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LETTER TO THE EDITOR

Inflammatory biomarkers at hospital discharge are associated with readmission and death in patients hospitalized for COVID-19

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Introduction

Even though the survival of patients admitted with coronavirus disease 2019 (COVID-19) has increased with approximately 20% over the past year [1], readmission and mortality rates remain high (19.9% and 9.1%, respectively, within 2 months after hospital discharge (ward and intensive care unit (ICU)—admissions combined) [2]. In community-acquired pneumonia, elevated interleukin (IL)-6 and IL-10 at hospital discharge are associated with mortality in the subsequent 3 and 6 months, despite initial clinical recovery [3]. We aim to evaluate whether elevated levels of IL-6 and IL-10 at hospital discharge are associated with readmissions and mortality in the following 12 months in patients with COVID-19.

Methods

This study was part of the Amsterdam University Medical Centers (UMC) COVID-19 biobank. Patients were prospectively included in the biobank if they were admitted to the Amsterdam UMC with COVID-19 and had provided written informed consent or not used the opt-out form. COVID-19 was defined as a positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR). IL-6 and IL-10 were measured in serial blood samples from March to May 2020 [4]. Patients who died during admission were excluded. Since biomarkers were measured in the first wave in The Netherlands, patients did not receive immunomodulatory therapy. Readmissions and mortality after hospital discharge were ascertained by contacting the general practitioner (GP). Biomarker measurements were done by using a Luminex platform [4]. Normally distributed data were analyzed by a t-test and nonparametric continuous data by Mann–Whitney *U* test. The ethics committee of the Amsterdam UMC approved the study.

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Results

One-hundred sixty-one patients who were discharged alive formed our cohort. The mean age was 62 years (SD 11.76), 106 (68%) were male, and patients had an average of one comorbidity (IQR [1–3]). Seventy-five patients (47%) required ICU care during admission. Thirty-four (21%) were readmitted (median time to readmission was 29 days, IQR [6–97]), and six (4%) died (median time to death 85 days, IQR [20–169]) in the 12 months following the initial hospitalization for COVID-19. Twenty-three patients were readmitted once, six patients twice, and five patients three or more times. The primary cause of the first readmission was dyspnea or respiratory insufficiency in fourteen (41%) patients, cardiovascular disease in seven (21%), and other causes in thirteen (38%) patients. Compared to patients without readmissions and/or mortality after discharge, patients with these adverse outcomes were older ($p=0.031$) and suffered from more comorbidities ($p=0.001$, Table 1).

At time of hospital discharge, most patients in both groups had zero or one abnormal vital parameter according to Halm's criteria [5] (criteria for clinical stability at hospital discharge). Lymphocytes and platelets were significantly lower at discharge in patients who were readmitted or died in the first 2 months following discharge ($p=0.002$ and $p=0.007$, respectively). The median concentrations of IL-6 and IL-10 at discharge were significantly higher in patients with these adverse outcomes in the first month ($p=0.005$ and $p<0.001$, respectively) and first 2 months ($p=0.031$ and $p=0.017$, respectively) following discharge (Fig. 1). At 12 months, the IL-6 and IL-10 concentration did not show significant differences. Biomarkers representing discharge were measured in the last 4 days before discharge. For the biomarker concentrations, we used 26 age and gender-matched controls from the outpatients clinic, with a mean age of 64 years (SD 15.5) of whom 18 (69%) were male (Fig. 1).

Discussion

This study shows that after hospitalization for COVID-19, elevated IL-6 and Il-10 concentrations at time of hospital discharge are associated with increased readmission and/or mortality rates over the subsequent 2 months. A similar association was found for lower lymphocyte and platelet concentration at discharge. Previous studies show that lymphopenia and low platelets have been associated with more severe infection [6] and IL-6 concentration is correlated with COVID-19 severity and in-hospital mortality [7]. Our findings could be of special relevance for patients who did not receive tocilizumab, since this recombinant humanized anti-IL-6 receptor monoclonal antibody inhibits the binding of IL-6 to both membrane and soluble IL-receptors [8].

This study has several limitations. Biomarkers representing hospital discharge were measured in the 4 days prior to discharge and were available in 70 (43%) patients. Second, we could not ascertain readmissions in ten (6%) patients in our cohort. Third, due to the lack of controls without COVID-19, we could not investigate if our findings are also true for other diseases. Fourth, the use of tocilizumab, which has been recommended by the World Health Organization as treatment for severely or critically ill patients with COVID-19 [9], will have influence of the IL-6 concentration at discharge. Even so, this study shows that COVID-19 patients with elevated IL-6 and IL-10 levels at hospital discharge were associated with an increased risk of readmission and/or death up to 2 months after hospital discharge when compared with those with normal circulating biomarkers.

Appendix

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Table 1 Clinical characteristics, stratified for readmissions and/or mortality in the first 2 months and 12 months after discharge

	Short term (2 months)			Long term (12 months)		
	Readmission and/or mortality ($n=23$)	No readmission and/or mortality ($n=138$)	*P* value	Readmission and mortality ($n=37$)	No readmission and/or mortality ($n=124$)	*P* value
Demographics						
Age, mean (SD)	68.07 (12.67)	60.96 (11.33)	**0.007**	65.62 (13.33)	60.88 (11.08)	**0.031**
Gender, male, no. (%)	16 (69.6%)	90 (65.2%)	0.865	24 (64.9%)	82 (66.1%)	1.000
BMI, median [IQR]	27.46 [24.56, 29.23]	27.75 [25.22, 32.14]	0.161	27.71 [24.57, 30.97]	27.36 [25.19, 31.87]	0.690
Number of comorbidities[1], median [IQR]	3.00 [1.50, 4.00]	1.00 [0.00, 3.00]	**0.001**	3.00 [1.00, 4.00]	1.00 [0.00, 3.00]	**0.001**
Admission						
qSOFA, median [IQR]	1.00 [0.00, 1.00]	1.00 [0.50, 1.00]	0.051	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	0.648
MEWS, median [IQR]	2.00 [1.00, 4.00]	4.00 [2.00, 5.00]	**0.033**	3.00 [1.00, 5.00]	4.00 [2.00, 5.00]	0.302
CT Severity Score[2], mean (SD)	10.59 (6.62)	12.73 (5.64)	0.177	11.57 (7.26)	12.58 (5.34)	0.476
Days between onset and admission, median [IQR]	10.00 [7.75, 14.00]	10.00 [7.00, 14.00]	0.828	10.00 [7.00, 14.00]	10.00 [7.00, 14.00]	0.860
Do not resuscitate order at admission[3], no. (%)	15 (71.4%)	14 (14.7%)	**< 0.001**	18 (60.0%)	11 (12.8%)	**< 0.001**
Do not intubate order at admission[3], no. (%)	9 (42.9%)	8 (8.4%)	**< 0.001**	11 (36.7%)	6 (7.0%)	**< 0.001**
Discharge						
Length of hospital stay (days), median [IQR]	6.00 [4.00, 8.00]	11.00 [6.00, 22.00]	**0.002**	7.00 [5.00, 17.00]	11.00 [6.00, 20.00]	0.121
Discharge location, no. (%)			**0.003**			**0.047**
Home	11 (47.8%)	56 (40.6%)		17 (45.9%)	50 (40.3%)	
Nursing home	3 (13.0%)	1 (0.7%)		3 (8.1%)	1 (0.8%)	
Other	2 (8.7%)	6 (4.3%)		3 (8.1%)	5 (4.0%)	
Rehabilitation	5 (21.7%)	66 (47.8%)		11 (29.7%)	60 (48.4%)	
Abnormal Halm's criteria for clinical stability at discharge[4,6], no. (%)			0.499			0.462
0	10 (55.6)	57 (60.0)		15 (60.0)	52 (59.1)	
1	8 (44.4)	33 (34.7)		10 (40.0)	31 (35.2)	
2	0 (0.0)	5 (5.3)		0 (0.0)	5 (5.7)	
Complications during admission						
Venous thromboembolism, no. (%)	6 (26.1)	38 (27.5)	1.000	10 (27.0)	34 (27.4)	1.000
Required ICU stay, no. (%)	5 (21.7)	70 (50.7)	**0.019**	13 (35.1)	62 (50.0)	0.161
Mechanical ventilation, no. (%)	4 (17.4)	67 (48.9)	**0.010**	12 (33.3)	59 (47.6)	0.185
Laboratory values at discharge[5]						
White blood cell count (10^9/L), median (SD)	6.14 (2.34)	6.89 (2.34)	0.497	6.57 (2.54)	6.88 (2.31)	0.707

Table 1 (continued)

	Short term (2 months)			Long term (12 months)		
	Readmission and/or mortality ($n=23$)	No readmission and/or mortality ($n=138$)	*P* value	Readmission and mortality ($n=37$)	No readmission and/or mortality ($n=124$)	*P* value
Lymphocytes (10^9/L), median [IQR]	0.68 [0.61, 0.70]	1.33 [1.07, 1.94]	**0.007**	0.70 [0.66, 1.45]	1.33 [1.07, 1.94]	0.103
Neutrophils (10^9/L), median [IQR]	3.96 [3.18, 4.99]	4.35 [3.00, 5.36]	0.760	4.90 [3.18, 5.72]	4.19 [3.00, 5.26]	0.734
Platelets (10^9/L), median [IQR]	202.00 [157.00, 204.00]	387.00 [272.00, 429.00]	**0.002**	215.50 [169.00, 349.50]	389.50 [272.75, 425.25]	**0.031**
C-reactive protein (mg/L), median [IQR]	61.25 [45.35, 80.78]	36.10 [17.30, 61.70]	0.225	46.50 [28.22, 80.78]	36.10 [17.30, 61.70]	0.473
LDH (U/L), median [IQR]	328.50 [296.75, 358.00]	282.50 [231.75, 363.50]	0.447	290.00 [249.50, 328.50]	287.00 [232.50, 368.50]	0.963
D-dimer (mg/L), median [IQR]	1.47 [1.18, 1.76]	2.40 [1.38, 4.16]	0.243	2.27 [2.05, 3.12]	2.22 [1.33, 4.07]	0.979

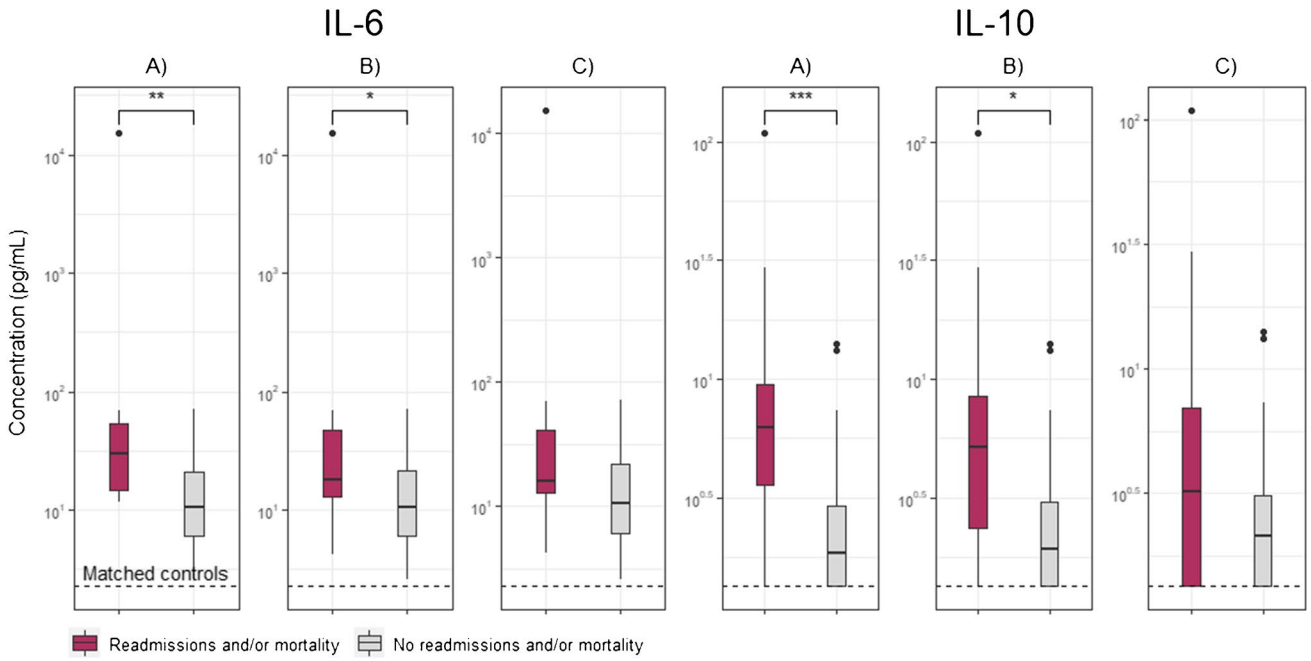
Significant values are shown in bold

Abbreviations: *BMI* body mass index, *ICU* intensive care unit, *LDH* lactate dehydrogenase, *MEWS* modified early warning score, *n* number, *qSOFA* quick sequential organ failure assessment

[1]Comorbidities include chronic cardiac disease, hypertension, chronic pulmonary disease, asthma, chronic kidney disease, liver disease, chronic neurologic disease, malignancy, chronic hematologic disease, HIV or aids, diabetes, rheumatic disorder, auto-immune disease, and dementia

[2–5]Percentage of missing values: [2] 44%, [3] 28%, [4] 14%, [5] between 51 and 64%

[6]One of the seven Halm's criteria (the ability to maintain oral intake) was not record



Panel A) the first month, panel B) 2 months and panel C) 12 months after discharge.
Abbreviations: IL, interleukin.
Matched controls: 26 age and gender matched controls from the outpatients clinic.
* represents a *p* value of <0.05, ** represents a *p* value of <0.01 and *** represents a *p* value of <0.001.

Fig. 1 Concentration interleukin-6 and interleukin-10 at hospital discharge, stratified for readmission and/or mortality

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Marleen A. Slim, Brent Appelman, and Lonneke A. van Vught. The first draft of the manuscript was written by Marleen A. Slim, W. Joost Wiersinga, and Lonneke A. van Vught, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare no competing interests.

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