LYMPHOCYTE SUBSET COUNTS IN COVID-19 PATIENTS: A META ANALYSIS

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Keck School of Medicine, U. Southern California
Los Angeles, CA
INTRODUCTION

• Update of the pandemic
• Case Fatality Rates
• COVID-19 and Immunopathogenesis
• Biomarkers of Disease Severity
• Lymphocyte subsets in COVID-19: A meta analysis
<table>
<thead>
<tr>
<th>Country</th>
<th>April 27th</th>
<th>July 13th</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>985,443</td>
<td>3,374,654</td>
</tr>
<tr>
<td>Spain</td>
<td>229,422</td>
<td>1,884,967</td>
</tr>
<tr>
<td>Germany</td>
<td>158,434</td>
<td>158,348</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>158,348</td>
<td>906,752</td>
</tr>
<tr>
<td>Turkey</td>
<td>112,261</td>
<td>330,123</td>
</tr>
</tbody>
</table>

Cases worldwide:

- 3,035,177
- 13,145,302

COVID-19 CASE FATALITY RATES
GLOBAL VS. UNITED STATES
JULY 14TH, 2020

<table>
<thead>
<tr>
<th>State</th>
<th>Confirmed Cases</th>
<th>Deaths</th>
<th>Case Fatality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York</td>
<td>407K</td>
<td>32,075</td>
<td>7.9%</td>
</tr>
<tr>
<td>California</td>
<td>336k</td>
<td>7,086</td>
<td>2.1%</td>
</tr>
<tr>
<td>Florida</td>
<td>282k</td>
<td>4,276</td>
<td>1.5%</td>
</tr>
<tr>
<td>Texas</td>
<td>274k</td>
<td>3,313</td>
<td>1.2%</td>
</tr>
<tr>
<td>New Jersey</td>
<td>177k</td>
<td>15,560</td>
<td>8.8%</td>
</tr>
</tbody>
</table>
COVID-19 PANDEMIC MARCH – JULY 2020
CALIFORNIA VS. NEW YORK
NEW CASES PER DAY

Each day shows new cases reported since the previous day. Updated less than 2 hours ago. Source: Wikipedia
About this data
COVID-19 PANDEMIC MARCH – JULY 2020
CALIFORNIA VS. NEW YORK
DEATHS PER DAY
UNANSWERED QUESTIONS

• What causes certain patients to experience severe disease while others remain mildly symptomatic or asymptomatic?
• Why are young children seemingly spared from severe disease?
• What role does the immune system play in the pathogenesis of COVID-19?
• Are there measurable immunological biomarkers that are predictive of severe disease and poor outcomes?
• Are there immunological biomarkers associated with response to treatment, viral clearance and recovery/convalescence?
SARS-COV-2 REPLICATION CYCLE AND INFLAMMATORY IMMUNOPATHOGENESIS

• The first step in infection is virus binding to a host cell through its target receptor angiotensin-converting enzyme 2 (ACE2)

• Cleavage of SARS-CoV-2 spike protein by cellular transmembrane serine protease 2 (TMPRSS2) allows for fusion between viral and cell membranes

• Virus enters cell through endocytosis where fusion of the membranes results in the release of the viral nucleocapsid into the cytosol of the infected cell

• Viral RNA is uncoated, replication and translation of polyproteins quickly ensues with the production of the replication-transcription complex which engages in negative-strand RNA synthesis for both full length genomic mRNA (new genomic RNA) and sub-genomic mRNA’s (structural and accessory proteins)

• Assembly of virions rapidly proceeds with the accumulation of new genomic RNA and structural components and then are released by exocytosis
Lung cells are destroyed as part of the viral replication cycle triggering a local immune response

- Recruiting monocytes and macrophage
- Release of cytokines and chemokines
- Priming of the adaptive T and B cell immune response
- In most cases this results in the resolution of the infection

However... in some cases a dysfunctional immune response occurs leading to a hyper-inflammatory state, acute respiratory distress syndrome, respiratory failure and death (70% of COVID-19 related deaths)

- The cytopathic viral response can also result in the release of large quantities of cytokines (cytokine storm) which leads to multi-organ damage, organ failure and death (28% of COVID-19 related deaths)

- The mechanisms by which SARS-CoV-2 subverts the body’s innate anti-viral response are not completely understood.
NORMAL VS. DYSREGULATED IMMUNE RESPONSE TO SARS-COV-2 INFECTION

NATURE REVIEWS | IMMUNOLOGY
Published online: 28 April 2020
NORMAL VS. DYSREGULATED IMMUNE RESPONSE TO SARS-COV-2 INFECTION

**Dysfunctional immune response**
- Excessive infiltration of monocytes, macrophages and T cells
- Systemic cytokine storm
- Pulmonary oedema and pneumonia
- Widespread inflammation and multi-organ damage

**Healthy immune response**
- Infected cells rapidly cleared
- Virus inactivated by neutralizing antibodies
- Minimal inflammation and lung damage
COMPONENTS OF THE IMMUNE SYSTEM IN COVID-19 – NEED FOR FURTHER INVESTIGATION

• The innate immune response – role in control of the early phases of infection vs. contribution to later adaptive immune response
• The pathologic vs. protective effects of cytokines, chemokines and their receptors
• Humoral immune response kinetics and protective immunity
• The role of T-cell mediated immunity – protective vs pathogenic
• Role of lifelong exposure to common coronavirus
• Relevance of T cell activation and exhaustion
• Importance of reg-T-cells in modulating the immune response
COVID-19
Biomarkers of Severe Disease and Death

- Several blood and immunological parameters may predict patients at higher risk of complications.

- Routine blood work - acute phase proteins, (e.g. CRP, serum amyloid protein), procalcitonin, lactate dehydrogenase, d-dimer, ferritin.

- Immunological biomarkers are particularly important as immunopathology has to be considered a key driver in the morbidity and mortality of COVID-19, e.g. elevated levels of IL-6, IL-8, IL-10, IL-2R, IL-1β, IL-18.

- Published reviews of several studies comprising over 55,000 COVID-19 patients consistently observe that the following markers predict disease severity: CRP, lactate dehydrogenase, d-dimer, decreased blood platelets and decreased peripheral blood lymphocyte counts (with normal or elevated neutrophil counts).

- Lymphopenia is the most frequently described prognostic marker and appears to predict morbidity and mortality even at early stages.
IMMUNOPHENOTYPING
T CELLS, T HELPER CELLS, T CYTOTOXIC CELLS, B CELLS AND NK CELLS
PERCENTAGES AND ABSOLUTE COUNTS

FLOW CYTOMETRY
“COVID-19 & LYMPHOCYTE SUBSETS”
NATIONAL LIBRARY OF MEDICINE – NIH LITERATURE SEARCH

- April 8th, 2020 = 12
- April 21st, 2020 = 31
- April 27th, 2020 = 98
- May 23rd, 2020 = 258

Complete Meta Analysis and Submit May 24th, 2020
- July 14th, 2020 = 432
LYMPHOCYTE SUBSET COUNTS IN COVID-19 PATIENTS: A META ANALYSIS


doi: 10.1002/cyto.a.24172 [Epub ahead of print]

Lymphocyte Subset Counts in COVID-19 Patients: A Meta-Analysis

Wei Huang, 1 Julie Berube, 1 Michelle McNamara, 1 Suraj Saksena, 1 Marsha Hartman, 1 Tariq Arshad, 1 Scott J. Bornheimer, 1 and Maurice O’Gorman 2

Abstract

A reduced peripheral blood absolute lymphocyte count with an elevated neutrophil count has been a consistent observation in hospitalized COVID-19 patients. In this brief meta-analysis, the reduction of lymphocyte subset counts in COVID-19 patients was investigated across 20 peer-reviewed studies meeting criteria for reporting lymphocyte subset counts and COVID-19 disease severity. CD4+ T cell, CD8+ T cell, B cell, NK cell and total lymphocyte cell counts all showed statistically significant reduction in patients with severe/critical COVID-19 disease compared to mild/moderate disease. T cell subsets showed the largest standardized magnitude of change. In some studies, multivariate analysis has shown that CD4 and/or CD8 T cells counts are independently predictive of patient outcomes.

Key terms: COVID-19; Immunophenotyping, Lymphocyte subset, T Cell subset, flow cytometry
LYMPHOCYTE SUBSET COUNTS IN COVID-19 PATIENTS: A META ANALYSIS

• Methods
  • Search PubMed for “COVID-19 Lymphocyte subsets” (n=258)
  • Exclude publications that did not include patient clinical characterization
  • Exclude those that did not include lymphocyte subset evaluations
  • Search returned 16 publications with lymphocyte subset counts and well characterized degrees of disease severity
  • An additional 4 publications found to meet these criteria using a Google search
  • CD4+ and/or CD8+ T cell counts from COVID-19 patients with varying degrees of disease severity were reported in all 20 publications
  • Compared peripheral blood lymphocyte subset counts in patient with mild/moderate disease to those with severe/critical disease that were hospitalized in China with a diagnosis of COVID-19 pneumonia
  • Disease status assignment across studies varies so were grouped into “mild/moderate” and “severe/critical”
    • Mild/moderate = mild, survival, moderate, non-aggravated and non-critical
    • Severe/Critical = deceased, non-survival, critical and aggravated disease
LYMPHOCYTE SUBSET COUNTS IN COVID-19 PATIENTS: A META ANALYSIS

• Results
  • The 20 publications included a total of 3,107 subjects
    • 2311 (76.6%) were classified as mild/moderate
    • 706 (23.4%) were classified as severe/critical
  • Sample sizes of subjects with CD4+ and CD8+ T cells counts varied from 17 to 499
    • A smaller subset of patients had absolute lymphocyte subset counts for B cells and NK cells
  • The mean cell counts were consistently decreased in Severe/Critical group and the differences in the weighted mean value of cell between the two groups were statistically significant for all cell types
  • The “fold changes” between Mild/Moderate and Severe/Critical groups for CD4 and CD8 T-cell counts are larger than for mean B cell, NK cell and total lymphocyte counts
MEAN LYMPHOCYTE SUBSET COUNTS ACROSS ARTICLES

### Table of Mean Lymphocyte Subset Counts

<table>
<thead>
<tr>
<th>Subset</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ β cells</td>
<td>430×10⁶</td>
<td>199×10⁶</td>
</tr>
<tr>
<td>CD8+ β cells</td>
<td>259×10⁶</td>
<td>119×10⁶</td>
</tr>
<tr>
<td>B-Cell</td>
<td>166×10⁶</td>
<td>111×10⁶</td>
</tr>
<tr>
<td>NK-Cell</td>
<td>139×10⁶</td>
<td>101×10⁶</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1089×10⁶</td>
<td>668×10⁶</td>
</tr>
</tbody>
</table>

Fold change (Moderate/Severe): 2.2×, 2.2×, 1.5×, 1.4×, 1.6×
Results (cont’d)

Meta-analysis was performed to calculate the standardized mean difference (SMD) and the 95% confidence interval between the Mild/Moderate and Severe/Critical groups for total lymphocytes, CD4+ T cells, CD8+ T cells, CD19+ B cells and CD16+CD56+ NK cell counts.

Lymphocyte subset SMD was significantly lower in the Severe/Critical group vs. the counts in the Mild/Moderate group.
STANDARD MEAN DIFFERENCES WITH 95% CONFIDENCE INTERVALS CD4+ AND CD8+ T CELLS

<table>
<thead>
<tr>
<th>Study</th>
<th>N mod</th>
<th>N severe</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng [3]</td>
<td>214</td>
<td>39</td>
<td>0.64 [0.36, 0.99]</td>
</tr>
<tr>
<td>Wang [4]</td>
<td>274</td>
<td>65</td>
<td>0.80 [0.42, 1.18]</td>
</tr>
<tr>
<td>Chen [5]</td>
<td>12</td>
<td>11</td>
<td>1.21 [0.38, 2.15]</td>
</tr>
<tr>
<td>Zhou [6]</td>
<td>12</td>
<td>5</td>
<td>1.16 [0.37, 2.06]</td>
</tr>
<tr>
<td>Qin [7]</td>
<td>17</td>
<td>27</td>
<td>0.72 [0.10, 1.34]</td>
</tr>
<tr>
<td>Wan [8]</td>
<td>102</td>
<td>21</td>
<td>0.85 [0.37, 1.34]</td>
</tr>
<tr>
<td>Liu [9]</td>
<td>21</td>
<td>18</td>
<td>1.04 [0.37, 1.71]</td>
</tr>
<tr>
<td>Du [10]</td>
<td>156</td>
<td>21</td>
<td>0.47 [0.21, 0.74]</td>
</tr>
<tr>
<td>He [11]</td>
<td>135</td>
<td>69</td>
<td>2.00 [1.05, 2.94]</td>
</tr>
<tr>
<td>Xu [12]</td>
<td>117</td>
<td>28</td>
<td>1.24 [0.80, 1.68]</td>
</tr>
<tr>
<td>Zheng [13]</td>
<td>63</td>
<td>36</td>
<td>0.63 [0.36, 0.90]</td>
</tr>
<tr>
<td>Liu [14]</td>
<td>30</td>
<td>40</td>
<td>1.70 [1.33, 2.07]</td>
</tr>
<tr>
<td>Dao [15]</td>
<td>479</td>
<td>20</td>
<td>0.64 [0.39, 0.89]</td>
</tr>
</tbody>
</table>

RE Model

<table>
<thead>
<tr>
<th>Study</th>
<th>N mod</th>
<th>N severe</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng [3]</td>
<td>214</td>
<td>39</td>
<td>0.61 [0.31, 0.91]</td>
</tr>
<tr>
<td>Wang [4]</td>
<td>274</td>
<td>65</td>
<td>0.77 [0.49, 1.06]</td>
</tr>
<tr>
<td>Chen [5]</td>
<td>12</td>
<td>11</td>
<td>1.71 [0.71, 2.71]</td>
</tr>
<tr>
<td>Zhou [6]</td>
<td>12</td>
<td>5</td>
<td>0.96 [0.14, 2.75]</td>
</tr>
<tr>
<td>Qin [7]</td>
<td>17</td>
<td>27</td>
<td>0.41 [0.20, 1.02]</td>
</tr>
<tr>
<td>Wan [8]</td>
<td>102</td>
<td>21</td>
<td>0.79 [0.31, 1.27]</td>
</tr>
<tr>
<td>Liu [9]</td>
<td>21</td>
<td>18</td>
<td>0.70 [0.11, 1.29]</td>
</tr>
<tr>
<td>Du [10]</td>
<td>156</td>
<td>21</td>
<td>0.67 [0.40, 1.18]</td>
</tr>
<tr>
<td>He [11]</td>
<td>135</td>
<td>69</td>
<td>1.70 [1.42, 2.69]</td>
</tr>
<tr>
<td>Xu [12]</td>
<td>117</td>
<td>28</td>
<td>0.86 [0.47, 1.25]</td>
</tr>
<tr>
<td>Zheng [13]</td>
<td>63</td>
<td>36</td>
<td>0.31 [0.17, 0.41]</td>
</tr>
<tr>
<td>Liu [14]</td>
<td>30</td>
<td>40</td>
<td>0.90 [0.35, 1.27]</td>
</tr>
<tr>
<td>Dao [15]</td>
<td>479</td>
<td>20</td>
<td>0.64 [0.39, 0.89]</td>
</tr>
</tbody>
</table>

RE Model
STANDARD MEAN DIFFERENCES WITH 95% CONFIDENCE INTERVALS CD19+ CELLS AND CD16/56+ NK CELLS
### Total Lymphocytes

#### "Moderate" vs "Severe"

<table>
<thead>
<tr>
<th>Study</th>
<th>N_mod</th>
<th>N_sev</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng [3]</td>
<td>352</td>
<td>124</td>
<td>0.68 [0.47, 0.89]</td>
</tr>
<tr>
<td>Wang [4]</td>
<td>274</td>
<td>65</td>
<td>0.63 [0.56, 1.11]</td>
</tr>
<tr>
<td>Chen [5]</td>
<td>10</td>
<td>11</td>
<td>1.41 [0.45, 2.36]</td>
</tr>
<tr>
<td>Zhou [6]</td>
<td>12</td>
<td>5</td>
<td>1.10 [0.17, 2.43]</td>
</tr>
<tr>
<td>Qin [7]</td>
<td>196</td>
<td>286</td>
<td>0.41 [0.22, 0.61]</td>
</tr>
<tr>
<td>Wan [8]</td>
<td>102</td>
<td>21</td>
<td>0.52 [0.05, 0.99]</td>
</tr>
<tr>
<td>Du [10]</td>
<td>158</td>
<td>21</td>
<td>0.46 [0.00, 0.92]</td>
</tr>
<tr>
<td>He [11]</td>
<td>135</td>
<td>69</td>
<td>1.48 [1.15, 1.80]</td>
</tr>
<tr>
<td>Xu [12]</td>
<td>117</td>
<td>28</td>
<td>1.15 [0.72, 1.59]</td>
</tr>
<tr>
<td>Liu [14]</td>
<td>30</td>
<td>46</td>
<td>1.69 [1.34, 2.44]</td>
</tr>
</tbody>
</table>

**RE Model**

- Standardized Mean Difference: 0.96 [0.64, 1.28]
- p-value: 0.00
T CELL SUBSETS AND COVID-19 – PREDICTOR OF MILD VS. SEVERE DISEASE

Absolute CD3+ T- lymphocytes, CD3+CD4+ and CD3+CD8+ T Cells Measured Upon Admission in Patients with Severe (n=11) vs Moderate (n=10) COVID-19 Disease Patients – Tongji Hospital, Wuhan China. March 27, 2020

T CELL SUBSETS AND COVID-19 MORTALITY
A PROSPECTIVE STUDY – WUHAN PULMONARY HOSPITAL, WUHAN CHINA

Table 4. Multivariate Logistic Regression Analysis of Mortality Risk Factors for Patients with COVID-19 Pneumonia.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>3.765 (1.146–17.394)</td>
<td>0.023</td>
</tr>
<tr>
<td>Cardiovascular or cerebrovascular diseases</td>
<td>2.464 (0.755–8.044)</td>
<td>0.007</td>
</tr>
<tr>
<td>CD3^+CD8^+ T cells ≤ 75 cell/μL</td>
<td>3.982 (1.132–14.006)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac troponin I ≥ 0.05 ng/mL</td>
<td>4.077 (1.166–14.253)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval, OR = odd ratio.

Predictor of mortality in 179 Patients with COVID-19 Pneumonia March 2020

T CELL SUBSETS AND COVID-19
Predictor of viral clearance, response to therapy and recovery

Ling Y et al *Chinese Medical Journal* 2020
• Study of 66 patients recovered from COVID-19 (28F/38M; Median age: 44 years)
• CD4+ T lymphocyte counts may help predict the duration of viral RNA detection in patient’s stool (P=0.01)

Zheng M et al *Cellular & Molecular Immunology* 2020
• Study included 55 patients with mild disease and 13 cases with severe disease
• Absolute T cell counts recovered during the convalescence phase of COVID-19
• Efficacious therapy was accompanied by an increase in T cell & Cytotoxic T cell counts

• Study of 25 laboratory-confirmed COVID-19 patients
• Analyzed T, B, NK cell counts in patients who successfully cleared SARS-CoV2 and compared to those who failed, after standardized treatment of 8-14 days
• Patients who cleared the infection had restored the number of CD3+, CD4+, CD8+ T cells and B cells compared to patients who remained viral RNA positive (post treatment)
OVERVIEW OF IMMUNOPHENOTYPING STUDIES IN COVID-19 PATIENTS

• Studies have largely come out of China
• Developing consensus - a decreased absolute lymphocyte count is related to severity of disease, while neutrophil counts remain normal or elevated
• Absolute T cell counts, CD4 and CD8 seem to be preferentially affected (decreased) in severe vs. moderate disease
• Increases in absolute T cell subset counts during hospitalization may be predictive of response to treatment and viral clearance – more studies are required.
• China has adopted guidelines for the “Diagnosis and Treatment of 2019 Novel Coronavirus (2019-nCoV) infected pneumonia” that include serial monitoring of T cell subsets.
A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)

Ying-Hui Jin¹, Lin Cai², Zhen-Shun Cheng³, Hong Cheng⁴, Tong Deng¹,⁵, Yi-Pin Fan⁶,⁷, Cheng Fang¹, Di Huang¹, Lu-Qi Huang⁶, Qiao Huang¹, Yong Han³, Bo Hu⁵, Fen Hu⁸, Bing-Hui Li¹,⁵, Yi-Rong Li⁹, Ke Liang¹⁰, Li-Kai Lin², Li-Sha Luo¹, Jing Ma⁸, Lin-Lu Ma¹, Zhi-Yong Peng⁹, Yun-Bao Pan⁹, Zhen-Yu Pan¹¹, Xue-Qun Ren⁹, Hui-Min Sun¹², Ying Wang¹³, Yun-Yun Wang¹, Hong Weng¹, Chao-Jie Wei², Dong-Fang Wu⁴, Jian Xia¹⁴, Yong Xiong¹⁰, Hai-Bo Xu¹⁵, Xiao-Mei Yao¹⁶, Yu-Feng Yuan⁷, Tai-Sheng Ye¹⁷, Xiao-Chun Zhang¹⁵, Ying-Wen Zhang¹⁷, Yin-Gao Zhang⁹, Hua-Min Zhang⁶,⁷, Yan Zhao¹⁴, Ming-Juan Zhao¹, Hao Z¹,⁵, Xian-Tao Zeng¹,⁸, Yong-Yan Wang⁶,⁷, Xing-Huan Wang¹², for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM)

5.5 Techniques for laboratory tests

5.5.1 Hematology examination

“In the early stage of the disease, the total number of leukocytes decreased or keeps normal, with decreased lymphocyte count or increased or normal monocytes”.

“High attention should be paid on the situation where the absolute value of lymphocyte is less than $0.8 \times 10^9$/L, or the numbers of CD4 and CD8 T cells are significantly decreased, which generally recommend rechecking the blood routine changes after 3 days.”

Published online: 06 February, 2020

Observational studies have consistently shown that immune status correlates with COVID-19 disease severity - Specifically T cell counts - both CD4 and CD8 T cells

- Severity of COVID-19 disease correlates with low blood albumin, hypertension, thrombocytopenia, increased blood IL-6 and procalcitonin
- Lymphopenia correlates with mortality, ARDS, and ICU care
- This meta analysis showed that the level of decrease in CD4 and CD8 T-cells predicts moderate vs. severe disease
- T cell counts also predict outcomes: ICU admission, treatment efficacy, viral clearance and recovery.
- CD4 and CD8 T cell subset counts are an independent predictor of COVID-19 outcome
- A limitation of this analysis is that all studies were performed in China and COVID-19 is now a global pandemic
What prospective studies are needed to further understand whether immune status measurements of COVID19+ patients can improve patient stratification and management?
- If patient is COVID+ → predict risk of progression to severe disease and/or admission to the ICU?
- If patient has severe disease and is in the ICU → predict risk for deterioration/mortality?
- If patient is undergoing treatment → predict improving immune status, viral clearance, and convalescence?

Pathogenesis of COVID-19 is still under investigation and the precise mechanism(s) leading to reduced peripheral blood lymphocyte subsets remains to be fully elucidated

Beyond the major lymphocyte subsets, how are other immune subsets involved? E.g. Naïve vs. Memory T and B cells, regulatory T cells, T cell activation markers, markers of Senescence and Exhaustion?

Can immune cell subsets and cytokine measurements be used together to improve prognostication?
AND THIS JUST IN JULY 15TH FROM U. PENNSYLVANIA
THANK YOU FOR YOUR ATTENTION