EVALUATION OF IMMUNE CELL EXHAUSTION, TOLERANCE, AND METABOLISM IN POST-COVID CONDTION

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Introduction

A proportion of SARS-CoV-2 (COVID) survivors have persistent symptoms lasting several months after the acute illness. This Post-Covid Condition (PCC) is defined by the World Health Organization as symptoms which impact daily functioning lasting 3 months or more from onset of COVID. A variety of symptoms have been reported, with some clinical overlap between PCC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). However, the underlying mechanism is unknown, and no diagnostic test or marker for this condition has been identified.

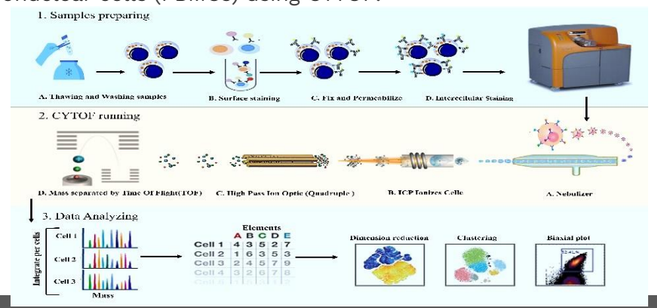
Objective

This study aims to determine whether PCC can be characterized by persistent dysfunctional immune response, including immune cell exhaustion, tolerance, or metabolism

Methods

70 Adults with laboratory proven SARS-CoV-2 infection were prospectively recruited between March – December 2020 and followed at 3-, 6-, and 12- months post infection. At each visit blood was collected and a COVID symptom questionnaire was administered. PCC was defined as having at least one moderate or severe symptom at 3 months post-infection. Twenty-eight participants (16 with PCC and 12 COVID controls) with samples and questionnaire data at all three time points were selected for analysis of markers of immune exhaustion, tolerance, and metabolism using Cytometry by Time of Flight (CYTOF) (Fig 1).

Figure 1. Analyzing the expression of cell markers of on peripheral blood mononuclear cells (PBMCs) using CYTOF.



Results

Figure 2. Baseline Characteristics

BASELINE CHARACTERISTICS		
DEMOGRAPHICS	PCC (N=16)	Control (N=12)
Age (years +/- SD)	52.7 (4.4)	48.3 (4.3)
Sex (N, %)		
Female	8 (50.0)	4 (33.3)
Male	8 (50.0)	8 (66.6)
Ethnicity (N, %)		
Caucasian	12 (75.0)	12 (100.0)
Asian	4 (25.0)	0
African	0	0
Hispanic	0	0
Other	0	0
MEDICAL COMORBIDITIES (N, %)		
Obesity (BMI >30)	4 (25.0)	5 (41.7)
Hypertension	6 (37.5)	1 (8.3)
Diabetes	5 (31.3)	1 (8.3)
Asthma	5 (31.3)	2 (16.7)
COPD	0	0
Pulmonary Fibrosis	0	0
OSA (on CPAP)	2 (12.5)	1 (8.3)
OSA (not on CPAP)	1 (6.3)	0
CAD	1 (6.3)	0
Active Malignancy	1 (6.3)	2 (16.7)
Psychiatric Condition	1 (6.3)	1 (8.3)
ACUTE COVID SEVERITY (N, %)		
No Medical Intervention Required	8 (50.0)	5 (41.7)
Emergency Department Visit	1 (6.3)	4 (33.3)
Hospitalized - Not Requiring O2 Supplemenation	2 (12.5)	0
Hospitalized - Requiring Non-invasive O2	1 (6.3)	2 (16.7)
ICU - Requiring Non-invasive O2	1 (6.3)	1 (8.3)
ICU - Requiring Mechanical Ventilation	3 (0)	0

There were no significant differences between the PCC and control groups in terms of age, sex, ethnicity, self-reported comorbidities, or severity of acute COVID illness (Fig 2). The most commonly reported symptom at 3 months was fatigue, occurring in 12 (75%) patients, followed by exertional dyspnea (11; 68.8%), chest tightness (10; 62.5%), myalgia, sleep disturbance, and palpitations (9; 56.3%), headache (8; 50%), congestion and rest dyspnea (7; 43.8%). Cough, sore throat, diarrhea, and anosmia, and fever were less common.

There were no differences in the proportions of T, B, NK or mononuclear cells between the PCC and control groups. In T cells and NK cells, the expression of inhibitory receptors TIGIT, PD1, and LAG3 were equivalent between the groups, as were markers of metabolism (CD98) and activation (CD69) (Fig 3). The expression of the CD69 and PD1 on B cells did not differ between groups. There were no detectable differences in the expression of FOXP3 or intracellular cytokines (IFN-g, TNF-α, IL-10). Expression of PD1 on CD8+ effector cells is significantly lower in the PCC group than in the non-PCC groups at month three (Fig 4A). In addition, there were some interesting results in the expression of inhibitory receptors on some T-cell subsets, as well as in age and gender-based subsets of the study population (summarized FIG 4B-E)

Figure 3. Results of Immune Cell Phenotyping in PCC group vs non-PCC group

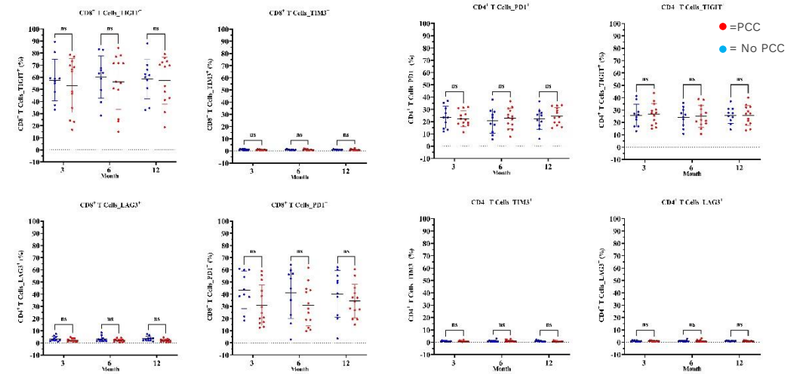
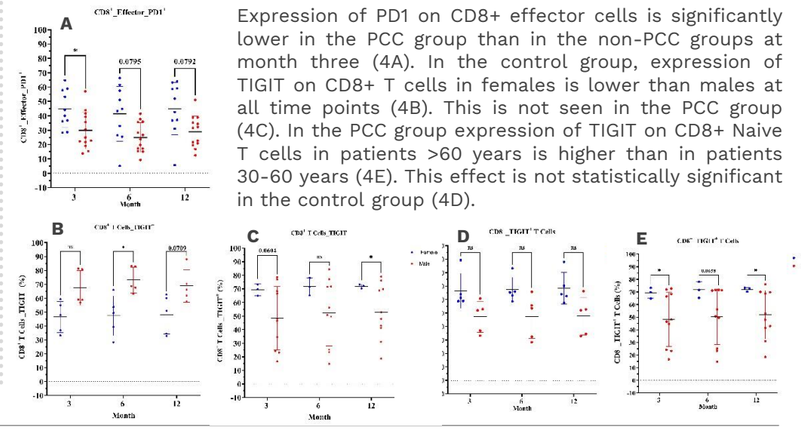


Figure 4. Expression of Inhibitory Receptors and Subgroup Analysis



Expression of PD1 on CD8+ effector cells is significantly lower in the PCC group than in the non-PCC groups at month three (4A). In the control group, expression of TIGIT on CD8+ T cells in females is lower than males at all time points (4B). This is not seen in the PCC group (4C). In the PCC group expression of TIGIT on CD8+ Naive T cells in patients >60 years is higher than in patients 30-60 years (4E). This effect is not statistically significant in the control group (4D).

Conclusions

- No markers of immune exhaustion, tolerance, or metabolism differentiate PCC from people who recovered fully post-COVID
- Limitations: small sample size, evolving clinical classification of PCC
- Significant variability in results of previous studies
- Further research needed to better characterize this condition in terms of clinical manifestations and underlying pathologic mechanisms

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