.48)	−1.16 (−1.90–−0.17)	0.232
FEV_1/FVC Z-score	**−0.43 (−1.60–0.22)**	**−0.14 (−0.99–0.80)**	**0.033**
Overall HRCT score	14.00 (10.75–18.00)	13.50 (9.00–16.00)	0.071
Timika score	**63.00 (45.00–80.00)**	**17.00 (3.00–65.00)**	**<0.001**
SGRQ total	21.61 (13.75–37.56)	29.27 (11.79–42.01)	0.572

HIV-negative participants demonstrated greater smoking exposure, greater radiographic severity and lower FEV_1/FVC ratios at baseline

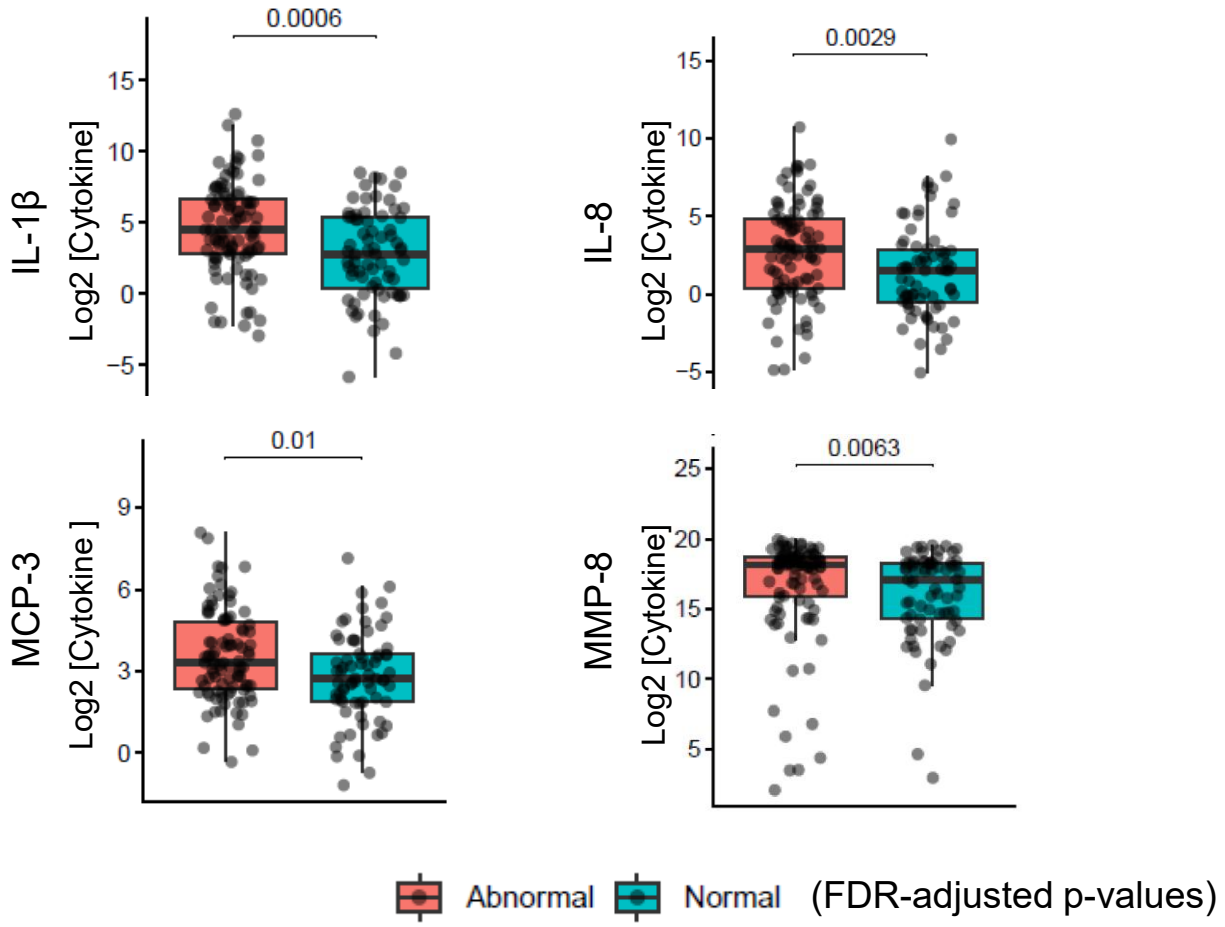
Baseline sputum cytokine profiles by HIV Status



Baseline cytokine profiles did not demonstrate clear clustering by HIV status

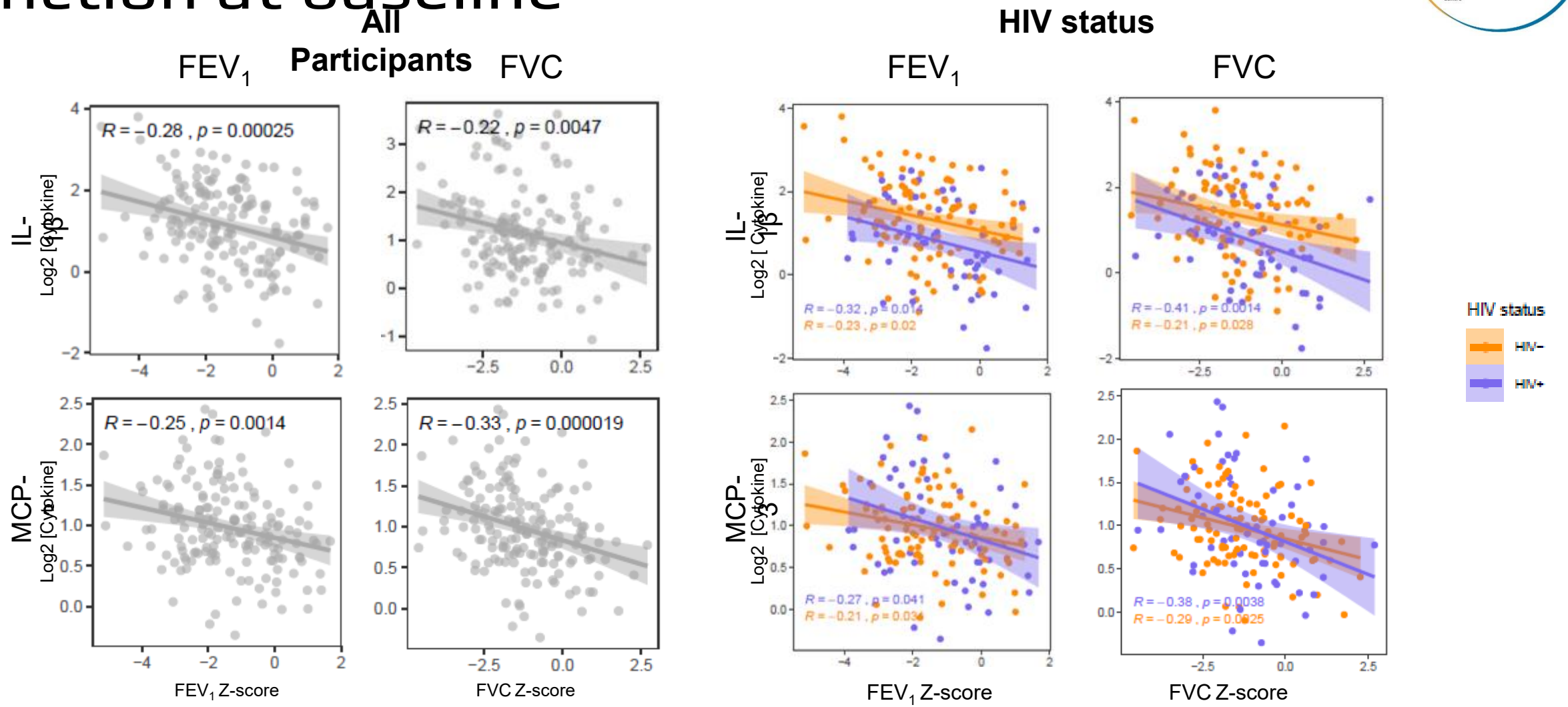
Sputum cytokines and lung function abnormality at baseline

Abnormal lung function:
Any PFT z scores <-1.65



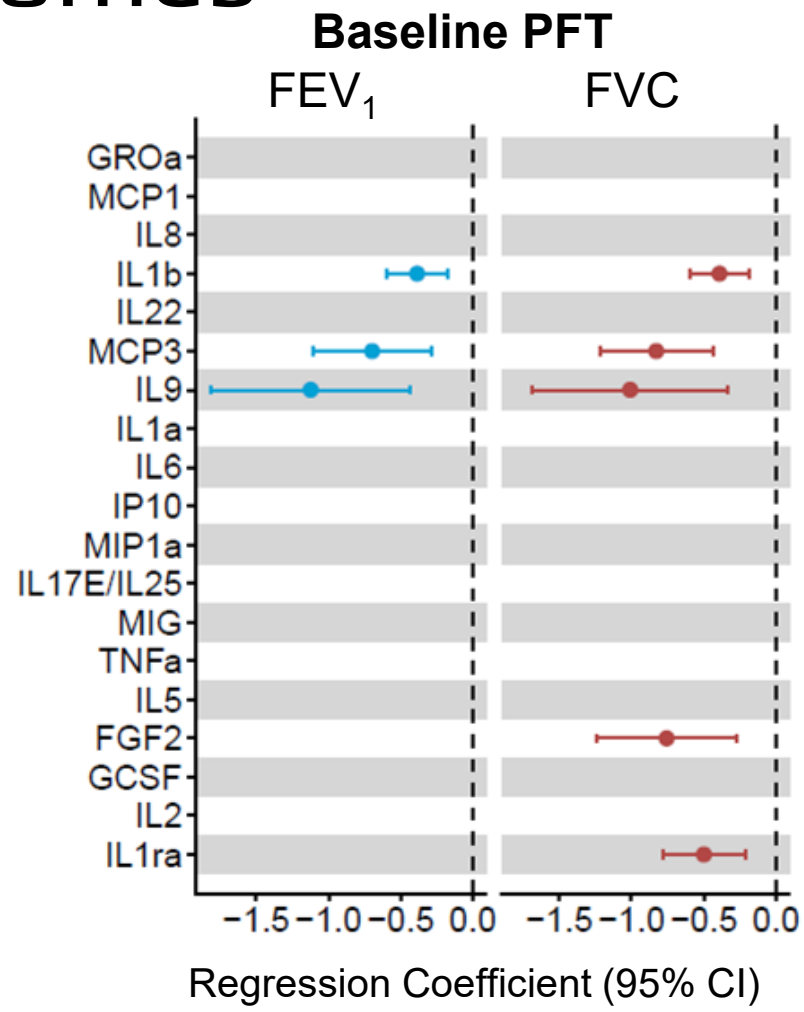
Abnormal lung function was associated with potentially heightened myeloid-driven inflammatory and tissue-remodelling responses

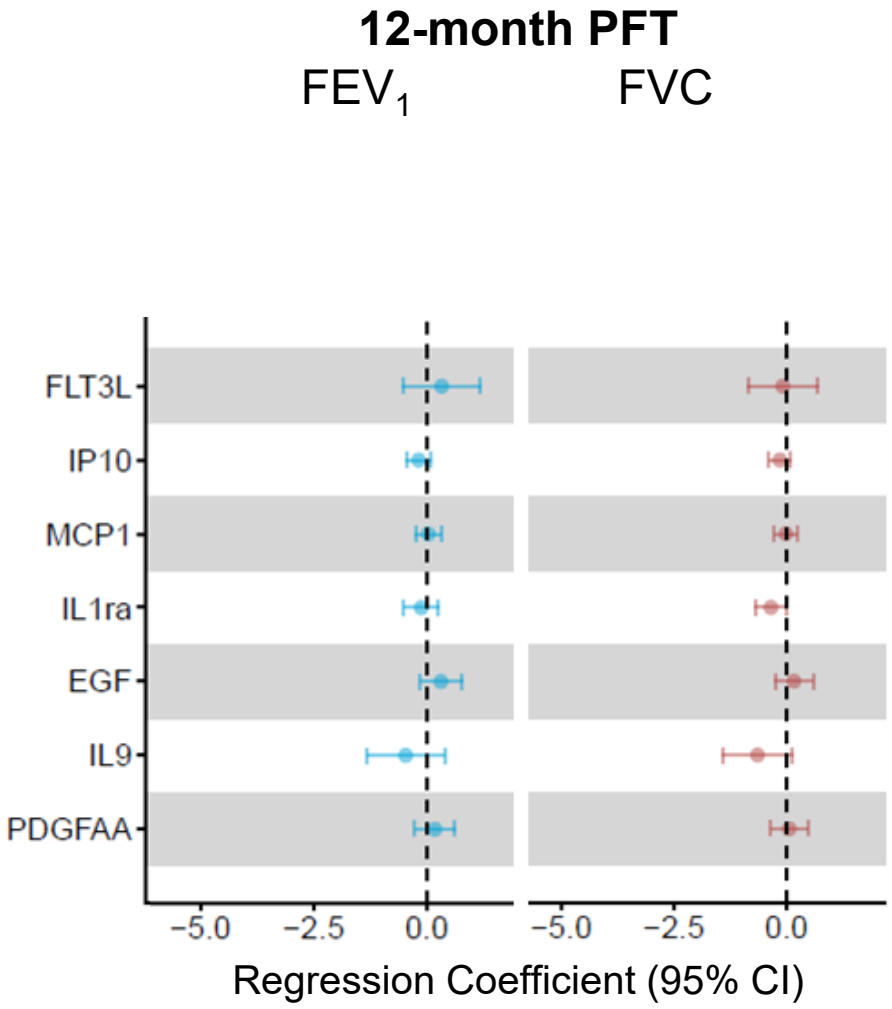
Sputum cytokine associations with lung function at baseline



Higher IL-1β and MCP-3 levels were associated with worse lung function at baseline

Early sputum cytokines and lung function outcomes

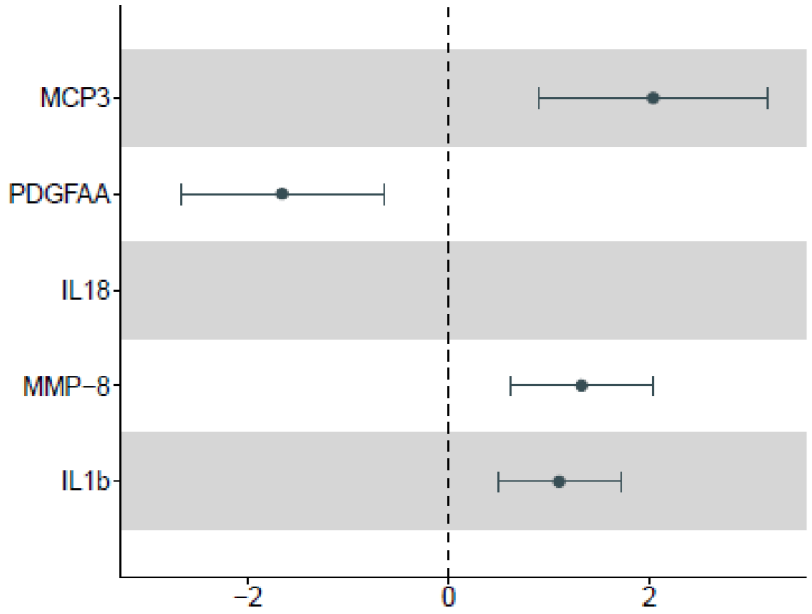




Early inflammation was associated with worse lung function at baseline, with fewer persistent associations at 12 months.

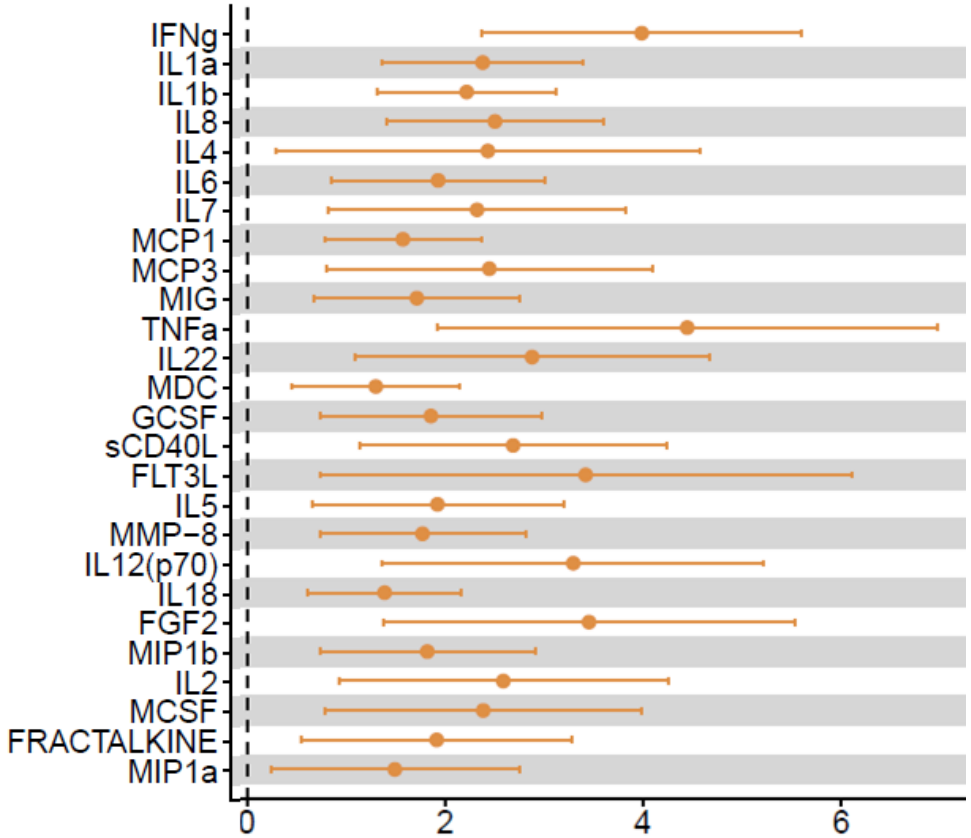
Early sputum cytokines and lung damage on HRCT

Baseline HRCT



Regression Coefficient (95% CI)

12-month HRCT



Regression Coefficient (95% CI)

Early inflammation associated with greater long-term structural lung damage , despite limited associations with baseline HRCT severity

Conclusions

- Baseline sputum inflammatory mediator profiles were associated with abnormal lung function and greater HRCT-defined structural lung damage.
- IL-1β, MCP-3, and MMP-8 demonstrated consistent associations with both early and long-term radiographic damage.
- Inflammatory associations appeared stronger for structural lung damage than for spirometric impairment, supporting HRCT as a sensitive marker of PTLD-related damage.
- The observed cytokine signatures suggest potentially a heightened myeloid-dependent inflammatory and tissue-remodelling responses during active TB disease.

Early inflammatory and tissue-remodelling signatures may represent mechanistic biomarkers and potential therapeutic targets for PTLD

Programmatic / Policy Implications

- Lung inflammation and damage at TB diagnosis may identify individuals at risk of PTLD and long-term respiratory morbidity.
- Inflammatory biomarkers measured during **EARLY TB treatment** could support risk stratification and targeted follow-up.
- Additional research is needed to develop scalable and cost-effective approaches for PTLD risk stratification in resource-limited settings.
- Inflammatory and tissue-remodelling pathways may represent targets for host-directed therapies to prevent and mitigate PTLD.

Traditionally, TB programmes have focused on microbiological cure. Our findings suggest that preserving long-term lung health should also be considered an important treatment outcome

Future Directions

- Complete multiplex cytokine profiling on the remaining sputum samples from the full INFIN-TB cohort.
- Apply longitudinal mixed-effects modelling to characterise cytokine trajectories during TB treatment and recovery.
- Define inflammatory endotypes associated with persistent structural lung damage and impaired recovery.
- Develop predictive models integrating inflammatory biomarkers, genomics, metabolomics, lung function, and imaging data to identify patients at highest risk of PTLD.

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