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Utility of Coronavirus Disease 2019 Immune Profiling for the Clinician at the Bedside*

KEY WORDS: coronavirus disease 2019; flow cytometry; immune endotypes; sepsis; severe acute respiratory syndrome coronavirus 2

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a global pandemic and the third leading cause of death in 2020 (1). However, the spectrum of disease has a wide range of clinical phenotypes with nearly 80% of cases being asymptomatic or mild (2). Recognizing host-pathogen immune interactions is key to understanding the clinical manifestations of the disease and identification of host immunophenotypes theoretically allows for personalization of care and prognostication. Yet, although the clinical course of the disease has been well described (2, 3), the immune response to the virus is less clearly delineated. Additionally, although several studies have demonstrated an association between clinical severity and immune markers such as leukocyte and lymphocyte counts, human leukocyte antigen–DR isotype (HLA-DR) expression on $CD14^+$ monocytes (mHLA-DR) expression, and cytokine profiles (4–11), their correlation with mortality is poorly described. Furthermore, although the immune response to a potent viral antigen likely differs from typical bacterial sepsis, these differences have not yet been clearly established.

In this issue of *Critical Care Medicine,* de Roquetaillade et al (12) explored the relationship between the immune profile of COVID-19 patients and clinical outcomes. Through a large patient cohort, they build upon prior studies on the host immune response to COVID-19 and advance our understanding

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of the pathophysiology of the disease by exploring immune responses over time, correlating these responses to mortality, and comparing profiles to a cohort of patients with bacterial sepsis.

de Roquetaillade et al (12) retrospectively evaluated the immune profiles of 247 consecutive patients with proven SARS-CoV2 infection at a single tertiary-care center in France between March and April 2020. This cohort is significantly larger than many of the studies published thus far (4–11). Patients were included if they had at least one immunophenotyping preformed during their hospital stay and were defined as "nonsevere" if they were admitted to the emergency department or ward and "severe" if they were admitted to the ICU. In total, 94 patients were classified as "severe," whereas 153 were classified as "nonsevere." Severe patients were further stratified as survivors or nonsurvivors and compared with a historical cohort of 108 patients with bacterial sepsis. The immune cells evaluated in the study by de Roquetaillade et al (12) were neutrophils, basophils, eosinophils, monocytes and mHLA-DR expression, CD4+ T cells, CD8+ T cells, B cells, and Natural Killer (NK) cells.

When compared with patients with nonsevere COVID-19, at baseline, severe COVID-19 patients had higher neutrophil and basophil counts, lower mHLA-DR expression, and lymphopenia accounted for by lower total CD3+, CD4+, CD8+ T cells, and NK cells ($p < 0.01$ for all measures). The findings of increased neutrophils, lymphopenia, and decreased T-cell and NK-cell counts are consistent with prior studies; however, there is significant heterogeneity in the literature, and reports of increased basophils and mHLA-DR are seemingly less common (4–11).

Immune profiles of severe COVID-19 survivors and nonsurvivors were then evaluated. The two cohorts had similar baseline immune alterations with elevated neutrophils, depressed total CD3+, CD4+, and CD8+ T-cell counts. However, after day 4 of hospitalization, immune profiles of survivors trended toward normalization, whereas alterations in the nonsurvivors persisted or worsened. This finding of immune correction among survivors was not present among the historical bacterial sepsis controls.

Finally, the authors compared the immune profiles of severe COVID-19 patients with historical controls with bacterial sepsis. They found that COVID-19 patients had higher baseline basophil, T-cell, and B-cell counts ($p < 0.01$ for all measures). When the authors further investigated the temporal evolution of the response in the two groups, patients with severe COVID-19 had lower neutrophils on days 8–12, higher mHLA-DR on days 2–4, higher basophil counts throughout the hospitalization, and higher B cell and eosinophil counts after the second week of ICU admission ($p < 0.01$ for all measures).

Although COVID-19 immunophenotyping has been widely explored, the longitudinal analysis of severe COVID-19 immune profiles for up to 3 weeks and the correlation of such features with mortality are unique features of the study by de Roquetaillade et al (12) when compared with available literature (5, 10). Additionally, the evaluation of eosinophils and basophils and the temporal evolution of these populations add to the growing body of literature exploring the role of these innate immune cells in the host response to COVID-19 (13, 14).

However, some limitations of the study by de Roquetaillade et al (12) must be noted. First, the study is a single-center retrospective observational study and has inherent selection bias limiting its generalizability. The heterogeneity of immunophenotyping panels and the variability of equipment and technical expertise across centers render multicenter trials of immune profiling often difficult to perform, and these biases might explain why discrepancies in immune profiles across studies are common.

Second, the study by de Roquetaillade et al (12) is prone to selection bias given the use of historical bacterial sepsis controls. This group was used as a comparator to the severe COVID-19 cohort, and the authors acknowledge that matching was imperfect. The cohort was chosen due to the similarity of mortality outcomes, but important clinical details are lacking. Septic patients appear to have higher illness severity indicated by Simplified Acute Physiology Score II ($p < 0.01$) and Sequential Organ Failure Assessment scores ($p < 0.01$), yet were nearly three times less likely to require mechanical ventilation (25% vs 75%; $p < 0.01$), possibly indicating fewer patients with primary respiratory illnesses. Further, treatment regimens of these patients were not reported, possibly confounding the results. Most notably, corticosteroids were administered to 47% of the severe COVID-19 patients (44), and their use was not reported for the septic patient cohort. In the management of COVID-19 patients, the use of antivirals and corticosteroids was

at the discretion of the treating physician and independent of the study, but little is known about the clinical management of the historical septic patients.

Third, the study by de Roquetaillade et al (12) characterizes COVID-19 patients as "nonsevere" and "severe" based on their admission location. This classification of disease severity places a high emphasis on triage decisions during a time when ICUs were overburdened. Objective variables of illness severity such as SAPS II, SOFA score, or the requirement for intubation or vasopressors may be more appropriate to compare the nonsevere and severe cohorts. Sparse data on the nonsevere COVID-19 patients are provided making the intercohort comparisons prone to confounding. Notably, severe COVID-19 patients were older ($p < 0.01$) and more likely to be male ($p < 0.01$), which are both known risk factors for poor outcome and thus likely confounding variables. Providing baseline characteristics for this cohort and performing analysis of adjusted outcomes may have strengthened the results.

In conclusion, the study by de Roquetaillade et al (12) provides novel immune profiling data using a large cohort of patients followed longitudinally. Although some of the conclusions of the study by de Roquetaillade et al (12) require further investigation for generalizability, the study provides a blueprint for developing personalized care for COVID-19. The methods of the study are highly reproducible, and the laboratory variables used in the study are commonly available and could easily be used in clinical practice. Although the exact immune footprint of COVID-19 remains elusive, the study by de Roquetaillade et al (12) adds to the literature by correlating immune profiles over time with outcomes of mortality. Future prospective studies should focus on establishing ideal controls for comparison, with careful attention to matching baseline and clinical characteristics. Ultimately, although not yet practice changing, the study by de Roquetaillade et al (12) is a step forward in providing individualized care to COVID-19 patients based on immune profiling.

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