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RESEARCH ARTICLE

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Longitudinal changes in inflammatory biomarkers among patients with COVID-19: A nationwide study in Iceland

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Abstract

Objectives: All SARS-CoV-2-positive persons in Iceland were prospectively monitored and those who required outpatient evaluation or were admitted to hospital underwent protocolized evaluation that included a standardized panel of biomarkers. The aim was to describe longitudinal changes in inflammatory biomarkers throughout the infection period of patients with COVID-19 requiring different levels of care.

Design: Registry-based study.

Setting: Nationwide study in Iceland.

Patients: All individuals who tested positive for SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) from February 28 to December 31, 2020 in Iceland and had undergone blood tests between 5 days before and 21 days following onset of symptoms.

Measurements and Main Results: Data were collected from the electronic medical record system of Landspitali–The National University Hospital of Iceland. Data analyses were descriptive and the evolution of biomarkers was visualized using locally weighted scatterplot smoothing curves stratified by the worst clinical outcome experienced by the patient: outpatient evaluation only, hospitalization, and either intensive care unit (ICU) admission or death. Of 571 included patients, 310 (54.3%) only required outpatient evaluation or treatment, 202 (35.4%) were hospitalized, and 59 (10.3%) were either admitted to the ICU or died. An early and persistent separation of the mean lymphocyte count and plasma C-reactive protein (CRP) and ferritin levels was observed between the three outcome groups, which occurred prior to hospitalization for those who later were admitted to ICU or died. Lower lymphocyte count, and higher CRP and ferritin levels correlated with worse clinical outcomes. Patients who were either admitted to the ICU or died had sustained higher white blood cell and neutrophil counts, and elevated plasma levels of procalcitonin and D-dimer compared with the other groups.

Conclusions: Lymphocyte count and plasma CRP and ferritin levels might be suitable parameters to assess disease severity early during COVID-19 and may serve as predictors of worse outcome.

KEYWORDS
ambulatory care, COVID-19, critical care, laboratory markers, outcome, SARS-CoV-2

Editorial Comment

Prediction of the severity of COVID-19 early after infection could strengthen the timing of treatment and enable individual and early treatment. Here, assessment of standard markers of inflammation (lymphocyte count, CRP, and ferritin) when the first symptoms were reported was associated with risk for later severity and outcome. The results from this unique nationwide cohort could be helpful in development of prediction models for COVID-19 severity.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global pandemic. The clinical manifestations are varied, ranging from asymptomatic infection to severe illness characterized by pneumonia and coagulopathy.[1,2] Severe COVID-19 can be associated with an unregulated proinflammatory immune response that can result in acute respiratory distress syndrome and multiorgan failure.[3] Dexamethasone, a potent anti-inflammatory agent, has been shown to reduce mortality in severely ill patients.[4]

Elevated plasma levels of inflammatory biomarkers and lowered lymphocyte counts in peripheral blood are common in patients with COVID-19.[5] Two studies from China that examined longitudinal changes in inflammatory biomarkers in hospitalized patients with COVID-19 found marked differences in levels of disease severity and concluded that specific parameters may serve as predictors of disease progression. Both studies included only hospitalized patients and used the day of hospital admission as reference time point.[6,7] There is currently a lack of studies examining longitudinal changes in biomarkers in nonhospitalized patients and in the earlier stages of COVID-19.

At the onset of the local epidemic, Icelandic authorities implemented robust public health measures, which included extensive diagnostic testing using real-time reverse transcription polymerase chain reaction (RT-PCR) and the establishment of Covid-19 Outpatient Clinic at Landspitali–The National University Hospital of Iceland (LUH), which was tasked with providing care for all persons with a documented SARS-CoV-2 infection.[8] Several RT-PCR testing strategies were implemented, including testing based on clinical suspicion, open-invitation population screening and screening at the border upon arrival to the country. Population-based seroprevalence studies later confirmed that the majority of infections were detected by these programs.[9,10] All individuals who tested positive for SARS-CoV-2 were enrolled into telehealth monitoring at the COVID-19 Outpatient Clinic where standardized interviews were carried out to guide the assessment of disease severity. Patients with concerning or worsening symptoms were referred for in-person evaluation, which included a standardized panel of blood tests.[8] This panel was also obtained for all patients who were admitted to hospital.

The aim of this study was to describe longitudinal changes in inflammatory biomarkers throughout the acute phase of COVID-19 in patients requiring different levels of care. Our hypothesis was that there would be an early and sustained separation of a subset of inflammatory markers between patients who required outpatient care only and those who became more severely ill.

2 | METHODS

2.1 | Ethics statement

This study was approved by the National Bioethics Committee of Iceland in Reykjavik (NBC-20-078) and the Landspitali–The National University Hospital Institutional Research Committee, waiving individual consent.

2.2 | Participants

This registry-based descriptive study included all persons who tested positive for SARS-CoV-2 by RT-PCR in Iceland between February 28 and December 31, 2020 and underwent blood tests between 5 days before and 21 days after the onset of symptoms.

Cases were identified by three testing strategies; targeted testing based on clinical suspicion, open-invitation population screening and border screening. Among those who were RT-PCR positive for SARS-CoV-2 at border screening, active infection was determined by an infectious disease specialist based on the presence of symptoms, cycle threshold value of the RT-PCR test, result of a repeated RT-PCR test and the presence of antibodies against SARS-CoV-2.

Individuals were excluded if an active infection was ruled out during initial assessment, if they never required in-person evaluation or hospital admission during telehealth monitoring, or if the date of symptom onset was missing (Figure 1).

2.3 | Data collection

Data collected consisted of de-identified data from the LUH electronic medical record system. All SARS-CoV-2-positive persons who were considered to have an active infection were enrolled into a telehealth service at the COVID-19 Outpatient Clinic and followed until the end of their isolation period, discharge from hospital or death.[8] During telehealth monitoring, clinical features were documented prospectively using standardized data entry forms. Clinical assessment upon outpatient evaluation or hospitalization included a standardized panel of blood tests, which included complete blood count (CBC), biochemical parameters, and several inflammatory biomarkers.

Demographic and clinical data were obtained from the standardized data entry forms used by the COVID-19 Outpatient Clinic and

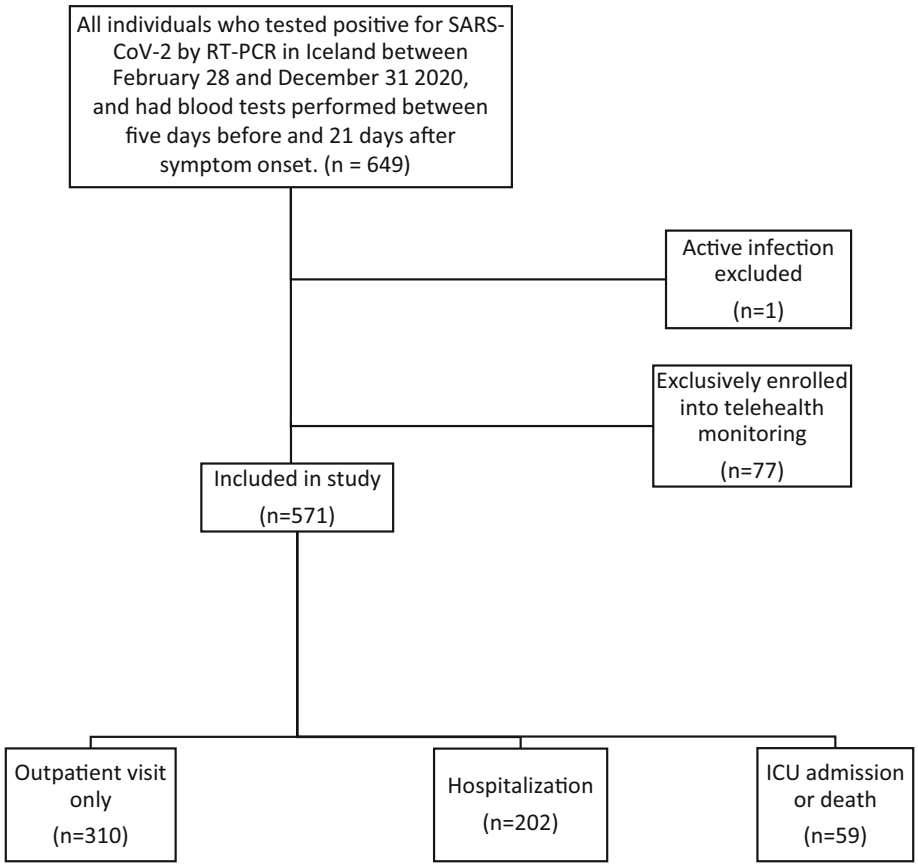

FIGURE 1 Flowchart illustrating selection of patients for the study

were supplemented by information on clinical care, including laboratory results and administered treatments, which was obtained from LUH electronic medical record system. The date of symptom onset was collected from the standardized data entry forms. However, if the date was missing from the data entry form, then it was retrieved from physician notes in the medical records. For this study, the following inflammatory biomarkers were examined: the white blood cell (WBC) count, neutrophil count, lymphocyte count and platelet count in peripheral blood, erythrocyte sedimentation rate (ESR), and plasma levels of C-reactive protein (CRP), procalcitonin (PCT), ferritin, and D-dimer.

Comorbidities were identified using the combination of the International Classification of Diseases, tenth revision diagnosis codes (recorded in any of the following three population-based sources: LUH electronic medical record database (from 2009), the Register of Primary Health Care Contacts (from 2004), and the Register of Contacts with Medical Specialists in Private Practice (from 2010)), and a filled prescription for a drug used in the treatment of the condition filled within the preceding 13 months of the positive RT-PCR test. Data on all filled drug prescriptions were collected from the Prescription Medicines Register. Detailed definition of each comorbidity can be found in Table S1.

All patients were classified into three groups based on the most severe clinical outcome experienced during follow-up: outpatient visit only, hospitalization, and intensive care unit (ICU) admission or death due to COVID-19.

2.4 | Statistical analyses

Statistical analyses were descriptive and performed using RStudio, version 1.4.1103 (RStudio Inc), run by R Statistical Software, version 4.0.4 (R Foundation for Statistical Computing). Categorical variables were summarized as frequencies and continuous variables as medians along with range and interquartile range (IQR). Longitudinal changes in inflammatory parameters from the date of symptom onset were visualized using locally weighted scatterplot smoothing (LOWESS) curves, which were compared by the worst clinical outcome experienced by patients. In the subset of patients who were later hospitalized or admitted to ICU, LOWESS curves were visualized with reference to the date of hospital and ICU admission. Boxplots were used for assessment of distribution of minimum and maximum values of inflammatory parameters between groups.

3 | RESULTS

3.1 | Study population

A total of 649 SARS-CoV-2-positive persons had a blood test performed during the study period, of whom 571 were included in the study. Of those, 310 (54.3%) required only outpatient evaluation, 202 (35.4%) were hospitalized, and 59 (10.3%) were either admitted to ICU or died (Figure 1). The median age was 57 years (IQR, 42–70),

TABLE 1 Clinical characteristics and inflammatory biomarkers in patients with COVID-19 who attended the outpatient clinic, were hospitalized, or were admitted to ICU or died

Characteristic	Outpatient visit only ($n = 310$)	Hospitalization ($n = 202$)	ICU admission or death ($n = 59$)	All patients ($n = 571$)
Age (years)	48.0 [36.0–58.0] (17.0–90.0)	69.5 [55.0–78.0] (1.0–99.0)	70.0 [62.0–75.5] (32.0–97.0)	57.0 [42.0–70.0] (1.0–99.0)
Males (*n*)	110 (35.5%)	107 (52.7%)	40 (67.8%)	257 (44.9%)
Females (*n*)	200 (64.5%)	95 (47.0%)	19 (32.2%)	314 (55.0%)
Follow-up time (days)	19.0 [15.0–22.0] (7.0–44.0)	21.0 [17.0–27.0] (3.0–210.0)	23.0 [14.8–30.0] (4.0–48.0)	19.0 [16.0–24.0] (3.0–210.0)
Comorbid conditions				
Hypertension (*n*)	56 (18.1%)	93 (46.0%)	30 (50.8%)	179 (31.3%)
Cardiovascular disease (*n*)	20 (6.5%)	42 (20.8%)	12 (20.3%)	74 (13.0%)
Congestive heart failure (*n*)	4 (1.3%)	32 (15.8%)	10 (16.9%)	46 (8.1%)
Diabetes mellitus (*n*)	22 (7.1%)	27 (13.4%)	13 (22.0%)	62 (10.9%)
COPD (*n*)	9 (2.9%)	17 (8.4%)	10 (16.9%)	36 (6.3%)
Chronic kidney disease (*n*)	13 (4.2%)	56 (27.7%)	19 (32.2%)	88 (15.4%)
Cancer (*n*)	19 (6.1%)	26 (12.9%)	10 (16.9%)	55 (9.6%)
Treatment				
Glucocorticoids (total)	1 (0.3%)	70 (34.7%)	26 (44.1%)	97 (17.0%)
Diagnosed before June 22, 2020 (*n*)	1 (0.8%, $n = 126$)	6 (8.3%, $n = 72$)	4 (13.8%, $n = 29$)	11 (4.8%, $n = 227$)
Diagnosed after June 22, 2020 (*n*)	0 (0.0%, $n = 184$)	64 (49.2%, $n = 130$)	22 (73.3%, $n = 30$)	86 (25.0%, $n = 344$)
Inflammatory marker				
WBC count ($\times 10^9$/L)	5.9 [4.8–7.4] (2.2–15.8)	5.8 [4.5–7.7] (1.5–21.7)	7.5 [5.7–10.3] (2.0–40.5)	6.2 [4.8–8.3] (1.5–40.5)
Number of patients without test (%)	1 (0.3%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Neutrophil count ($\times 10^9$/L)	3.4 [2.6–4.7] (0.7–10.6)	3.7 [2.5–5.3] (0.3–19.9)	5.5 [3.9–8.0] (1.1–25.5)	4.0 [2.7–5.9] (0.3–25.5)
Number of patients without test (%)	1 (0.3%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Lymphocyte count ($\times 10^9$/L)	1.8 [1.4–2.2] (0.4–4.4)	1.3 [0.9–1.8] (0.2–8.4)	1.0 [0.7–1.5] (0.1–7.3)	1.3 [0.9–1.8] (0.1–8.4)
Number of patients without test (%)	1 (0.3%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Platelets ($\times 10^9$/L)	242 [196–306] (72–583)	234 [177–311] (65–875)	253 [195–317] (57–662)	241 [185–312] (57–875)
Number of patients without test (%)	1 (0.3%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
ESR (mm/h)	12 [6–22] (1–95)	24 [12–43] (2–116)	35 [18–55] (2–97)	16 [7–33] (1–116)
Number of patients without test (%)	31 (10.0%)	37 (18.3%)	11 (18.6%)	79 (13.8%)
CRP (mg/L)	5 [3–22] (3–134)	29 [3–69] (3–520)	42 [13–106] (3–523)	26 [7–68] (3–523)
Number of patients without test (%)	1 (0.3%)	2 (1.0%)	0 (0.0%)	3 (0.5%)
PCT (μg/L)	0.04 [0.03–0.06] (0.02–3.40)	0.09 [0.06–0.15] (0.02–74.68)	0.15 [0.08–0.40] (0.02–422.55)	0.09 [0.05–0.16] (0.02–422.55)
Number of patients without test (%)	14 (4.5%)	13 (6.4%)	1 (1.7%)	28 (4.9%)

TABLE 1 (Continued)

Characteristic	Outpatient visit only ($n = 310$)	Hospitalization ($n = 202$)	ICU admission or death ($n = 59$)	All patients ($n = 571$)
Ferritin (μg/L)	185 [96–372] (7–3298)	488 [269–828] (11–4710)	952 [484–1473] (22–10,138)	492 [232–925] (7–10,138)
Number of patients without test (%)	9 (2.9%)	10 (5.0%)	0 (0.0%)	19 (3.3%)
D-Dimer (mg/L)	0.44 [0.31–0.66] (0.04–79.50)	0.86 [0.54–1.35] (0.13–46.64)	1.44 [0.85–2.80] (0.17–69.25)	0.86 [0.50–1.53] (0.04–79.50)
Number of patients without test (%)	32 (10.3%)	11 (5.4%)	1 (1.7%)	44 (7.7%)

Note: Categorical variables are shown as number (percentage) and continuous variables as median ([IQR], (range or min–max)). One patient admitted to hospital and 11 patients who were either admitted to the ICU or died had missing final date of follow-up.

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; PCT, procalcitonin; WBC, white blood cells.

and was higher among those experiencing more severe clinical outcomes. The majority of the patients were female ($N = 314$, 55.0%), although patients who were hospitalized, or admitted to the ICU or died were predominantly male ($n = 257$, 67.8%). Almost half of the study population had one or more documented comorbidities ($n = 263$, 46.1%), such as hypertension (31.3%), chronic kidney disease (15.4%), cardiovascular disease (13.0%), and diabetes mellitus (10.9%). A total of 97 patients were treated with systemic corticosteroids with a notable change in practice occurring on June 22, 2020,[4] after which a markedly higher proportion of patients who were admitted to the ICU or died received such treatment (73.3% vs. 13.8%).

The results of the CBC varied between outcome groups (Table 1). In patients who were admitted to ICU or died, the total number of WBC, neutrophils, and platelets were markedly elevated, while lymphocyte counts were decreased, compared with the other outcome groups. A similar difference was observed in inflammatory and coagulation markers between outcome groups, with higher levels of ESR, CRP, ferritin, and D-dimer associated with worse clinical outcomes (Table 1). Moreover, a similar difference was observed for a subset of inflammatory markers when stratified by age and comorbidities (Table S2). The proportion of patients who had abnormal levels of biomarkers in their first blood sample varied considerably by their final outcome (Table 2). The distribution of biomarkers by group is shown in Figures S1 and S2.

3.2 | Longitudinal changes in inflammatory parameters

The longitudinal changes in inflammatory biomarkers throughout the acute infection phase for the three outcome groups are shown in Figure 2 (see also Figures S3 and S4). Both the mean total WBC and neutrophil counts increased between the 8th and the 14th day of symptomatic disease in all patients. Compared with other outcome groups, patients who were later admitted to the ICU or died had persistently higher mean WBC and neutrophil counts from day 3 since the onset of symptoms. However, in the days preceding hospital admission the difference in mean WBC and neutrophil counts between patients who were later admitted to ICU or died and those who were admitted to a general hospital ward were marginal (Figure S5). By contrast, mean lymphocyte counts were lower in patients who were later admitted to hospital or ICU and the difference is visible immediately before hospital admission. Both mean CRP and ferritin levels were higher in patients who required increased levels of care. Separation of CRP levels occurred between the 3rd and the 11th day from symptom onset and separation of ferritin levels was sustained throughout the entire period of acute illness. The mean value of both biomarkers separated in the days prior to hospital admission (Figure 3) and rose in the days preceding admission to ICU or death (Figure S6). Only patients who were later either admitted to ICU or died had a noticeable elevation of PCT levels (Figure S3), and this tended to occur following

TABLE 2 Inflammatory biomarkers outside of the normal range in the first blood sample collected from patients with COVID-19 who attended the outpatient clinic, were hospitalized, or were admitted to ICU or died

Inflammatory marker	Outpatient visit only ($n = 310$)	Hospitalization ($n = 202$)	ICU admission or death ($n = 59$)	All patients ($n = 571$)
Leukocytosis (WBC > 10.5 × 10^9/L)	11/307 (3.6%)	15/201 (7.3%)	5/59 (8.5%)	31/567 (5.5%)
Neutrophilia (Neutrophils > 7.0 × 10^9/L)	8/307 (2.6%)	17/201 (8.4%)	8/59 (13.6%)	33/567 (5.8%)
Lymphopenia (Lymphocytes < 1.0 × 10^9/L)	14/307 (4.6%)	60/201 (29.9%)	26/59 (44.1%)	100/567 (17.6%)
High CRP (>10 mg/L)	109/307 (35.5%)	133/200 (66.5%)	57/59 (96.6%)	299/566 (52.8%)
High PCT (>0.05 μg/L)	85/294 (28.9%)	153/189 (81.0%)	54/58 (93.1%)	292/541 (54.0%)
Hyperferritinemia (>400 μg/L, >150 μg/L if female <50 years)	87/299 (29.1%)	95/192 (49.5%)	41/59 (69.5%)	223/550 (40.5%)
High D-dimer (>0.5 mg/L, >0.01 mg/L*age if >50 years)	86/276 (31.2%)	113/191 (59.2%)	44/58 (75.9%)	243/525 (46.3%)

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin; WBC, white blood cell.

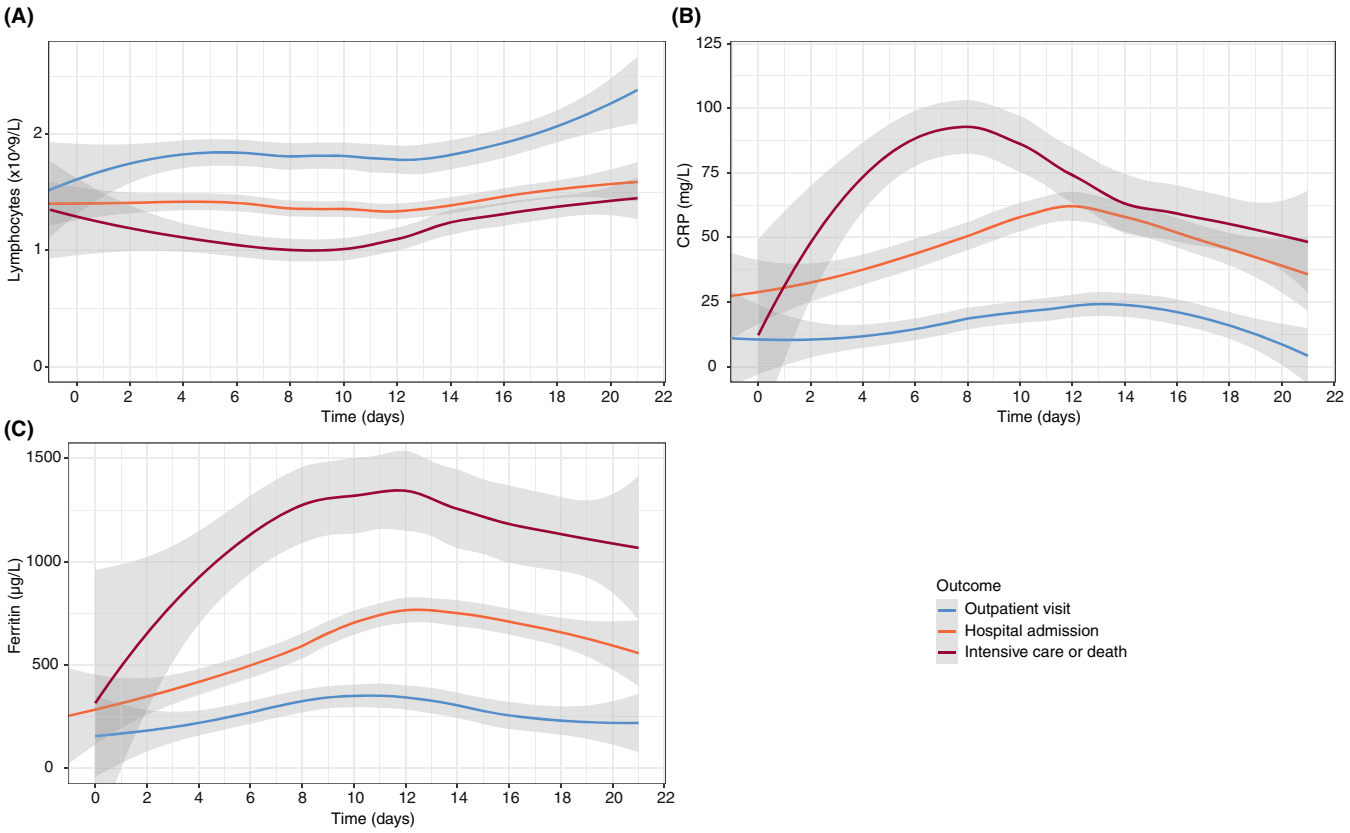

FIGURE 2 Longitudinal changes in inflammatory parameters from the onset of symptoms among groups of patients with COVID-19 who attended the outpatient clinic, required hospitalization or were either admitted to ICU or died. The *y*-axis shows the conditional mean with a 95% confidence interval (gray) of lymphocyte count (A), CRP (B), and ferritin (C) plasma levels in patients who only visited the outpatient clinic (blue), were hospitalized (orange) and were either admitted to the ICU or died (red). The *x*-axis shows the number of days since the onset of symptoms. CRP, C-reactive protein; ICU, intensive care unit

the ICU admission (Figure S6). Finally, D-dimer levels increased in the second half of the acute phase of COVID-19 in all outcome groups (Figure S3), with the mean value being slightly higher among those later admitted to ICU in the days preceding hospital admission.

4 | DISCUSSION

In this registry-based study, longitudinal changes in levels of inflammatory biomarkers were compared in COVID-19 patients who later required different levels of care. Our results suggest that lower

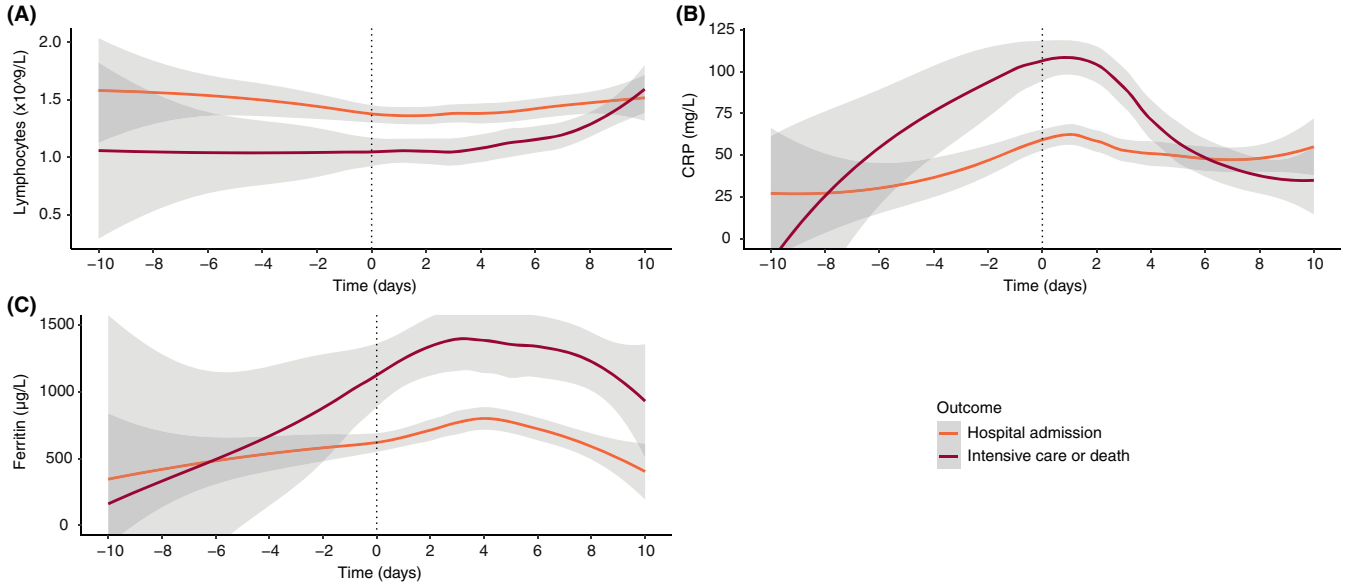

FIGURE 3 Longitudinal changes in inflammatory parameters in reference to the date of hospital admission among patients with COVID-19 who were hospitalized or were either admitted to ICU or died. The *y*-axis shows the conditional mean with a 95% confidence interval (gray) of lymphocyte count (A), CRP (B), and ferritin (C) plasma levels in patients who were hospitalized (orange) and either admitted to the ICU or died (red). The *x*-axis shows the time in days where zero is defined as the day of hospital admission. CRP, C-reactive protein; ICU, intensive care unit

lymphocyte counts and higher levels of CRP and ferritin early in the course of illness are associated with later development of more severe disease and that these biomarkers might be incorporated into prognostic decision tools to identify patients who are likely to benefit most from early treatment in the outpatient setting, regardless of age and comorbidities. This comparison was made possible by the standardized management of all SARS-CoV-2-positive individuals by the dedicated COVID-19 Outpatient Clinic,[9,10] which ensured that the date of symptom onset was available for all individuals and the same laboratory parameters were ordered (given that a blood sample was deemed necessary), regardless of disease severity. This unique standardized approach allowed us to describe longitudinal changes in inflammatory biomarkers in both nonhospitalized and hospitalized patients during the days before hospital admission and to compare this with biomarkers obtained during hospital and ICU admission.

Impaired and unregulated immune response is essential to the pathogenesis of severe COVID-19.[3] Low lymphocyte counts are common among patients with COVID-19.[5] Early in the disease, this phenomenon could potentially be due to direct infection of lymphocytes by SARS-CoV-2. Later in the disease course there is likely an additional component of unregulated immune response causing inflammatory mediators to induce apoptosis of lymphocytes or to destroy lymphoid organs, both resulting in a decreased number of lymphocytes.[11] Both CRP and ferritin are acute phase proteins whose plasma concentration increases following an acute inflammatory response, with elevated ferritin levels being more common in viral infections than bacterial infections.[12] The results of the current study are consistent with an earlier report of longitudinal changes in CRP levels from the onset of symptoms.[13] Moreover, our findings support the conclusions drawn from a recent systematic review that found high levels of ferritin to correlate with poor clinical outcomes and suggested that ferritin could predict a severe course of COVID-19.[14] The studies included in the systematic review were all based on hospitalized patients and thus could not determine whether high ferritin levels were a feature of SARS-CoV-2 infection in general or consequence of severe disease. Our study adds to the current literature by demonstrating an early and sustained separation of lymphocyte counts, and CRP and ferritin levels between patients who later require hospital admission and those who required outpatient management only. In addition, we show that those who are later admitted to ICU or die have lower lymphocyte counts and higher plasma levels of CRP and ferritin in the days preceding hospital admission than those who are cared for in general hospital wards. This finding provides strong evidence that lymphocyte count and CRP and ferritin levels may be useful biomarkers for the assessment of disease severity during outpatient evaluation and might serve as early predictors of adverse clinical outcomes.

Other inflammatory markers, such as platelet count, were less useful for early classification of disease severity, even though thrombocytopenia has been associated with more severe clinical manifestations and increased mortality in COVID-19.[15] Similarly, our findings show that plasma PCT levels were high in patients who were admitted to the ICU or died, but the elevation mainly occurred after the ICU admission. A sudden rise in PCT levels shortly before death has been reported previously, most likely resulting from bacterial superinfection and development of sepsis as a complication of SARS-CoV-2 infection.[16] Our findings suggest that PCT would not be a useful parameter for prognostication as it generally rises after intensive therapy has already been initiated. D-Dimer elevation can be seen both during inflammation and thrombotic events, a known complication of

COVID-19.[17,18] We show that D-dimer correlated with worse outcome and that those who were later admitted to ICU or died had marginally higher levels in the days preceding hospital admission than did those who were only admitted to a general ward, suggesting that D-dimer could potentially be used as a prognostic marker.

Our study does have some limitations. Although all SARS-CoV-2-positive individuals were managed using a structured approach, including a standardized laboratory panel, laboratory tests were only obtained if clinically indicated and after the infection status was known to the responsible physician. This means that our observations can only apply to known cases that are undergoing evaluation of concerning symptoms. Furthermore, as laboratory tests were performed when clinically indicated, those who were sicker had more frequent blood sampling, which may bias the longitudinal analysis to more severe values. Strengths of the study include the standardized approach and nationwide cohort. Since most patients who ultimately were admitted to the hospital had one or more set of standardized blood tests obtained during outpatient assessment in the days preceding admission, we are confident that the assessment of inflammatory markers in this cohort is relatively unbiased. The standardized panel of blood tests that was carried out in the majority of patients undergoing evaluation, including outpatients, minimizes the risk for selection bias regarding which parameters were obtained. No differences were seen in the trajectories of inflammatory markers before and after June 22, 2020, when the benefits of dexamethasone[4] were evident and the usage of the drug in the treatment of hospitalized patients requiring oxygen supplementation had become standard of care (Figures S7–S9).

5 | CONCLUSION

This registry-based study showed that increased inflammatory response was related to adverse clinical outcomes. Lymphocyte count and CRP and ferritin levels might be best suited for assessment of disease severity and potentially serve as early predictors of adverse clinical outcome in COVID-19 patients. Neutrophil counts and ferritin levels should be monitored in hospitalized COVID-19 patients as they might predict a critical illness and mortality. Future studies should address the evolution of lymphocyte counts and CRP and ferritin levels by dates of symptom onset in a prognostic model in a larger cohort to further validate their predictive value for clinical outcome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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