Impact of monocyte-related modulators and kidney function on mortality in hospitalized patients with COVID-19

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Abstract
Patients with chronic kidney disease (CKD) are at high risk of severe complications from COVID-19 and functional monocyte disturbances have been implicated to play a role. Our objective was to analyse the association between kidney function and monocyte modulatory factors, with risk of mortality in patients with COVID-19. Hospitalized patients with COVID-19 (n = 110) were included and in-hospital mortality was analysed with unadjusted and adjusted multiple logistic regression analysis. Plasma levels of monocyte chemoattractant factors (MIP-1α, MCP-1, IL-6) and a monocyte immune modulator (sCD14) were analysed and correlated to kidney function and risk of mortality. Monocyte modulatory factors were also determined in CKD patients without infection (disease controls) and in healthy subjects. Patients who died in hospital were more often in CKD stages 3-5, with lower estimated glomerular filtration rate (eGFR) and had significantly higher MIP-1α and IL-6 levels than survivors. In multiple regression analyses adjusted for age, sex and eGFR, both high MCP-1 and high MIP-1α were significantly associated with risk of in-hospital mortality. Apart from impaired kidney function, also the concentrations of MCP-1 and MIP-1α add important prognostic information in hospitalized patients with COVID-19. These data provide an increased understanding of the impact of monocyte modulators in patients with COVID-19 and normal or impaired kidney function, and warrant consideration in the pursuit of new effective therapies.

1 | INTRODUCTION

The clinical symptoms associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are variable, ranging from asymptomatic infection to severe pneumonia with respiratory failure.1 COVID-19-related hospitalization and mortality have been associated with age, male gender, obesity, diabetes mellitus, severe asthma, liver disease, stroke, neurological disorders, dementia, autoimmune diseases and malignancies.2,3

An analysis of clinical phenotypes linked with increased risk of COVID-19-associated hospital admission showed that patients with chronic kidney disease (CKD) are at high risk of complications due to COVID-19.4

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Other studies have revealed that patients with CKD are at higher risk of mortality than those with many other risk factors.\(^5\)\(^-\)\(^9\) Furthermore, the association between CKD and in-hospital mortality persists in analyses adjusted for covariates known to associate with worse COVID-19 outcomes, suggesting that CKD confers a risk for patients with severe COVID-19, beyond that associated with comorbid conditions.\(^6\)

The mechanisms underlying the increased susceptibility to severe COVID-19 in CKD remains unclear. Severe infections are common in CKD and are the second most common cause of death.\(^10\) There is abundant evidence that disorders of both the innate and adaptive immune systems contribute to the increased rate and severity of infections.\(^11\) Likewise, the chronic systemic inflammation that characterizes CKD patients may also contribute to higher morbidity and mortality.\(^12\)

Monocytes play a fundamental role in both innate and adaptive immunity and have been implicated in complications and progression of CKD.\(^13\)\(^,\)\(^14\) Functional abnormalities in monocytes are also directly linked to a higher risk of infection.\(^15\)\(^-\)\(^17\) This is important since excessive monocyte and macrophage activation, together with the occurrence of a cytokine storm and pulmonary injury, are serious complications of COVID-19.\(^18\) Morphologic and functional differences in monocytes are more pronounced in COVID-19 patients requiring prolonged hospitalization, indicating that monocytes play a key role in COVID-19 pathogenesis.\(^19\) However, there is scanty information on monocyte modulators which may link monocyte dysfunction with mortality in COVID-19 patients with normal or impaired kidney function.

Since monocyte dysfunction plays a key role in both CKD and COVID-19 pathogenesis, we analysed monocyte-related modulators and the risk of mortality in relation to kidney function in patients with COVID-19. Herein we show, for the first time, that levels of modulators of monocyte recruitment add significant prognostic information, regardless of kidney function, in patients with COVID-19.

\section{Materials and Methods}

\subsection{Study population}

We included 110 patients with COVID-19 admitted to Danderyd University Hospital, Stockholm, Sweden, during the first pandemic wave in April to June 2020. We included all patients $>18$ years of age in whom we had information on kidney function at admission. Clinical features in a subgroup of these patients have been described elsewhere.\(^20\) We report both plasma creatinine and estimated glomerular filtration rate (eGFR) since COVID-19 patients may both comprise patients with pre-existing CKD and patients with acute kidney injury (AKI), as eGFR may be more accurate in CKD than in AKI. Data on albuminuria were not routinely collected. All patients were diagnosed with COVID-19 based on reverse transcriptase polymerase chain reaction viral RNA detection of nasopharyngeal or oropharyngeal swabs. In-hospital mortality was analysed. Routine laboratory blood analyses of patients with COVID-19 were performed at the Karolinska University Hospital Laboratory, Stockholm, Sweden. Of patients with COVID-19, 86 (78\%) had prophylactic anticoagulation with low-molecular weight heparin and 6 (5\%) patients received glucocorticoids because of chronic obstructive pulmonary disease, but none of the patients with COVID-19 had the high doses of steroids that now are recommended in severe disease. No antivirals or hydroxychloroquine were used in these patients. Thus, the concentrations of monocyte mediators in this cohort of patients with COVID-19 were not influenced by high doses of immune modulatory treatment, which is a strength when interpreting the results. At the time of blood sampling, 95 (86\%) patients were hospitalized at a general ward, 11 (10\%) patients at an intermediate care unit and 4 (4\%) patients at the intensive care unit.

We also included 33 sex- and eGFR-matched patients with mild-to-severe CKD without infection as disease controls. This group was not matched with age. We also included 35 healthy subjects, which were sex- and age matched with COVID-19 patients. The rationale for including a disease control group was to compare the concentration of inflammatory markers in COVID-19 patients with normal or impaired kidney function to those in patients with pre-existing CKD and corresponding eGFR, but without infection.

\subsection{Analysis of inflammatory molecules in plasma using multiplex immunoassay with Luminex}

Blood samples were drawn into EDTA tubes (Vacutainer; Becton Dickinson) from patients up to 7 days (median 2 days) after hospital admission. Plasma was prepared by centrifugation at 2000g for 20 min at room temperature and stored in $-80^\circ$C freezer for further analysis. We aimed to analyse the levels of monocyte chemotactic protein (MCP)-1/CCL2, macrophage inflammatory protein (MIP)-1$\alpha$/CCL3, interleukin (IL)-6 and soluble cluster of differentiation (CD)14. We applied the human magnetic Luminex assay, premixed 2-plex (Catalogue no. LXSADM-2, Lot no. L L134759; R&D Systems) to analyse sCD14 and premixed 21-plex (Catalogue no. LXSADM-21, Lot no. L134758; R&D systems) for MCP-1, MIP-1$\alpha$ and IL-6.
After removing tubes from the freezer and thawing, the plasma samples were centrifuged at 16,000 g for 4 min and then diluted 1:200 for analysis of sCD14 and 1:2 for analysis of cytokines. The assays were performed according to the manufacturer’s instructions and the plates were analysed by Bio-plex MAGPIX Multiplex reader (Bio-Rad). A pooled plasma was used as control for inter-plate comparisons.

2.3 Statistical analysis

The analyses were performed comparing three groups of individuals: (a) patients admitted with COVID-19, (b) patients with identified CKD without infection matched for eGFR (disease controls) and (c) healthy controls. All values are given as median and interquartile range (IQR). Median eGFR in patients with COVID-19 was 84 mL/min/1.73 m². Patients with COVID-19 were further divided into two groups based on median eGFR: eGFR ≤ 84 mL/min/1.73 m² and eGFR > 84 mL/min/1.73 m² and with respect to CKD stages. Since the values were not normally distributed in all groups, comparisons between groups were performed using the non-parametric Kruskal-Wallis test, and comparison between two groups with Mann-Whitney U test. Dunn’s post hoc test was applied for multiple comparisons following the Kruskal-Wallis test. Spearman’s rank correlation test was applied to determine the relationship between eGFR and laboratory data. Chi-square test and Fisher’s exact test were used in analyses of contingency tables. Risk of mortality was analysed by multiple logistic regression analyses using odds ratio (OR). Results from unadjusted regression analyses and analyses adjusted for age, sex and eGFR. A P < .05 was considered significant. Statistical analyses were done in GRAPHPAD PRISM 8.3 (GraphPad Software, Inc.), STATISTICA version 10 (StatSoft, Inc.) and IBM SPSS STATISTICS 25 (IBM Corp.).

3 RESULTS

3.1 Comparisons between patients with COVID-19, patients with CKD and healthy subjects

Demographic characteristics and laboratory findings of all participants are presented in Table 1. Patients with COVID-19 were significantly older than both control groups and had higher eGFR than disease controls, and lower eGFR than healthy subjects (Table 1). C-reactive protein (CRP) was higher in COVID-19 patients compared to both control groups. MIP-1α was lower in patients with COVID-19 compared to both control groups, IL-6 was higher and MCP-1 concentrations were similar. Soluble CD14 was higher in patients with COVID-19 compared to both groups of controls (Table 1). Differences in immune modulators were consistent when a sub-group of eGFR- and sex-matched COVID-19 patients was compared to CKD patients (Table 2). This indicates that the levels of monocyte-related modulators were largely dependent on the SARS-CoV-2 infection and not a consequence of kidney dysfunction.

3.2 In-hospital mortality in patients with COVID-19

Characteristics of patients who died in hospital are shown in Table 3. Deceased patients were older and mainly males, had lower eGFR, higher CRP, higher white blood cell (WBC) count, higher MIP-1α and higher IL-6 levels than COVID-19 patients who survived.

3.3 Unadjusted and adjusted risk of in-hospital mortality with COVID-19

Unadjusted multiple logistic regression analysis of in-hospital mortality and regression analyses adjusted for age, sex and eGFR are shown in Table 4. Age, eGFR, CRP, WBC count, MCP-1, MIP-1α and IL-6 levels were significantly associated with risk of in-hospital mortality in unadjusted analyses. Patients with high CRP, WBC count, MCP-1 and MIP-1α had significantly higher risk of in-hospital mortality in the model adjusted for both age, sex and eGFR. Due to the limited number of patients and events, the adjusted analyses need to be interpreted cautiously.

3.4 Unadjusted risk of in-hospital mortality with COVID-19 in patients with lower eGFR

In addition, we specifically analysed mortality risk in patients with eGFR ≤ 84 mL/min/1.73 m², i.e. below median eGFR, in patients with COVID-19. In unadjusted logistic regression analyses, the risk of in-hospital mortality was significantly associated with high age (P < .05, OR 1.079 [CI 1.008-1.155]), high WBC count (P < .05, OR 1.206 [1.034-1.408]) and a high level of MIP-1α (P < .05, OR 1.010 [1.000-1.019]).

There were not enough patients and events to perform adjusted regression analyses of risk of in-hospital mortality in this sub-group.
### TABLE 1 Comparisons between all 110 patients with COVID-19, patients with chronic kidney disease (CKD) without COVID-19 infection and healthy subjects

|                      | COVID-19 (N = 110) | CKD patients (N = 33) | Healthy subjects (N = 35) | P, K-W |
|----------------------|--------------------|-----------------------|---------------------------|--------|
|                      | Median             | IQR                   | Median                    | IQR    | Median | IQR |
| Age (y)              | 60                 | 50–69                 | 55                        | 45–58  | 50     | 39–57 |
| BMI (kg/m²)          | 28                 | 25–32                 | 25                        | 24–28  | 24     | 22–27 |
| Creatinine (μmol/L)  | 73                 | 58–89                 | 122                       | 107–160| 72     | 66–77 |
| eGFR (mL/min/1.73 m²) | 84                 | 67–90                 | 53                        | 40–65  | 102    | 96–108|
| Potassium (mmol/L)   | 3.9                | 3.6–4.2               | 4.3                       | 4.0–4.4| 4.0    | 3.9–4.2|
| CRP (mg/L)           | 99                 | 63–174                | 1.6                       | 0.9–4.3| 0.89   | 0.31–2.2|

Monocyte recruitment (chemoattractants)
- **MCP-1 (pg/mL)**: 350 vs. 362, **P < .001**
- **MIP-1α (pg/mL)**: 320 vs. 385, **P < .001**
- **IL-6 (pg/mL)**: 27.8 vs. 4.7, **P < .001**

Monocyte function (immune modulating mediator)
- **sCD14 (ng/mL)**: 2094 vs. 1098, **P < .001**

**Abbreviations:** CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein; sCD14, soluble cluster of differentiation 14.

*Kruskal-Wallis test.

Post hoc analyses:
- **P < .01** comparing COVID-19 and CKD patients; **P < .0001** comparing COVID-19 and healthy controls.
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- **P < .0001** comparing COVID-19 and CKD patients; **P < .001** comparing COVID-19 and healthy controls.

### TABLE 2 Comparison between a sub-group of eGFR-matched patients with COVID-19 and patients with chronic kidney disease (CKD) without COVID-19 infection

|                      | COVID-19 (N = 33) | CKD (N = 33) | P² |
|----------------------|--------------------|--------------|----|
|                      | Median             | IQR          | Median | IQR |               |
| Age (y)              | 68.0               | 55.5–80.5    | 55.0   | 44.5–58.0 | **<.001** |
| BMI (kg/m²)          | 27.5               | 25.7–30.0    | 25.0   | 23.5–28.0 | .05        |
| Creatinine (μmol/L)  | 1.10               | 0.92–1.55    | 1.38   | 1.21–1.81 | .01        |
| eGFR (mL/min/1.73 m²) | 55.0               | 39.5–68.0    | 53.0   | 40–65   | NS         |
| Potassium (mmol/L)   | 4.0                | 3.8–4.2      | 4.3    | 4.0–4.4 | <.05       |
| CRP (mg/L)           | 98.0               | 67.5–200.8   | 1.6    | 0.9–4.3 | <.001      |

Monocyte recruitment (chemoattractant)
- **MCP-1 (pg/mL)**: 405 vs. 362, **NS**
- **MIP-1α (pg/mL)**: 332 vs. 385, **<.05**
- **IL-6 (pg/mL)**: 36.7 vs. 4.7, **<.001**

Monocyte function (immune modulating mediator)
- **sCD14 (ng/mL)**: 2394 vs. 1098, **<.001**

**Abbreviations:** CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein; sCD14, soluble cluster of differentiation 14.

*Mann-Whitney U test.*
The novel and primary finding in this study is that apart from impaired kidney function, also immune modulating factors related to monocyte cell recruitment, MCP-1 and MIP-1α, are associated with increased risk of in-hospital mortality in patients with COVID-19, both in unadjusted and adjusted regression analyses. Furthermore, a high concentration of MIP-1α in the subgroup of COVID-19 patients with eGFR below the median was also significantly associated with in-hospital mortality. We acknowledge that the number of patients and events, and also that the small differences in actual values of MCP-1 and MIP-1α, limit the interpretation of these results.

Patients with COVID-19 who died in hospital had significantly lower eGFR, higher CRP, IL-6 and MIP-1α than patients who survived the disease. In multiple logistic regression analysis adjusted for age, sex and eGFR, the level of both MIP-1α and MCP-1 continued to have a significant impact on in-hospital mortality. This indicates that concentrations of MIP-1α and MCP-1 add significant and important prognostic information in patients with COVID-19, regardless of kidney function.

To facilitate the clinical interpretation of these data, we included two control groups: one sex- and eGFR-matched group of patients with an impairment in kidney function corresponding to patients with COVID-19, but without infection (CKD disease controls), and healthy subjects. The differences observed when we compared all patients with COVID-19 to controls, were still present when we compared a subgroup of COVID-19 patients with an eGFR-matched group with CKD. This indicates that the observed immune activation may be regarded as a consequence of the acute SARS-CoV-2 infection, rather than caused by a systemic inflammation due to kidney dysfunction.

Monocytes play an orchestrating role in the pathogenesis of complications associated with severe COVID-19, and factors that activate monocytes and are responsible for cell recruitment into tissues, have recently gained increased attention. The first step in the recruitment

| TABLE 3 | Characteristics (median values) of patients with COVID-19 who died (n = 15) or survived (n = 95) in hospital |
| --- | --- | --- |
| | Survived (%) | Deceased (%) | P<sup>a</sup> |
| Gender | | | |
| Female | 41 | 13 | <.05 |
| Male | 59 | 87 | |
| CKD stage | | | |
| 0 | 47 | 20 | <.01<sup>b</sup> |
| 2 | 40 | 33 | |
| 3 | 6 | 40 | |
| 4 | 4 | 7 | |
| 5 | 2 | 0 | |
| Age (y), median (IQR) | 58.0 (48.0-67.0) | 69 (61-82) | .01 |
| BMI (kg/m²), median (IQR) | 28.4 (24.5-31.8) | 26.5 (25.5-27.5) | .01 |
| Creatinine (mg/dL), median (IQR) | 70.5 (55.0-83.0) | 92.0 (77.0-111.0) | <.01 |
| eGFR (mL/min/1.72m²), median (IQR) | 87.0 (71.0-83.0) | 62.0 (45.0-75.0) | <.05 |
| CRP (mg/L), median (IQR) | 93.5 (60.0-155.5) | 180.5 (106.8-298.5) | <.05 |
| WBC count (×10⁹/L), median (IQR) | 6.1 (4.6-8.0) | 10.1 (7.5-14.3) | <.01 |
| MCP-1 (pg/mL) | 330 (228-457) | 560 (307-938) | NS |
| MIP-1α (pg/mL) | 309 (267-371) | 389 (320-436) | <.05 |
| IL-6 (pg/mL) | 23.4 (13.0-55.0) | 58.8 (47.1-126.2) | <.05 |
| sCD14 (ng/mL) | 2075 (1523-2497) | 2124 (1819-2186) | NS |

Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; IQR, interquartile range; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein; sCD14, soluble cluster of differentiation 14; WBC, white blood cell.

<sup>a</sup>Chi-square analysis.
<sup>b</sup>Fisher’s exact test.
of monocytes requires chemoattractant factors, such as MCP-1 and MIP-1α. In this study, we report that both MCP-1 and MIP-1α levels are associated with increased risk of in-hospital mortality in patients with COVID-19. This was observed in unadjusted regression analyses as well as in the model adjusted for age, sex and eGFR. The level of these chemoattractant factors therefore seems to impact mortality in COVID-19 more than kidney function itself.

Several studies have reported elevated circulating levels of MCP-1 and MIP-1α in patients with COVID-19, especially in patients requiring intensive care. We report that the absolute level of MCP-1 in COVID-19 patients does not differ from a matched disease control group (CKD patients) nor from our healthy control group. This observation is of interest since it indicates that the association to mortality is not by necessity a direct consequence of the peripheral concentrations of MCP-1. We have previously reported that the concentration of MCP-1 is higher in the interstitium of CKD patients and that it impacts the monocyte phenotype at the site of inflammation. It is not known if patients with COVID-19 have a higher extravascular concentration of MCP-1, in general, or if the receptor for CCL2 (CCR2/CD192) is unequally expressed on target cells.

MIP-1α is best known for its proinflammatory and chemotactic effects, but it can also induce coagulation disturbances, which often is observed in severe COVID-19. The MIP-1α concentration in patients was lower compared to both matched CKD patients and healthy individuals. This is important since a low systemic level of MIP-1α has previously been linked to a high risk of venous thromboembolism in glioma and rash in ZIKAV-infected patients. However, the interpretation of this should be made with caution since the haemostasis disturbances in COVID-19 patients must be viewed from a much broader context.

Early during the pandemic, it was recognized that an excessive monocyte activation and cytokine storm was a hallmark of severe disease in COVID-19 patients, and that the information provided by routine blood tests was limited. Therefore, additional markers for monocyte activation were evaluated. Here we report an increased sCD14 level compared to healthy subjects which is in line with other studies. We extend this observation and report that the level is also higher compared to patients with CKD, and that the level was higher in the patient group with lower eGFR. Regardless the cause, the absolute level did not associate with mortality.

This study has limitations. Apart from a relatively small patient sample size, a co-infection with bacteria might affect the results of the immune response in patients with SARS-CoV-2 infection. We do not have information on kidney function before COVID-19 and we do not know whether an increase in plasma creatinine at the time of sampling was caused by SARS-CoV-2 infection with AKI or pre-existing CKD, or whether the rise was related to other factors, such as dehydration or acute haemodynamic instability. Urine samples were not systematically collected. In addition, one regression analysis of risk of mortality in COVID-19 patients was made in a sub-group of patients with an eGFR below 60 mL/min/1.73 m².

| TABLE 4 | Unadjusted and adjusted (age, sex and eGFR) logistic regression analysis, odds ratio (OR) with 95% confidence intervals (CI) of risk of in-hospital mortality in patients with COVID-19 |
|---------|----------------------------------------------------------------------------------|
| **Unadjusted analysis** | **Adjusted for age, sex and eGFR** |
| **Age (y)** | **P** | **OR** | **95% CI** | **P** | **OR** | **95% CI** |
| Age (y) | <.01 | 1.071 | 1.023-1.122 | | |
| Sex (male) | .055 | 4.527 | 0.967-21.196 | | |
| BMI (kg/m²) | NS | 0.960 | 0.867-1.064 | NS | 0.978 | 0.864-1.107 |
| CRP (mg/L) | <.01 | 1.009 | 1.003-1.015 | <.05 | 1.007 | 1.001-1.014 |
| WBC count (x10⁹/L) | <.001 | 1.292 | 1.116-1.497 | .001 | 1.462 | 1.164-1.836 |
| eGFR (mL/min/1.73 m²) | <.01 | 0.969 | 0.947-0.991 | | |
| Monocyte recruitment (chemoattractants) | | | | |
| MCP-1 (pg/mL) | <.05 | 1.001 | 1.000-1.002 | <.05 | 1.001 | 1.000-1.002 |
| MIP-1α (pg/mL) | <.05 | 1.005 | 1.001-1.010 | <.01 | 1.007 | 1.002-1.012 |
| IL-6 (pg/mL) | <.05 | 1.006 | 1.001-1.012 | NS | 1.006 | 0.999-1.012 |
| Monocyte function (immune modulating mediator) | | | | |
| sCD14 (ng/mL) | NS | 1.000 | 1.000-1.000 | NS | 1.000 | 1.000-1.000 |

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein; sCD14, soluble cluster of differentiation 14; WBC, white blood cell.
the median, which was close to the normal range of kidney function. This may introduce a risk when interpreting those results. The study has several strengths. Patients were prospectively enrolled and protocol blood samples were collected early at admission. Patient information, level of care and treatments were systematically recorded. Furthermore, the patients in this study were hospitalized early during the first pandemic wave before recommendations of early treatment with therapeutic doses of anticoagulants and high doses of steroids were in place, indicating that the patients in this study are treatment naïve, which is important when studying monocyte immune features. We also compared the results in patients with COVID-19 to two groups of controls, both disease controls with matched eGFR and healthy subjects, which has not been the case in many other reports.

A better understanding of the subsets of monocytes/macrophages which drive disease pathology is important for the development of appropriate therapeutic interventions. Interfering with upstream signals causing cytokine production can effectively dampen the occurrence of the cytokine storm. Interfering with cytokine-mediated signalling pathways could also reduce hyper-inflammation in patients with severe COVID-19. Published trials indicate beneficial effects of IL-6 inhibitors. Circulating CD14+ monocytes accumulate in inflamed tissues using the chemokine receptor CCR2 and CCR2 blockade could potentially reduce the accumulation of pathological monocytes in inflamed tissues. Moreover, cytokine signatures could be of value to predict disease outcomes, to monitor the disease and to individualize treatment strategies.

To summarize, we demonstrate that the monocyte chemoattractant factors MCP-1 and MIP-1α are associated with in-hospital mortality in patients with COVID-19. Our data show that, apart from impaired kidney function, MCP-1 and MIP-1α levels add significant prognostic information to previously established risk factors. Moreover, this study provides an increased understanding of the impact of monocyte recruitment mediators to the development of COVID-19-associated complications, which warrant special consideration in the pursuit and development of new effective therapies.

**AUTHOR CONTRIBUTIONS**

SHJ, JL and CT contributed to conceptualization, funding acquisition and project administration. CT and SH contributed to investigation. CT, SH and LM contributed to data curation. SHJ, JL, CT and LM contributed to methodology. SS, LM, JL and SHJ contributed to formal analysis, validation and writing original draft. All authors contributed to reviewing and editing.

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**CONFLICT OF INTEREST**

None of the authors have any disclosures to report.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are openly available from corresponding author.

**ETHICS APPROVAL**

The study complied with the Declaration of Helsinki, and informed consent was obtained from all healthy individuals and patients, or in the case of incapacity, their next of kin. The protocol was approved by the Swedish Ethical Review Authority (Community study, reference number 2020-01 653).

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