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Research Article

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Courses of inflammation and infection markers differ in ICU patients with severe COVID-19 under Casirivimab and/or Tocilizumab application: An Observational Study

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Abstract

Background: The outcome and longitudinal course of inflammation and infection markers were unknown in COVID-19 patients on the ICU treated without (N) or with SARS-CoV-2 specific monoclonal antibodies (casirivimab / imdevimab, C) or antibodies against interleukin-6 (IL-6) receptors (tocilizumab, T), solely, or in combination of both (C + T).

Methods: In a retrospective observational study, in critically ill N, C, T, C + T COVID-19 patients admitted to the ICU with the CoV-2 delta-variant between August 2021 and February 2022, 28-day mortality and 30-day time course of infection and inflammation markers were evaluated.

Results: Out of 95 patients with COVID-19, 29 patients were not treated (N), 17 with C, 16 with T, 33 with C + T. Mortality rates in N, C, T, and C + T, were 24%, 35%, 56%, and 24%, being higher in T compared to N and C + T ($p = 0.05$). Prolonged leukocyte, procalcitonin (PCT), C-reactive protein (CRP) and interleukin 6 (IL-6) elevations were detected in nonsurvivors compared to survivors in C + T within the first two weeks, IL-6 in the first days in T. In N, higher PCT, CRP, IL-6 and ferritin occured in nonsurvivors in the first days.

Conclusion: Sporadically measured IL-6 and CRP in T is less useful. Longlasting IL-6 receptor blockade may be deleterious in COVID-19. High IL-6 may hint at poor prognosis within the first days in T, leukocytes, PCT, CRP and IL-6 in the first two weeks in C + T, and PCT, CRP, IL-6 and ferritin within the first days in N.

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Keywords: Antibodies, Monoclonal; Casirivimab; COVID-19; Critical illness; Ferritin; Interleukin-6 inhibitors; Mortality; Procalcitonin; Spike Glycoprotein; Tocilizumab

Background

COVID-19 is a biphasic disease with viral replication and a high viral load in the initial phase overlapping after 5 -7 days with a following overwhelming hyperinflammatory phase with immune mediated damage in severe cases [1]. In the initial phase, SARS-CoV-2 specific monoclonal antibodies (casirivimab and imdevimab) have been adviced in guidelines for IgG-seronegative patients with COVID-19 to reduce viral load [2,3]. In the hyperinflammatory phase, a humanized anti-human IL-6 receptor (IL-6R) antibody (tocilizumab) has been recommended in rapid progressive disease [2-4].

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The longitudinal course of leucocyte counts, procalcitonin (PCT), C-reactive protein (CRP) and IL-6 has been monitored in 16 COVID-19 patients treated with tocilizumab [5]. Under tocilizumab, IL-6 serum concentrations peaked around day 3-5 and stayed elevated for many days. IL-6R blockade led to a sustained suppression of CRP for approximately 14 days rendering its clinical use as a biomarker of infection useless ("CRP-blind spot"). Leukocyte count and PCT were rather unaffected by tocilizumab. No differences between survivors and nonsurvivors were detected. The authors stated that the relevance of these phenomena has still not been elucidated in COVID-19 and should be seen in an individual context. Increased infection risk has been reported during blockade of IL-6R with bacterial, viral and opportunistic infections [6].

Between August 2021 and February 2022, critically ill COVID-19 patients admitted to the ICU of the Clinic for Anaesthesiology and Intensive Care Medicine at the University of Ulm with the CoV-2 delta variant have been treated without or with casirivimab / imdevimab and / or tocilizumab solely or in combination, as adviced by the COVID-19 guidelines at that time. However, outcome and course of infection and inflammation parameters during the ICU stay were unclear under treatment with casirivimab / imdevimab and / or tocilizumab solely or in combination. Therefore, the present retrospective, observational study was performed to find out how many critically ill COVID-19 patients were treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Moreover, the present study should clarify the length of stay on the ICU, outcome and longitudinal course of infection and inflammation parameters in these four groups, and whether there are differences in survivors and nonsurvivors. We focus on the time course of leukocyte counts, PCT, CRP, IL-6 and ferritin serum concentrations during the ICU stay.

We hypothesized that mortality would increase from patients without indication for C or T, over those with C, T up to C + T. It was expected that under application of C, infection and inflammation markers would be lower over time than in T and C + T. In patients with T, high serum concentrations of IL-6 and low ones of CRP over time were expected, and probably higher infection markers. Moreover, higher infection and inflammation markers were expected in nonsurvivors compared to survivors in the four groups.

Methods

Study subjects

In a retrospective observational study, critically ill COVID-19 patients admitted to the ICU with the CoV-2 delta-variant between august 2021 and february 2022 were evaluated (ethics application nr. 129/22 of the ethics commssion of the university Ulm; NCT 06233357).

IgG seronegative SARS-CoV-2 spike antibody (< 0,80 U/ml) COVID-19 patients were treated with one dose of subcutaneous casirivimab and imdevimab, 1200 mg (600 mg of each). Patients with CRP > 75 mg/l or IL-6 > 75 ng/l were treated with one dose of intravenous tocilizumab 8 mg/kg body weight.

Study specific assessments

Due to the National Institute of Allergy and Infectious Diseases (NIAID) and WHO ordinal scale (7), patients with SARS-CoV-2 infection and COVID-19 disease are classified to suffer from critical illness and have respiratory failure, septic shock, and/or multiple organ dysfunction. With WHO ordinal scale 4, patients are hospitalized and receive oxygen by mask or nasal canula, with 5 need non-invasive ventilation or high-flow oxygen, with 6 intubation and mechanical ventilation, with 7 ventilation and additional organ support, such as vasopressors, renal replacement therapy or extracorporal membrane oxygenation (ECMO), and 8 represents death. These stages were associated with high risks of overwhelming health care systems and mortality [8,9].

28-day mortality and 30-day time course of routine laboratory data, i.e., leukocyte counts and serum concentrations of CRP, PCT, IL-6 and ferritin in four patient groups, i. e., N, C, T, C+T, were evaluated. Missing data were not replaced.

Statistical analyses

Comparisons of parameters are presented as box-plots with median values, 25%-percentiles and 75%-percentiles, minimal and maximal values. For the comparison of frequencies between the N, C, T and C + T groups, contingency tables with 95% confidence intervals (95% CI) are given. Mann-Whitney test was used for comparisons of independent unpaired values. For the comparison of frequencies between the four groups, Fisher's exact test with contingency tables with 95% CI for odds ratios are given. p-values below 0.05 were considered statistically significant.

Results

Clinical effects

In total, 102 COVID-19 patients were admitted to the ICU. In seven patients, laboratory data were available for one day, only. Thus, 95 patients remained for evaluation. Out of these 95 patients, 29 patients were not treated with C and/or T (N), 17 with C, 16 with T, 33 with C + T. Patient baseline characteristics and risk factors or the four patient groups are summarized in table 1. Length of stay on the ICU in N, C, T, and C + T, was in median 6, 5, 7 and 15 days, respectively (Table 2). Mortality rates in N, C, T, and C + T, were 24%, 35%, 56%, and 24%, respectively.

Four-times higher odds ratios for mortality were detected in the T group than in the N as well as the C + T group (Table 3).

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Table 1: Patient baseline characteristics and risk factors

Baseline parameter	**Median (range) or n/N (%)**			
	Casirivimab	**Tocilizumab**	**Casirivimab + Tocilizumab**	**Without Casirivimab / Tocilizumab**
n =	**17**	**16**	**33**	**29**
Age	56 (24 – 87)	56 (38 – 82)	55 (26 – 82)	58 (27 – 84)
Gender				
female	9 (53%)	5 (31%)	16 (48%)	9 (31%)
male	8 (47%)	11 (69%)	17 (52%)	20 (69%)
BMI	29 (21 – 47)	28 (24 – 52)	30 (18 – 58)	26 (16 – 49)
Blood group				
A	10 (59%)	7 (44%)	11 (33%)	13 (45%)
B	0 (0%)	4 (25%)	6 (18%)	2 (7%)
AB	0 (0%)	1 (6%)	0 (0%)	0 (0%)
O	5 (29%)	3 (19%)	10 (30%)	9 (31%)
n. a.	2 (12%)	1 (6%)	6 (18%)	5 (17%)
Comorbidities				
Arterial hypertension	6 (35%)	8 (50%)	9 (27%)	13 (45%)
Cardiovascular disease	3 (18%)	3 (19%)	5 (15%)	10 (34%)
Diabetes mellitus	5 (29%)	4 (25%)	5 (15%)	6 (21%)
Hyperlipoproteinemia	2 (12%)	1 (6%)	4 (12%)	3 (10%)
COPD/Asthma bronchiale	2 (12%)	3 (19%)	5 (15%)	2 (7%)
Chronic inflammatory bowel disease	1 (6%)	0 (0%)	0 (0%)	3 (10%)
Metabolic Syndrome	10 (59%)	11 (69%)	15 (45%)	12 (41%)
Arthritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SARS-CoV-2 ct-value day 0	23 (14 – 26)	24 (17 – 38)	22 (16 – 29)	22 (15 – 36)
Spike antibody	10.8 (<0.4 -11,189.0)	172 (3.5 – 25,000.0)	4.3 (<0.4 – 54.7)	155 (<0.4 - >25,000.0)
SARS-CoV-2 vaccinated				
Yes	4 (24%)	7 (44%)	5 (15%)	8 (28%)
No	11 (65%)	8 (50%)	25 (76%)	15 (52%)
Not applicable	2 (12%)	1 (6%)	3 (9%)	6 (21%)
Days of symptoms	5 (0 – 11)	12 (1 – 28)	7 (0 – 13)	9 (0 – 29)
Severity of disease				
SAPSII	34 (6 – 43)	32 (18 – 57)	29 (13 – 52)	32 (14 – 64)
WHO scale initial / maximal				
n.a.	0 / 0	0 / 0	1 / 1	0 / 0
	(0% / 0%)	(0% / 0%)	(3% / 3%)	(0% / 0%)
3	0 / 0	1 / 0	0 / 0	4 / 3
	(0% / 0%)	(6% / 0%)	(0% / 0%)	(14% / 10%)
4	13 / 3	9 / 0	23 / 2	18 / 5
	(76% / 18%)	(56% / 0%)	(70% / 6%)	(62% / 17%)
5	4 / 5	5 / 2	8 / 10	6 / 7
	(24% / 29%)	(31% / 13%)	(24% / 30%)	(21% / 24%)
6	0 / 0	0 / 2	1 / 6	1 / 3
	(0% / 0%)	(0% / 13%)	(3% / 18%)	(3% / 10%)

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7	0 / 3	1 / 3	0 / 6	0 / 4
	(0% / 18%)	(6% / 19%)	(0% / 18%)	(0% / 14%)
8	0 / 6	0 / 9	0 / 6	0 / 7
	(0% / 35%)	(0% / 56%)	(0% / 24%)	(0% / 24%)
Complications				
Thrombosis	0 (0%)	1 (6%)	0 (0%)	3 (10%)
Bleedings	1 (6%)	4 (25%)	4 (12%)	5 (17%)
Bacterial superinfection	8 (47%)	13 (81%)	19 (58%)	17 (59%)
Bacteremia	2 (12%)	7 (44%)	7 (21%)	8 (28%)
Viral superinfection / reactivation	1 (6%)	2 (13%)	2 (6%)	6 (21%)
Fungal superinfection	4 (24%)	7 (44%)	11 (33%)	5 (17%)
Fungemia	1 (6%)	0 (0%)	1 (3%)	0 (0%)
Therapy				
Dexamethason	16 (94%)	14 (88%)	31 (94%)	23 (79%)
Remdesivir	13 (76%)	6 (38%)	26 (79%)	10 (34%)
Catecholamines	5 (29%)	9 (56%)	12 (36%)	8 (28%)
Renal replacement	0 (0%)	3 (19%)	1 (3%)	2 (7%)
ECMO	0 (0%)	6 (38%)	6 (18%)	8 (28%)
ICU length of stay	5 (1 – 22)	15 (1 – 57)	7 (1 – 45)	6 (0 – 55)
Outcome				
Survivors	11 (65%)	7 (44%)	25 (75%)	22 (76%)
Nonsurvivors	6 (35%)	9 (56%)	8 (24%)	7 (24%)

BMI body mass index, COPD chronic obstructive pulmonary disease, ct cycle threshold, ECMO extracorporal membrane oxygenation, ICU intensive care unit, n number, N percentage of patients within the respective group, SAPSII Simplified Acute Physiology Score II, SARS-CoV-2 severe acute respiratory syndrome coronavirus type 2, WHO World Health Organization

Table 2: Length of stay in COVID-19 patients without or with casirivimab / imdevimab and / or tocilizumab

	1 LOS Median (min – max)	2 LOS Median (min – max)	p
1 Casirivimab vs. 2 Tocilizumab	**5 (1 – 22)**	**15 (1 – 57)**	**0.007**
1 Casirivimab vs. 2 Casirivimab + Tocilizumab	5 (1 – 22)	7 (1 – 45)	0.156
1 Casirivimab vs. 2 no Casirivimab no Tocilizumab	5 (1 – 22)	6 (0 – 55)	0.250
1 Tocilizumab vs. 2 Casirivimab + Tocilizumab	15 (1 – 57)	7 (1 – 45)	0.077
1 Tocilizumab vs. 2 no Casirivimab no Tocilizumab	15 (1 – 57)	6 (0 – 55)	0.122
1 Casirivimab + Tocilizumab vs. 2 no Casirivimab no Tocilizumab	7 (1 – 45)	6 (0 – 55)	0.992

LOS length of stay, min minimum, max, maximum. Bold numbers highlight marked differences between groups. Mann-Whitney test. $p < 0.05$

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Table 3: Frequencies of casirivimab / imdevimab or tocilizumab treated COVID-19 patients regarding the endpoint mortality

Treatment group	Frequencies							
	Survivors	Nonsurvivors	Total	Fisher's exact test				
	n (%)	n (%)	n	p	OR	95%CI	Reciprocal OR	95%CI
N	22 (76%)	7 (24%)	29	0.505	1.71	0.50 - 6.90	0.58	0.15 - 2.00
C	11 (65%)	6 (35%)	17					
n	33	13	46					
N	22 (76%)	7 (24%)	29	**0.051**	**4.04**	**1.13 - 12.97**	0.25	0.08 - 0.88
T	7 (44%)	**9 (56%)**	16					
n	29	16	45					
N	22 (76%)	7 (24%)	29	>0.999	1.01	0.34 - 3.11	0.99	0.32 -2.9
C + T	25 (76%)	8 (24%)	33					
n	47	15	62					
C	11 (65%)	6 (35%)	17	0.303	2.36	0.55 - 9.30	0.42	0.11 - 1.86
T	7 (44%)	9 (56%)	16					
n	18	15	33					
C	11 (65%)	6 (35%)	17	0.511	0.59	0.16 - 1.99	1.71	0.50 -6.12
C + T	25 (76%)	8 (24%)	33					
n	37	14	51					
C + T	25 (76%)	8 (24%)	33	**0.053**	**4.02**	**1.19 - 12.98**	0.25	0.08 - 0.84
T	7 (44%)	**9 (56%)**	16					
n	32	17	59					

Absolute (n) and relative (%) mortality frequencies are presented. Bold numbers highlight marked differences between groups. C Casirivimab, T Tocilizumab, C + T Casirivimab + Tocilizumab, N Without Casirivimab / Tocilizumab, n numbers, OR, odds ratio, 95%CI, 95% confidence interval

Effects on inflammation and infection markers

Comparison of the four patient groups

Compared to day 0, leukocytes were increased up to 30 days in C and C + T, in contrast to T and N (Table 4, Figure 1, 3). No differences compared to day 0 were detected in the C, T and C + T groups, lower values in N in the third week regarding PCT (Table 4, Figures 1,4). CRP values were lower than day 0 in N, and profoundly lower in T and C + T up to 30 days (Table 4, Figures 1,5). IL-6 serum concentrations compared to day 0 did not differ in C, were higher in C + T within the first two weeks and, lower in T and N from the third week onwards, especially in nonsurvivors (Table 4, Figures 2,6). Regarding ferritin, no differences compared to day 0 were detected in C and C + T, and lower values from the third and fourth week onwards in N and T, especially in nonsurvivors (Table 4, Figures 2,7).

Comparison of survivors and nonsurvivors in the four patient groups

Regarding leukocytes, no differences between survivors and nonsurvivors were detected in the C, T, and N group (Figure 3). Leukocyte counts were lower in survivors than in nonsurvivors from day 8 to 10 in the C + T group.

PCT serum concentrations did not differ between survivors and nonsurvivors in the C and T group, and were lower in survivors than in nonsurvivors from day 2 to 10 in the C + T group, and from day 1 to 5 in the N group (Figure 4).

CRP serum concentrations did not differ between survivors and nonsurvivors in the C and T group, and were lower in survivors than in nonsurvivors from day 5 to 9 in the C + T group, and from day 1 to 4 in the N group (Figure 5).

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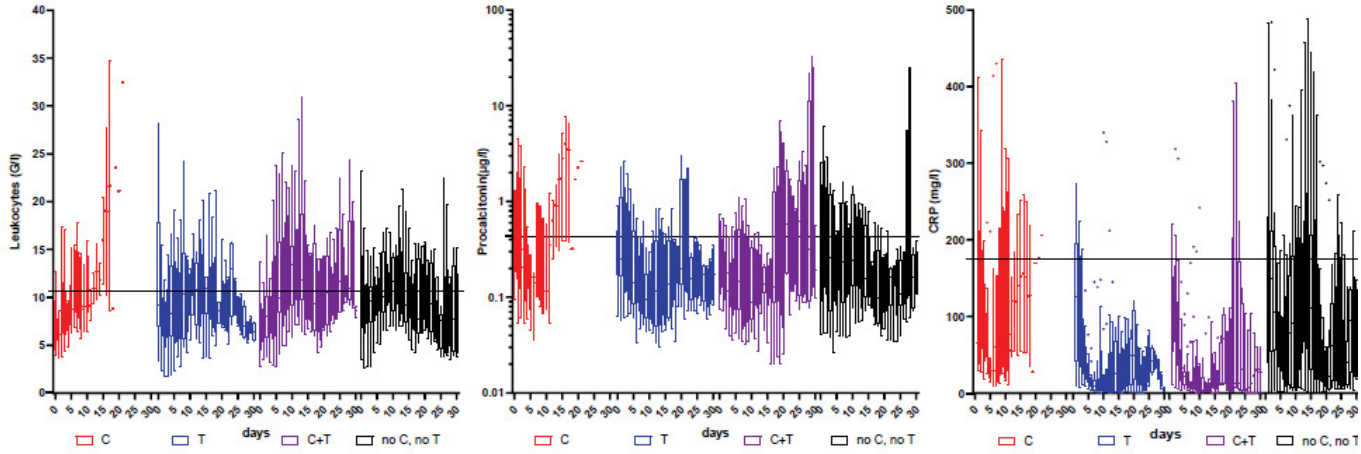

Figure 1: Time course of leukocytes, procalcitonin and CRP serum concentrations in COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Note that procalcitonin values are given on a logarithmic scale. Black line denotes median value of the respective parameter of the N patients on day 0

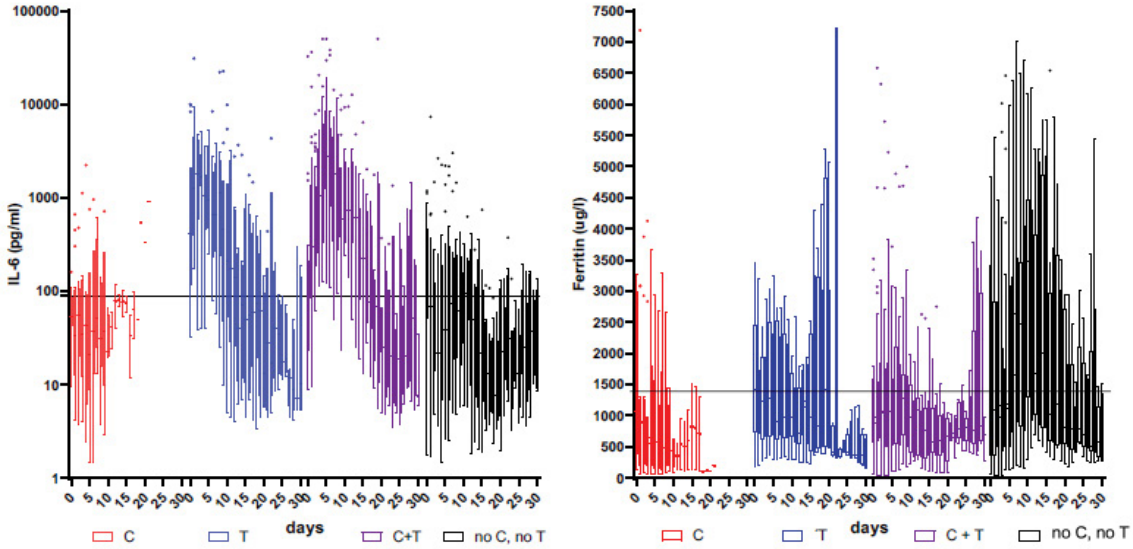

Figure 2: Time course of interleukin 6 (IL-6) and ferritin serum concentrations in COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Note that interleukin 6 values are given on a logarithmic scale. The black line denotes the median value of the respective parameter of the N patients on day 0

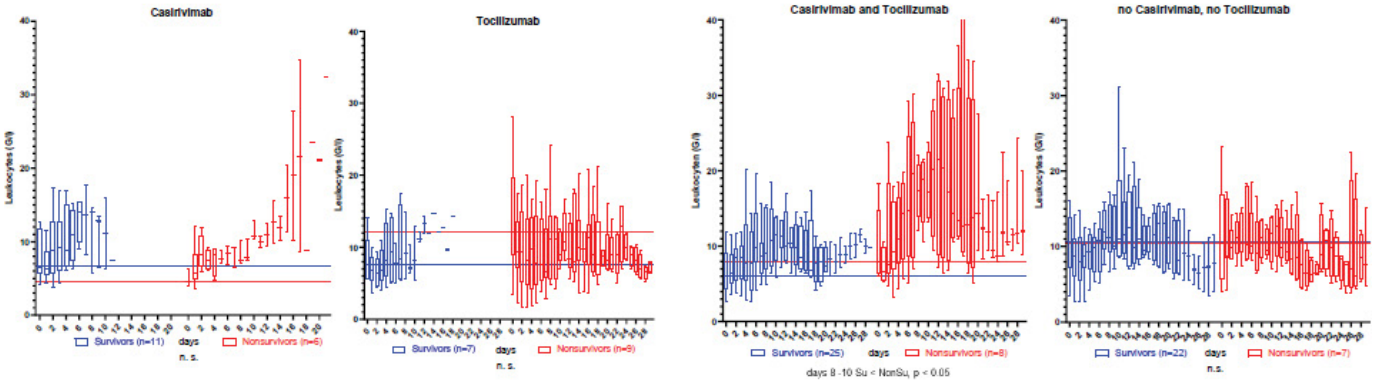

Figure 3: Time course of leukocytes in survivors and nonsurvivors of COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Comparison of days 1 – 30 with day 0. The blue line represents the median value of the survivors and the red line of the nonsurvivors at day 0. Mann-Whitney U-test for comparison of survivors and nonsurvivors, n. s.: not significant, Su: survivors, NonSu: nonsurvivors, *p < 0.05

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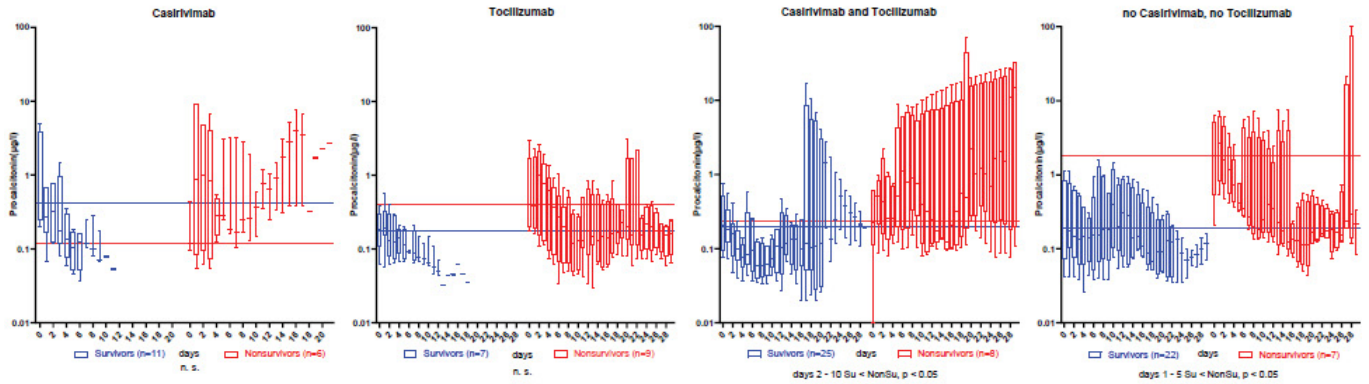

Figure 4: Time course of procalcitonin (PCT) serum concentrations in survivors and nonsurvivors of COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Comparison of days 1 – 30 with day 0. The blue line represents the median value of the survivors and the red line of the nonsurvivors at day 0. Note that procalcitonin values are given on a logarithmic scale. Mann-Whitney U-test for comparison of survivors and nonsurvivors, n. s.: not significant, Su: survivors, NonSu: nonsurvivors, *p < 0.05

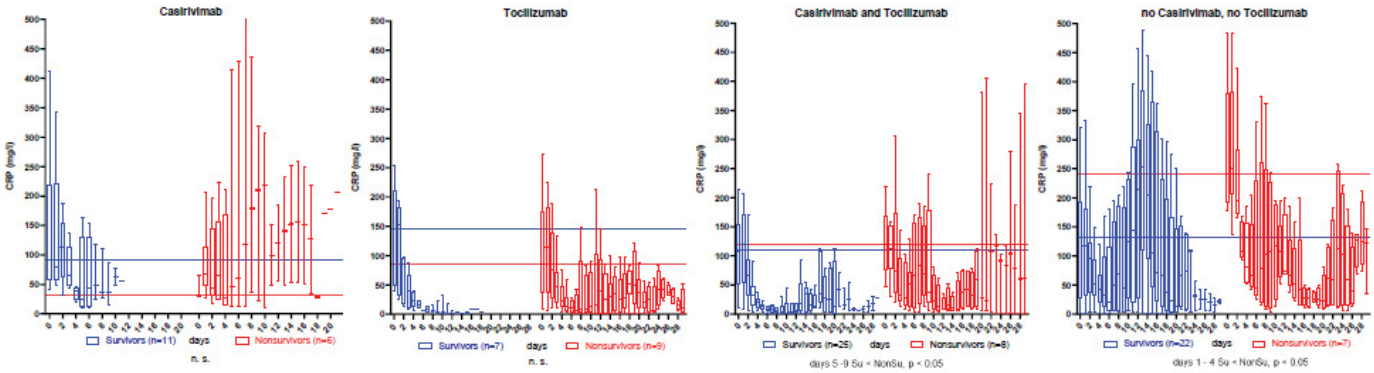

Figure 5: Time course of C-reactive protein (CRP) serum concentrations in survivors and nonsurvivors of COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Comparison of days 1 – 30 with day 0. The blue line represents the median value of the survivors and the red line of the nonsurvivors at day 0. Mann-Whitney U-test for comparison of survivors and nonsurvivors, n. s.: not significant, Su: survivors, NonSu: nonsurvivors, *p < 0.05.

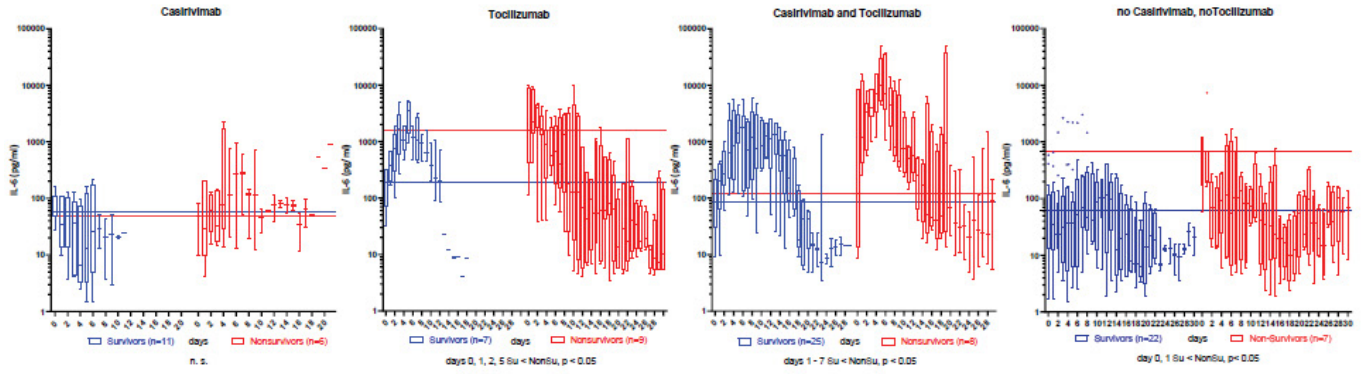

Figure 6: Time course of interleukin 6 (IL-6) serum concentrations in survivors and nonsurvivors of COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Comparison of days 1 – 30 with day 0. The blue line represents the median value of the survivors and the red line of the nonsurvivors at day 0. Note that IL-6 values are given on a logarithmic scale. Mann-Whitney U-test for comparison of survivors and nonsurviviors, n. s.: not significant, Su: survivors, NonSu: nonsurvivors, *p < 0.05.

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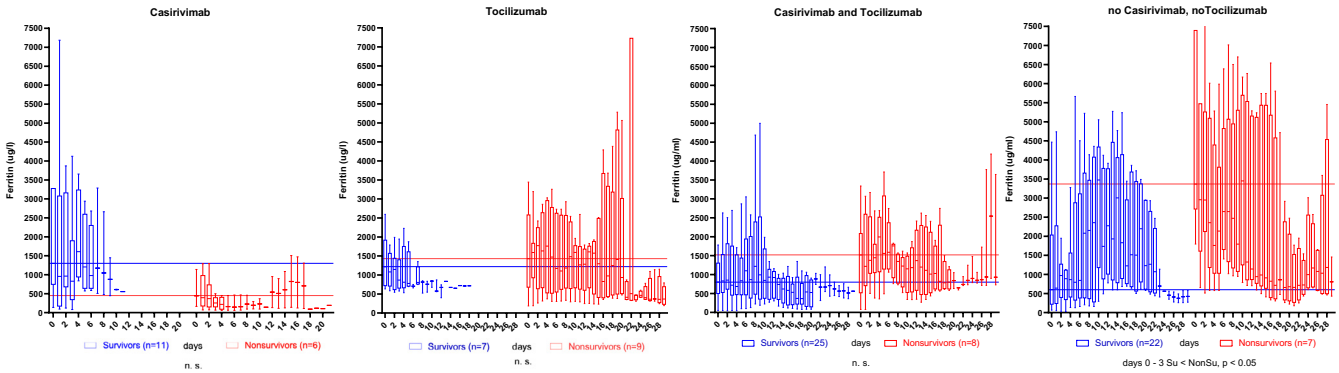

Figure 7: Time course of ferritin serum concentrations in survivors and nonsurvivors of COVID-19 patients treated without (N) or with casirivimab / imdevimab (C) or tocilizumab (T), solely, or in combination of both (C + T). Comparison of days 1 – 30 with day 0. The blue line represents the median value of the survivors and the red line of the nonsurvivors at day 0. Mann-Whitney U-test for comparison of survivors and nonsurvivors, n. s.: not significant, Su: survivors, NonSu: nonsurvivors, *p < 0.05

Table 4: Time-course of infection and inflammation parameters in COVID-19 patients without/with casirivimab/imdevimab and/or tocilizumab

Intervention	Patients	Comparison day 0 vs. days 1 – 30 (↓, ↑, p < 0.05)				
		Leukocytes	PCT	CRP	IL-6	Ferritin
Casirivimab	All	↑6-7 ↑13-17 ↑20-22	0	0	0	0
	Survivors	0	0	↓4-5	0	0
	Nonsurvivors	↑10-17 ↑20-22	0	0	0	0
Tocilizumab	All	↓28-30	0	↓4-17 ↓21-23 ↓28-30	↓13-30	↓23-26 ↓28-30
	Survivors	0	0	0	0	0
	Nonsurvivors	↓27-30	0	↓5-11 ↓14-15 ↓21-23 ↓28-30	↓12-30	↓25-26 ↓28-30
Casirivimab + Tocilizumab	All	↑6-16 ↑25-28	0	↓3-16 ↓18-20 ↓22-28	↑**1-13**	0
	Survivors	↑8-14	0	↓3-16 ↓18-20 ↓24-27	↑**2-13**	0
	Nonsurvivors	↑8-11	0	↓10-15	↑**2-17**	↓21
No Casirivimab Tocilizumab	All	↓25	↓16-23	↓3-6 ↓17-20 ↓25-26	↓16-20 ↓23-25	0
	Survivors	0	0	0	0	0
	Nonsurvivors	0	↓16-26 ↓29-30	↓4-10 ↓13-16	↓12-21 ↓23-25	↓16-17 ↓19-23 ↓26-27 ↓29-30

Comparison of the time-course of infection and inflammation parameters in COVID-19 patients without or with casirivimab / imdevimab and / or tocilizumab. ↓ values day 1 – 30 lower than day 0, ↑ values day 1 – 30 higher than day 0. Bold signs and numbers highlight different direction of response compared to other groups

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Table 5: Infection and inflammation parameters over time in COVID-19 survivors and nonsurvivors without/with casirivimab/imdevimab and/or tocilizumab

Parameter	Days with values of survivors < nonsurvivors, p < 0.05			
	Casirivimab	Tocilizumab	Casirivimab + Tocilizumab	No Casirivimab Tocilizumab
Leukocytes			8 - 10	
Procalcitonin, PCT			2 - 10	1 - 5
C-reactive protein, CRP			5 - 9	1 - 4
Interleukin 6, IL-6		0 – 2, 5	1 - 7	0 - 1
Ferritin				0 - 3

Days and time frames are presented in which infection and inflammation parameters in survivors were marekedly lower (p < 0.05) than in nonsurvivors within the four COVID-19 groups.

IL-6 serum concentrations did not differ between survivors and nonsurvivors in the C group, and were lower in survivors than in nonsurvivors on days 0 to 2 and 5 in the T group, and from day 1 to 7 in the C + T group and on day 0 and 1 in the N group (Figure 6).

Ferritin serum concentrations did not differ between survivors and nonsurvivors in the C, T and C + T groups, and were lower in survivors than in nonsurvivors from day 0 to 3 in the N group (Figure 7).

Differences between survivors and nonsurvivors in infection and inflammation parameters over time in COVID-19 patients in the four groups without or with C and / or T are summarized in table 5.

Discussion

The main results of the present study are that there may be high numbers of critically ill COVID-19 patients who need distinct immunomodulatory therapies and will have divergent time course of infection and inflammatory markers and prognosis. The usefulness of IL-6 and CRP in T patients as clinical markers will be limited, if used sporadically and not on a longitudinal basis. Since T patients had the highest mortality rate, longlasting IL-6 receptor blockade may be deleterious in critically ill COVID-19 patients. High IL-6 values within the first days in T patients may hint at poor prognosis. Prolonged leukocyte, PCT, CRP and IL-6 elevations in the first two weeks may depict nonsurvivors in C + T patients. High PCT, CRP, IL-6 and ferritin within the first days may be associated with poor prognosis in N patients.

The hyperinflammatory phase is characterized by an increase in proinflammatory cytokines and mediators, such as IL-2, IL-6, TNF-alpha, G-CSF, CRP and Ferritin [10,11]. IL-6 and ferritin play a major role in the pathophysiology of COVID-19. Regulatory proteins of SARS-CoV-2 use iron. Ferritin is involved in iron dependent defense mechanisms to bacterial and viral infections, reducing iron dependent growth of bacteria and replication of virus. Elevated ferritin levels in diseases with hyperinflammation, such as virus triggered HLH, sepsis or organ failure may hint at the hyperinflammatory phase in COVID-19 [12,13]. In severe COVID-19, ferritin serum concentrations > 300 ug/ml were associated with increased mortality [14]. In addition, persistently high ferritin and IL-6 serum concentrations were detected in dying COVID-19 patients [14]. Also, in the present study, ferritin serum concentrations were markedly higher in nonsurvivors than survivors in N, and IL-6 in T, C + T and N within the first days after admission on the ICU.

Casirivimab / imdevimab, a SARS-CoV-2 specific monoclonal antibody, reduced the duration of symptomatic disease and the duration of a high viral load among outpatient participants who became infected [15]. Casirivimab / imdevimab reduced the risk of hospitalization or death compared with no treatment in patients with mild to moderate COVID-19 in outpatient infusion centers caused by the SARS-Cov-2 Delta variant [16-18]. Additionally, in the present study, critically ill patients treated early with casirivimab, solely, had a low mortality rate, also.

Due to beneficial effects of low dose glucocorticoids (Recovery trial (NCT04381936) [19] on COVID-19 hyperinflammation and getting standard of care in 2020, reducing proinflammatory signaling was expected to save patients' lives [20]. In this context, IL-6 receptor blockade with tocilizumab and sarilumab including glucocorticoids in the majority of patients (>80%) revealed beneficial effects regarding respiratory and cardiovascular organ support-free days, and improved survival in patients requiring organ support, i. e. high-flow nasal cannulae, noninvasive and invasive ventilation and / or any vasopressors or inotropes within 24 hours after starting organ support in the ICU [21]. In hospitalised COVID-19 patients with 82% receiving systemic corticosteroids with hypoxia and systemic inflammation (CRP > 75 mg/l), tocilizumab improved survival and other clinical outcomes such as discharge from hospital, regardless of the amount of respiratory support, and effects were additional to the benefits of systemic corticosteroids [22]. In a metaanalysis with 27 trials, IL-6 antagonists were associated with lower 28-day all-cause mortality and no difference in secondary infections [23]. On the other hand, in less severely

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ill patients, IL-6 blockade did not prove benefit in intubation rate, extracorporeal membrane oxygenation or death in several trials using IL-6 blockade [23-29]. Moreover, in the interpretation of IL-6, the dual effect as proinflammatory as well as anti-inflammatory cytokine has to be considered. In hyperinflammation in COVID-19, proinflammatory effects are assumed to be mediated via soluble IL-6 receptors [30-32]. Thus, a decrease of IL-6 in the hyperinflammatory phase is desirable. Via membrane bound IL-6 receptors, anti-inflammatory and or regenerative functions are mediated, such as proliferation of the intestinal epithelium, inhibition of epithelial apoptosis and metabolic control in the liver [32]. Thus, too pronounced decrease or inhibition of IL-6, or prolonged blockade of IL-6 receptors as with tocilizumab, may be deleterious regarding regeneration and healing. These effects might have contributed to the highest detected mortality rate found in the T group. The present study reassured the previously reported long lasting depression of CRP and IL-6 by tocilizumab [5]. Thus, sporadic analyses of CRP and IL-6 may not be helpful after tocilizumab application. However, longitudinal analyses manifested markedly lower IL-6 in survivors than nonsurvivors within the first days in T, C + T and N, as well as lower CRP within the first days in N and the second week in C +T.

The strengths of the present study are that it reveals insights in a well-defined, critically ill COVID-19 population treated in the initial and hyperinflammatory phase with the delta virus variant of CoV-2. The results may help to design future studies. The detected subgroups of patients might be a basis in future to evaluate results of clinical studies in highly heterogenous patient populations with different baseline risk and design studies in patients with infectious diseases with a hyperinflammation background to increase the number of responders and reduce harm.

One of the limitations to draw conclusions of the present study is the low number of patients within distinct subgroups of survivors and nonsurvivors. Thus, relevant differences may have been missed and significant differences may be overinterpreted. However, the results may be helpful to generate hypotheses. Patients were treated when C, T or C + T was indicated based on guidelines. Since there was no control group within the C, T and C+ T group, in the presented study, natural course of the disease cannot be excluded. However, the different patterns of cytokine decreases and increases reflect the major role of viral replication and IL-6 inhibition in the initial and later phase. Moreover, as demonstrated by the various differences between the four groups with different effects on CRP, IL-6 and ferritin, subgroup specific diagnostics and therapy has to be performed.

We have to keep in mind that monoclonal antibodies (mAb) against SARS-CoV-2 react very specifically, the magnitude of neutralization reduction varied greatly among mAb, and there is evolution of resistance to mAbs by SARS-CoV-2 by epitope single amino acid substitutions in the spike protein [33]. Thus, the results of the present study cannot be generalized to other CoV-2 variants without investigations performed with these CoV-2 strains.

Conclusions

In conclusion, in critically ill COVID-19 patients within the initial and hyperinflammation phase, effects of casirivimab and / or tocilizumab on endpoints mortality, infection and inflammation markers differ.

It is supposed that application of specific monoclonal antibodies against the CoV-2 virus will have beneficial effects in the inital phase lowering viral load and transmission into deleterious hyperinflammation. In the hyperinflammatory phase, we might have to be cautious with long lasting inhibitory effects of IL-6 receptor blockade.

Abbreviations

C: casirivimab / imdevimab; 95% CI: 95% confidence interval; CoV-2: corona virus 2; C + T: casirivimab / imdevimab plus tocilizumab; CRP: C reactive protein; ECMO: extracorporeal membrane oxygenation; IL-6: interleukin 6; IL-6R: interleukin 6 receptor; LOS: length of stay; N: no casirivimab / imdevimab and no tocilizumab; NonSu: nonsurvivors; n. s.: not significant; Su: survivors; PCT: procalcitonin; T: tocilizumab; WHO: World Health Organization.

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Authors' Contributions

MW, NM, AO and KT contributed to the conception and design of the study. AO, NM, KT and MW generated, collected and assembled the data. Data analysis and interpretation: MW and NM analyzed and interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

All data generated or analysed during this study are included in this published article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

Ethics approval has been given by the ethics commssion of the university Ulm, application nr. 129/22; NCT 06233357. Due to the fact, that clinical and laboratory data were gathered in routine care, no additional blood has been drawn, no diagnostic and no intervention in addition had been performed, the ethic's committe waived informed consent.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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