Inflammation and Mortality in COVID-19 Hospitalized Patients With and Without Type 2 Diabetes

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Abstract

Context: COVID-19 mortality is increased in patients with diabetes. A common hypothesis is that the relationship of inflammation with COVID-19 mortality differs by diabetes status.

Objective: The aim of this study was to determine the relationship of inflammation with mortality in COVID-19 hospitalized patients and to assess if the relationship differs by strata of type 2 diabetes status.

Methods: A case-control (died-survived) study of 538 COVID-19 hospitalized patients, stratified by diabetes status, was conducted at Columbia University Irving Medical Center. We quantified the levels of 8 cytokines and chemokines in serum, including interferon (IFN)-α2, IFN-γ, interleukin (IL)-1α, IL-1β, IL-6, IL-8/CXCL8, IFN-γ-induced protein 10 (IP10)/CXCL10 and tumor necrosis factor α (TNF-α) using immunoassays. Logistic regression models were used to model the relationships of log-transformed inflammatory markers (or their principal components) and mortality.

Results: In multiple logistic regression models, higher serum levels of IL6 (adjusted odds ratio [aOR]: 1.74, 95% CI [1.48, 2.06]), IL-8 (aOR: 1.75 [1.41, 2.19]) and IP10 (aOR: 1.36 [1.24, 1.51]), were significantly associated with mortality. This association was also seen in second principal component with loadings reflecting similarities among these 3 markers (aOR: 1.88 [1.54-2.31]). Significant positive association of these same inflammatory markers with mortality was also observed within each strata of diabetes.

Conclusion: We show that mortality in COVID-19 patients is associated with elevated serum levels of innate inflammatory cytokine IL6 and inflammatory chemokines IL-8 and IP10. This relationship is consistent across strata of diabetes, suggesting interventions targeting these innate immune pathways could potentially also benefit patients with diabetes.

Key Words: cytokine storm, chemokines, CXCL10, type 2 diabetes, innate immunity, SARS-CoV-2, death, IL-6 inhibitor

Abbreviations: BH, Benjamini-Hochberg; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CUIMC, Columbia University Irving Medical Center; CVD, cardiovascular disease; FDR, false discovery rate; HbA1c, glycated hemoglobin A1c; IFN, interferon; IP10, IFN-γ-inducible protein 10 (CXCL10); IL, interleukin; PC1/PC2, principal components 1 or 2; PCA, principal component analysis; PCR, polymerase chain reaction; TNFα, tumor necrosis factor-α.

Inflammation plays a major role in COVID-19 immunopathology and disease severity (1). SARS-CoV-2 utilizes angiotensin converting enzyme 2 (ACE2) as a receptor for entry into the host cells. ACE2 is expressed by many cell types throughout the body, including innate immune cells such as monocytes and macrophages (1). Recognition of the virus by pathogen recognition receptors results in production of cytokines and chemokines, such as interleukin (IL)-6, IL-1β and tumor necrosis factor α (TNF-α) and interferon gamma-induced protein 10 (IP10)/CXCL10, that are necessary to mount an effective innate immune response against SARS-CoV2 infection (2).

However, unresolved inflammation has been linked to COVID-19 disease severity and mortality. In fact, increased cytokines (eg, IL-6 and TNFα) and chemokines (eg, CXCL10 and CCL2) are a hallmark of the cytokine release syndrome observed in COVID-19 (3, 4) as well as severe acute respiratory syndrome (SARS) (5) and Middle East respiratory syndrome (MERS) (5, 6). In line with this, various studies have shown that circulating levels of inflammatory cytokines IL-6 and TNFα are higher among COVID-19 patients with more severe disease or mortality compared with those with less severe disease (3, 4, 7).

Based on these findings, various immunomodulatory agents, such as dexamethasone (8) and cytokine inhibitors (9, 10), have been tested and shown to be among the more effective therapeutic agents against adverse COVID-19 outcomes. For example, the efficacy of IL-6 blockade in improving COVID-19 outcomes, including mortality, was recently shown in the REMAP-CAP (9) and RECOVERY (10) randomized trials. However, other randomized trials have shown apparent contradictory results with no effect of IL-6 blockade on COVID-19 adverse outcomes (11-14).

The reasons for the discrepancy in effect of IL-6 as well as other immunomodulatory agents between studies are not
clear (12) but of obvious clinical significance for the treatment of COVID-19 patients. One hypothesis is that differences in study population characteristics could explain the discrepancy (12). Related to this is whether the link between inflammatory profile and mortality is the same across strata of comorbidities (eg, type 2 diabetes status). For example, people with type 2 diabetes have dysregulated immunity even in the absence of infections, with higher levels of inflammation compared to individuals without type 2 diabetes (15); but data are lacking on whether the relationship of inflammation with mortality is similar between those with and without type 2 diabetes. If there is a difference in the relationship, the efficacy of immunomodulatory agents in COVID-19 might differ by diabetes status and would have implications for treatment strategies in this population with diabetes. Differences in the relationship of inflammation with mortality might also exist based on strata of other risk factors (eg, disease severity, age, sex) and comorbidities (hypertension and obesity), as was observed for the effect of dexamethasone by disease severity (8).

To address these research gaps, we conducted a case-control (died-survived) study of hospitalized COVID-19 patients, stratified by type 2 diabetes status. Our primary goal was to determine the association between inflammation and mortality. The secondary goal was to assess whether the association between inflammation and mortality was consistent across strata of diabetes. Potential confounding by other risk factors was addressed by eligibility criteria (exclusion of other comorbidities), matching (disease severity and age), and covariate adjustment. Exploratory goals of this study were to determine whether the relationship of inflammation with mortality was consistent across strata of other comorbidities (ie, disease severity, age, sex, body mass index, ethnicity, and hypertension).

Methods

Study Cohort

To address our primary objective of assessing the relationship of inflammation with mortality, we conducted a case-control (died-survived) study of 538 COVID-19 patients hospitalized at Columbia University Irving Medical Center (CUIMC) between March and September 2020. Both cases and controls were selected from those with SARS-CoV2 infection confirmed by detection of SARS-CoV2 transcripts using reverse transcription polymerase chain reaction (PCR).

Inclusion criteria for this study were reverse transcription PCR-confirmed SARS-CoV2 infection, hospitalization at CUIMC for at least one day, available outcome and covariate data as well as serum samples from the CUIMC COVID-19 biobank. Exclusion criteria were those with a past medical history of type 1 diabetes, cardiovascular disease (CVD), asthma, and chronic obstructive pulmonary disease (COPD). A combination of international classification of diseases (ICD) codes was used to exclude patients meeting the exclusion criteria. The rationale for excluding these individuals was to address potential confounding by these comorbidities in answering our primary and secondary (by type 2 diabetes status) objectives.

All cases that met the eligibility criteria were selected and a random sample of matched survived controls were selected. Controls were matched to cases on age and disease severity at sampling (using the ratio of arterial oxygen partial pressure [PaO₂] to fractional inspired oxygen [FiO₂]) (16-18). Matching on age was based on decade of life. Matching on disease severity was based on the following PaO₂:FiO₂ ratio categories: <150, 150 to 300, 300 to 400, and > 400. We identified 205 cases and 333 controls, where cases were those who died and controls were those who survived.

To address our secondary objective to determine whether the relationship between inflammation and mortality was different by type 2 diabetes status, this case-control study was stratified by type 2 diabetes status (ascertained by ICD codes), with 238 patients with diabetes (58 died and 180 survived) and 300 patients without diabetes (147 died and 153 survived). Data on other relevant variables, including age, sex, ethnicity, disease severity, body mass index (BMI), known type 2 diabetes, laboratory data for random glucose and glycated hemoglobin (HbA1c), diabetes medications, and known status for hypertension, cancer, chronic kidney disease, chronic liver disease, and HIV were obtained from patient medical records.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) at Columbia University. All guidelines for human experimentation from the U.S. Department of Health and Human Services were followed.

Laboratory Procedures

Serum samples were collected from patients using standardized procedures as part of the CUIMC COVID-19 biobank and stored in −80°C until further use. For this study, we selected the earliest available serum sample from each patient. We measured levels of interferon (IFN)-α2, IFN-γ, IL-1α, IL-1β, IL-6, IL-8, IP10 and TNF-α in duplicate samples using multiplex
Table 1. Characteristics by case (died) and control (survived) status

| Characteristic                  | All        | Cases (died) | Controls (survived) |
|--------------------------------|------------|--------------|---------------------|
| **Age, years**                 | 69.8 (13.9) | 72.8 (12.8)  | 68.0 (14.2)         |
| **Disease severity, PaO₂/FiO₂**| 260.1 (165.1) | 214.9 (140.2) | 287.9 (173.1)       |
| **Body mass index, kg/m²**     | 29.3 (12.5)  | 29.1 (13.3)  | 29.4 (12.0)         |
| **Gender**                     | Male       | 330 (61)     | 132 (64)            | 198 (59)          |
|                                | Female     | 208 (39)     | 73 (26)             | 135 (41)          |
| **Ethnicity**                  | Hispanic   | 291 (54)     | 121 (59)            | 170 (51)          |
|                                | Non-Hispanic | 125 (23)    | 38 (19)             | 87 (26)           |
|                                | Other      | 122 (23)     | 46 (22)             | 76 (23)           |
| **Hypertension**              | No         | 346 (64)     | 153 (75)            | 193 (58)          |
|                                | Yes        | 192 (36)     | 52 (25)             | 140 (42)          |
| **Sample collection date**     | March 2020 | 69 (13)      | 39 (19)             | 30 (9)            |
|                                | April 2020  | 393 (73)     | 149 (73)            | 244 (73)          |
|                                | After April 2020 | 76 (14) | 17 (8) | 59 (18) |

Data are presented as no. (%) of subjects or mean (SD). Cases were defined as hospitalized COVID-19 patients who died, and controls were hospitalized COVID-19 patients who were alive.
(1.48, 2.06), 1.75 (1.41, 2.19), and 1.36 (1.24, 1.51), respectively. Table 2 also provides ORs and $P$ values for associations between mortality and each log-transformed inflammatory marker from logistic regressions adjusting for age, disease severity, gender, ethnicity, BMI, hypertension status, and type 2 diabetes status. It shows that log-IL6, log-IL8, and log-IP10
are still significantly associated with mortality after FDR correction (BH-adjusted \( P < 0.01 \)), with odds ratio 1.53 (1.29-1.85), 1.82 (1.43-2.36), and 1.28 (1.14-1.44), respectively. The results were similar in models further adjusting for date of sample collection (data not shown).

### Association Between Mortality and Inflammation: Impact of Type 2 Diabetes Status
We next address our secondary objective on whether the association between mortality and inflammation was different by type 2 diabetes status. In multiple logistic regression models of the combined population with and without type 2 diabetes, there were no significant interactions between diabetes status and any inflammatory markers after adjusting for age, disease severity, gender, ethnicity, BMI, and hypertension status (data not shown). We further conducted stratified analyses by diabetes status. Supplementary Table 2 (19) displays means (SDs) of the 3 identified markers stratified by diabetes and mortality status. Logistic regression analysis results stratified by type 2 diabetes status is summarized in Table 3. Among patients without diabetes, there are significant associations between mortality and log-IL6, log-IL8, and log-IP10 (BH-adjusted \( P < 0.01 \)), which are consistent with the results on the entire cohort. Among patients with type 2 diabetes, no significant associations are observed after FDR correction, likely due to the smaller sample size.

However, we noticed that although these 3 inflammatory mediators are not statistically significant among patients with type 2 diabetes, the effect estimates were similar and in the same direction as in the entire cohort. Therefore, we conducted PCA analysis within patients with type 2 diabetes, within patients without type 2 diabetes, and within the entire cohort, respectively. Loadings of the first 2 principal components (PCs) are summarized in Supplementary Table 3 (19), where the first 2 PCs explain 57.2%, 58.2%, and 56.3% of variance, respectively. We observed that the first PC (PC1) had loadings all positive, with high loadings (>0.3) of IFN\( \gamma \), IL1\( \alpha \), IL1\( \beta \), and TNF\( \alpha \). PC2 had loadings of different directions for different inflammatory mediators, with positive and high loadings of only IL6, IL8, and IP10. Table 4 shows the association results between mortality and the first PC, and the second PC separately. The first PC is not associated with mortality in any of the 3 cohorts as expected, as PC1 simply averaged the 8 markers with the same-direction-loading. The second PC, which can be considered as an aggregated effect of the 3 markers, log-IL6, log-IL8, and log-IP10, were associated with mortality after adjusting for covariates in both patients with and without diabetes, as well as the combined cohort, with odds ratio 1.79 (1.26-2.62), 1.93 (1.51-2.52), and 1.88 (1.54-2.31), respectively. The first 2 PCs were also plotted in the 3 cohorts, respectively (Supplementary Figure 2 (19)). We note that PC2 can separate cases and controls more when compared with PC1 in all 3 cohorts.

Results for PC2 were also similar in the combined cohort (OR: 1.91 [1.56-2.36]), in patients with diabetes (OR: 1.83 [1.27-2.71]), and in patients without diabetes (OR: 1.95 [1.56-2.36]); when further adjusting for other comorbidities, including cancer, chronic kidney disease, chronic liver disease, and HIV. Among patients with diabetes, 93% and 55% had random glucose and HbA1c data available; results for PC2 were similar in

### Table 3. Associations between inflammation and mortality stratified by DM status

| DM | Univariable model (N = 238) | Multivariable model (N = 233) * | Adjusted odds ratio (95% CI) | Raw P value | FDR P value |
|---|---|---|---|---|---|
| Log(IFN\( \gamma \)) | 0.94 (0.80, 1.10) | 0.47 | 0.55 | 0.94 (0.77, 1.14) | 0.54 | 0.62 |
| Log(IL1\( \alpha \)) | 0.94 (0.77, 1.13) | 0.50 | 0.55 | 0.86 (0.68, 1.07) | 0.18 | 0.29 |
| Log(IL1\( \beta \)) | 0.91 (0.77, 1.08) | 0.29 | 0.46 | 0.80 (0.64, 0.98) | 0.03 | 0.14 |
| Log(IL6) | 1.70 (1.32, 2.25) | <0.01 | <0.01 | 1.32 (0.98, 1.80) | 0.07 | 0.19 |
| Log(IL8) | 1.52 (1.05, 2.23) | 0.03 | 0.08 | 1.61 (1.05, 2.54) | 0.03 | 0.14 |
| Log(IP10) | 1.43 (1.22, 1.71) | <0.01 | <0.01 | 1.17 (0.96, 1.44) | 0.13 | 0.25 |
| Log(TNF\( \alpha \)) | 1.08 (0.84, 1.38) | 0.55 | 0.55 | 1.04 (0.76, 1.42) | 0.82 | 0.82 |

| NDM | Univariable model (N = 300) | Multivariable model (N = 268) * | Adjusted Odds ratio (95% CI) | Raw P value | FDR P value |
|---|---|---|---|---|---|
| Log(IFN\( \gamma \)) | 0.98 (0.86, 1.12) | 0.78 | 0.91 | 1.00 (0.87, 1.16) | 0.97 | 0.97 |
| Log(IL1\( \alpha \)) | 0.98 (0.84, 1.14) | 0.80 | 0.91 | 0.99 (0.84, 1.17) | 0.90 | 0.97 |
| Log(IL1\( \beta \)) | 0.99 (0.87, 1.13) | 0.93 | 0.93 | 1.01 (0.87, 1.17) | 0.92 | 0.97 |
| Log(IL6) | 1.64 (1.33, 2.06) | <0.01 | <0.01 | 1.65 (1.31, 2.147) | <0.01 | <0.01 |
| Log(IL8) | 1.77 (1.34, 2.39) | <0.01 | <0.01 | 1.98 (1.46, 2.79) | <0.01 | <0.01 |
| Log(IP10) | 1.28 (1.13, 1.45) | <0.01 | <0.01 | 1.34 (1.17, 1.56) | <0.01 | <0.01 |
| Log(TNF\( \alpha \)) | 1.11 (0.92, 1.35) | 0.26 | 0.49 | 1.09 (0.89, 1.35) | 0.41 | 0.65 |

Abbreviations: DM, diabetes mellitus; FDR, false discovery rate; NDM, no diabetes mellitus.
*Multivariable models adjusted for age, disease severity, gender, ethnicity, body mass index, and hypertension. Some patients were dropped out due to missing data in BMI.
+Formal tests confirm no interaction by DM status (data not shown).
In this study, we assessed the relationship of inflammation with mortality in COVID-19 hospitalized patients, and we observed that serum level of 3 innate cytokine and chemokines, IL6, IL8, and IP10, were associated with mortality. Importantly, our results suggest that there is no interaction by type 2 diabetes status; this positive and significant association between inflammation and mortality was consistent across strata of diabetes as well as other risk factors, including disease severity, age, and BMI. These results suggested that dysregulated innate immune response may play an important role in COVID-19 mortality, regardless of diabetes and other risk factor strata. Thus, immunomodulatory therapeutics such as IL-6 inhibitors have the potential to reduce mortality in populations with and without comorbidities. If future interventional studies should confirm this, it would have direct implications for treatment management of COVID-19 patients.

Among the 8 markers assessed in this study, only 3 markers, IL6, IL8, and IP10, were associated with mortality. We selected the 8 markers (TNFα, IL1β, IFNα2, and IFNγ in addition to the other markers) based on prior studies of COVID-19 patients that had shown an association of these markers with severe disease or mortality (3, 4, 7, 20-22). A likely reason for the differences in findings between our study and other studies is our unique study population. In addition to the other markers, we also included disease severity, age, BMI, hypertension, and diabetes (only in entire cohort). Some patients were dropped out due to missing data in BMI.

| Entire cohort | Univariable model (N = 538) | Multivariable model (N = 501) * |
|--------------|-----------------------------|---------------------------------|
|              | Odds ratio (95% CI) | P value | Adjusted odds ratio (95% CI) | P value |
| PC1          | 1.13 (1.02, 1.25) | 0.02     | 1.09 (0.97, 1.23) | 0.14 |
| PC2          | 2.01 (1.69, 2.41) | <0.01    | 1.88 (1.54, 2.31) | <0.01 |
| DM           | Univariable model (N = 238) | Multivariable model (N = 233) * |
|              | Odds ratio (95% CI) | P value | Adjusted odds ratio (95% CI) | P value |
| PC1          | 1.09 (0.93, 1.29) | 0.29     | 0.98 (0.79, 1.21) | 0.84 |
| PC2          | 2.13 (1.59, 2.94) | <0.01    | 1.79 (1.26, 2.62) | <0.01 |
| NDM          | Univariable model (N = 300) | Multivariable model (N = 268) * |
|              | Odds ratio (95% CI) | P value | Adjusted odds ratio (95% CI) | P value |
| PC1          | 1.12 (0.98, 1.28) | 0.10     | 1.15 (0.99, 1.34) | 0.07 |
| PC2          | 1.81 (1.46, 2.28) | <0.01    | 1.93 (1.51, 2.52) | <0.01 |

*Multivariable models adjusted for age, disease severity, gender, ethnicity, body mass index (BMI), hypertension, and diabetes (only in entire cohort). Some patients were dropped out due to missing data in BMI.

models further adjusting for hemoglobin A1c (OR: 1.82 [1.35-2.51]) or random glucose (OR: 1.96 [1.25-2.94]). Adjusting for metformin use in diabetics also did not change the PC2 results (OR: 1.77 [1.24-2.60]). Overall, these results further suggest that IL6, IL8, and IP10 are associated with mortality; and these results are consistent across strata of diabetes.

**Association Between Mortality and Inflammation: Impact of Other Risk Factors**

As the immune profile is known to differ by factors such as disease severity, age, BMI, or sex, we next conducted several exploratory analyses examining whether the observed relationship of mortality and inflammation were consistent across strata of other COVID-19 mortality risk factors. For example, is the relationship of inflammation with mortality consistent among those with more severe as compared to less severe disease? To explore these questions, we conducted stratified analysis of the PCs with mortality, adjusting for the other covariates including diabetes, across strata of disease severity (PaO2:FIO2 ratio categories: < 300 and ≥ 300). We observed that PC2, with high loadings of IL6, IL8, and IP10, was significantly (P < 0.05) associated with mortality in each of 4 strata of disease severity. We conducted similar analysis (ie, separate analysis for each risk factor) across the strata of age (< 70 and ≥ 70), BMI (obese and not obese), sex, ethnicity, and hypertension status (Supplementary Table 4 (19)). We selected the 8 markers with severe disease or mortality (3, 4, 7, 20-22) to include disease severity, age, and BMI. These results suggested that dysregulated innate immune response may play an important role in COVID-19 mortality, regardless of diabetes and other risk factor strata. Thus, immunomodulatory therapeutics such as IL-6 inhibitors have the potential to reduce mortality in populations with and without comorbidities. If future interventional studies should confirm this, it would have direct implications for treatment management of COVID-19 patients.

**Discussion**

In this study, we assessed the relationship of inflammation with mortality in COVID-19 hospitalized patients, and our results further confirm the role of these mediators such as disease severity, older age, and obesity, which themselves can impact inflammation and mortality. Additional exploratory analyses examining whether the observed association of these markers with mortality might be different in populations without COPD, CVD, asthma, and type 1 diabetes, but who do not have these comorbidities. Further, we also matched and accounted for important covariates, including disease severity, age, and BMI. These results suggested that dysregulated innate immune response may play an important role in COVID-19 mortality, regardless of diabetes and other risk factor strata. Thus, immunomodulatory therapeutics such as IL-6 inhibitors have the potential to reduce mortality in populations with and without comorbidities. If future interventional studies should confirm this, it would have direct implications for treatment management of COVID-19 patients.
and other important risk factors. The IL-6 blockade interventional studies suggest that IL-6 plays a causal role in mortality at least in certain settings (9, 12). In addition, we noted that IL-8 and IP10 were also associated with mortality. IL-8 is a pro-inflammatory chemokine produced by macrophages and other cells, and it is involved in recruiting and activating neutrophils (23). IL-8 could directly contribute to the increased levels of neutrophils observed in COVID-19, with higher levels resulting in increased mortality (20). IP10 is an IFN-γ inducible protein produced by various immune cells, including macrophages, T cells, and dendritic cells, and it has pro-inflammatory and anti-angiogenic functions (24). Related to COVID-19, studies suggest that early on IP10 has an important role in viral clearance while unresolvable high levels could contribute to immunopathology, including acute lung injury (25). Given the high loadings of IL6, IL8, and IP10 in PCA analysis, these markers might potentially share a common mechanism or pathway that is contributing to mortality and will need to be studied further.

While studies have assessed the relationship of inflammation with mortality, studies are lacking on whether this relationship is different across strata of type 2 diabetes. Our results on type 2 diabetes suggest that there is no interaction by diabetes status in the relationship between inflammation and mortality. Both formal interaction tests and results from the stratified analysis confirmed this. Potential differences in the relationship of inflammation with mortality by type 2 diabetes status could have meant that different anti-inflammatory agents or different doses might need to be utilized for those with diabetes relative to those without diabetes. However, our results do not support the hypothesized role of diabetes status in impacting the relationship of inflammation with mortality, and these findings provide a biological mechanism to explain the increased mortality associated with type 2 diabetes (15). Of note, the results from individual analysis of each marker in stratified analysis among those with type 2 diabetes were not significant but this was likely due to multiple comparison adjustments in a smaller sample size; our PCA analysis supports this, where PC2, with high loadings of IL6, IL8, and IP10, was associated with mortality within both strata of diabetes. These results were also confirmed in models that adjusted for glucose levels. We should note that our stratified analysis was designed for and our findings are applicable to the overall populations; we did not have the appropriate power to further assess whether among those with type 2 diabetes, there were difference by additional strata of diabetes-specific risk factors such as glucose control, duration of diabetes, or diabetes medications (15).

In addition to diabetes, we also explored whether the relationship of inflammation with mortality differed by other risk factors. For example, inflammation is known to be different by disease severity, obesity, age, sex, and other comorbidities (eg, hypertension) (20, 26, 27); thus, inflammation could potentially have a different relationship with mortality within strata of these risk factors. However, our exploratory results showed a consistent and positive association of these same markers (ie, PC2) with mortality within each of the strata of these risk factors. As with diabetes, we did not have the power to further look at additional strata (eg, hypertensive medications) of risk factors. Regardless, these findings suggest a strong relationship of inflammation with mortality that is consistent across strata. While our results suggest that these pathways are theoretically relevant targets (ie, there is an association) to reduce mortality, regardless of additional risk factors, this will have to be confirmed by well-designed interventional studies (eg, using IL-6 inhibitors) conducted across different strata of risk factors. Regarding discrepancy between studies of IL-6 inhibitors (11-14), it is possible that other factors (eg, specific product, dose or duration, or timing of the intervention rather than these study population characteristics) could explain the results; alternatively, despite the association across strata, it is possible that the intervention is less effective in certain strata (eg, very advanced disease).

Limitations of this study were smaller sample sizes within strata of risk factors (eg, glucose control and diabetes), lack of generalizability to populations with CVD, asthma, type 1 diabetes, and COPD, a focus on limited number of immune markers that were only pro-inflammatory, and conduct of the study in a pandemic setting with challenges in data collection (eg, missing data for HbA1c or quality of medication data). It is also not clear whether our data from earlier in the pandemic would be as generalizable to more recent times, given advances in treatment. Our study also has multiple strengths. One is related to the eligibility criteria and study design that addresses potential confounding by comorbidities, disease severity, and other risk factors. Our sample size was adequate for both the primary and secondary questions. We assessed multiple markers of inflammation that are relevant in the context of COVID-19 and linked them to well-characterized clinical and mortality data.

In conclusion, our study showed that 3 immune markers of inflammation with mortality, with consistent and positive associations through strata of type 2 diabetes and other risk factors. Our results support existing efforts to target these pathways and provide supportive data to suggest that the interventions may be effective across strata of diabetes and other risk factors; future interventional studies will be needed to confirm this.

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Author Contributions
J.G. conducted the data analysis and wrote the primary version of the manuscript. W.H.L., J.E.Z., and A.C.U. contributed to study design, data collection, data interpretation, and manuscript review. A.B. contributed to data management and collection. R.N. contributed to study design, laboratory analysis, and data interpretation. S.N. contributed to study design, data analysis and interpretation, and manuscript writing and review. R.S. led the conceptual design, and contributed to data collection, analysis, and manuscript writing and review. All authors have approved the final manuscript and agreed to publication. R.S. is the guarantor of this work, and as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures
No competing interests declared.

Data Availability
Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the data determinations for patients with the severe COVID-19.

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