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Association of Inflammatory Biomarkers with Immunosuppression Management and Outcomes in Kidney Transplant Recipients with COVID-19

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ABSTRACT

Background. Kidney transplant recipients with coronavirus disease 2019 (COVID-19) are at increased risk for adverse outcomes, such as acute kidney injury (AKI), intensive care unit (ICU) admission, and death. The association of inflammatory biomarkers with outcomes and the impact of changes in immunosuppression on biomarker levels are unknown.

Methods. We investigated factors associated with a composite of AKI, ICU admission, or death, and whether immunosuppression changes correlated with changes in inflammatory biomarkers and outcomes in kidney transplant recipients with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction.

Results. Of 59 patients, 50% had estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Patients who discontinued calcineurin inhibitors (CNIs) had higher peak high-sensitivity C-reactive protein (hs-CRP) than those who maintained the same dose (median, 344; interquartile range [IQR], 145-374 vs median, 41; IQR, 22-116 mg/L, $P = .03$). Of the patients, 73% were hospitalized, 22% had admissions to the ICU, and 20% died. Of the 56% with AKI, 35% required dialysis. All patients with AKI but without pulmonary manifestations recovered to 10% of baseline creatinine levels. Factors associated with the composite outcome were eGFR <60 mL/min/1.73 m^2 (odds ratio [OR], 5.833; 95% confidence interval [CI], 1.880-18.099; $P = .002$), hs-CRP (OR, 1.011/unit increase; 95% CI, 1.002-1.021; $P = .019$), white blood cell count (OR, 1.173/unit increase; 95% CI, 1.006-1.368; $P = .041$), and decreased or discontinued CNI (OR, 4.286; 95% CI, 1.353-13.572; $P = .013$). eGFR<60 mL/min/1.73 m^2 (OR, 11.176; 95% CI, 1.581-79.001; $P = .016$), and peak hs-CRP (OR, 1.010/unit increase; 95% CI, 1.000-1.020; $P = .049$) remained associated with the composite in the multivariable model.

Conclusions. Kidney transplant recipients with COVID-19 have high rates of ICU admissions, AKI, and death. Those with eGFR<60 mL/min/1.73 m^2 are at highest risk. CNI reduction is associated with higher inflammatory biomarkers, correlating with worse outcomes. More studies are needed to determine if this association should drive clinical management.

COMORBID conditions, such as hypertension, diabetes mellitus, and cardiovascular disease, increase the morbidity and mortality of coronavirus disease 2019 (COVID-19) in the general population. In addition to one or more of these, kidney transplant recipients (KTRs) also harbor a unique set of elements, such as exposure to induction therapies, duration of maintenance immunosuppression, and

Support was provided by training grant 5T32DK007257-38 from the National Institutes of Diabetes and Digestive and Kidney Diseases (MM). S. Susan Hedayati is supported by the Yin Quan-Yuen Distinguished Professorship in Nephrology at the University of Texas Southwestern Medical Center, Dallas, Texas.

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0041-1345/20
https://doi.org/10.1016/j.transproceed.2021.08.002

periods of immunosuppression augmentation, that may increase the risk for complications in the setting of COVID-19 infection. Furthermore, different classes of immunosuppression add a unique layer of complexity to a population already debilitated with concomitant medical conditions.

In KTRs with COVID-19, safety and efficacy of potential therapeutics, acute kidney injury (AKI) incidence and rates of recovery, and cautious, but time-sensitive adjustments of immunosuppression are several areas worth investigation to guide clinical management. Although AKI is an important prognosticator of future chronic kidney disease, there is a paucity of data on rates of AKI in this setting. The existing data are variable, ranging from 20% to 50% in published cohorts [1-5]. Rates of AKIs requiring renal replacement therapy (RRT) show less variability ranging from 11% to 23% [5-7]. However, rates of renal recovery after AKI are not widely reported. In fact, most of published literature to date has been descriptive reports from transplant centers recounting experiences with COVID-19 in KTRs, describing outcomes, and proposing a generalized immunosuppression management plan based on these experiences [1,5-9].

In KTRs with COVID-19, the optimal immunosuppression management is unknown. For example, reduction may halt progression of severe respiratory illness but it may not ameliorate (and may cultivate) the cytokine storm phenomena and increase mortality risk [10,11]. Therapeutic strategies have intuitively employed immunosuppression reduction similar to that in other viral illnesses, specifically cytomegalovirus and polyomavirus [12,13]. Lowering or cessation of antimetabolite has been the mainstay strategy in the majority of viremic states requiring hospitalization. Thus, it is not surprising that a comparable approach was employed by transplant nephrologists at the inception of the pandemic. However, these reports did not sufficiently examine independent risk factors associated with outcomes in KTRs hospitalized with COVID-19, using well-controlled, multivariate models.

Additionally, the independent role of inflammatory biomarkers in outcome prediction or the effects of changes in immunosuppressant regimen on the levels of these biomarkers in the setting of kidney transplantation and COVID-19 are still unclear. To our knowledge, few studies reported that plasma C-reactive protein (CRP) levels are elevated in patients with COVID-19 and may correlate with severity of disease and death [6,14,15]. An observational study from the French Registry of Solid Organ Transplant Recipients described that elevated CRP was associated with severe COVID-19 disease [5] but did not explore association of CRP with outcomes such as AKI. Additionally, to our knowledge, no studies have explored the association of changes in baseline immunosuppression regimen with changes in inflammatory biomarkers or effect on outcomes in kidney transplant patients.

The present study was, therefore, designed to address these knowledge gaps using the following aims:

- Investigate factors associated with a prespecified outcome of AKI, intensive care unit (ICU) admission or death in KTRs with COVID-19 infection;
- Describe how the immunosuppression regimen was modified and what COVID-19 treatments were delivered;
- Determine whether changes made to the immunosuppression regimen correlated with outcome measures and changes in markers of inflammation; and
- Describe time to recovery of AKI at 90 days after COVID-19 infection for those who experienced AKI.

MATERIALS AND METHODS

Study Participants

This analysis used data from the electronic health records at the University of Texas Southwestern Medical Center outpatient clinics, William P. Clements University Hospital, and Parkland Health and Hospital System in Dallas, Texas. All KTRs from the William P. Clements University Hospital and Parkland Health and Hospital System with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test from March 1, 2020 to October 1, 2020 were included. Individuals with nonfunctioning kidney allografts were excluded. The study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Clinical and Laboratory Variables

Demographic variables, past medical history, and medication data were collected at the time of positive SARS-CoV-2 PCR test and throughout the illness using the electronic health records. Laboratory variables, including inflammatory biomarkers if available, were also obtained. Any COVID-19−specific treatments used were evaluated, as well as any changes (discontinuation or dose increase or decrease) to the individual's baseline immunosuppression regimen while infected with COVID-19. To determine differences due to illness severity, participants were grouped by presence or absence of pulmonary manifestations of COVID-19, defined as either requiring any form of supplemental oxygen, mechanical ventilation, or a pulmonary infiltrate noted on chest x-ray. To evaluate the differences due to kidney donor type, patients were grouped by either having a living or deceased donor.

Outcome Measures

Participants were followed prospectively for ≤90 days after the diagnosis of COVID-19. The prespecified primary outcome was defined as a composite of AKI, admission to the ICU, or death. Prespecified secondary outcomes included each component of the composite assessed separately. AKI was defined using Kidney Disease: Improving Global Outcomes clinical practice guidelines. The recovery of AKI, another prespecified secondary outcome measure, was defined as a decrease in the serum creatinine to within 10% of the baseline serum creatinine value within 90 days after a positive SARS-CoV-2 test. Patients who died or were initiated on maintenance dialysis were considered to have not recovered from AKI.

Statistical Analysis

Baseline variables were reported using proportions for categorical variables, means ± standard deviation for continuous variables with a Gaussian distribution, and median (interquartile range [IQR]) for those with a non-Gaussian distribution. Univariate and multivariate logistic

regression models were used to investigate the associations of clinical factors with the outcomes of AKI, ICU admission, or death taken as a composite. Odds ratio (OR) with 95% confidence intervals (CIs) were reported. Variables that were significantly associated with the outcome measure in univariate models ($P < .1$) were included in the multivariable model and the final model was selected using stepwise backward selection method, with an a priori retention $P < .1$. Variables tested included age, race, sex, presence of diabetes mellitus, baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, time since transplantation <1 year, maintenance immunosuppression with an antimetabolite before COVID-19−positive test, insurance status (patients holding no insurance or Medicaid were combined into a group and patients holding Medicare or private medical insurance were combined into another group), high sensitivity C-reactive protein (hs-CRP), white blood cell count (WBC), calcineurin inhibitor (CNI) regimen change, and presence of pulmonary manifestations as described above. Covariates that were retained in the multivariable backward selection model were age, eGFR <60 mL/min/1.73 m^2, peak hs-CRP, peak WBC, decrease or discontinuation of CNI, and COVID-19 pulmonary manifestations.

Adjustments to maintenance immunosuppression regimen, including changes in medications and dosing, were described after COVID-19 diagnosis. In addition, the proportion of patients receiving COVID-19 −specific treatments such as high-dose steroids (IV hydrocortisone, dexamethasone, or methylprednisolone), remdesivir, interleukin 6 inhibitors, convalescent plasma, azithromycin, hydroxychloroquine, anticoagulation, supplemental oxygen, ICU, mechanical ventilation, and vasopressors was described.

The distribution of changes in inflammatory biomarkers (baseline, peak, and final hospitalization values) were described using box plot, medians, IQR, and the correlations with immunosuppression regimen modifications were investigated in 2- and 3-level comparisons. The 2-level comparisons were between no changes in medication vs decreased or discontinued and nonparametric Mann-Whitney U test was performed. The 3-level comparisons were no change in mediation vs decrease in medication vs discontinuation in medication and nonparametric analysis of variance (Kruskal-Wallis test) followed by Dunn's test with P-values adjusted with Holm's method at $\alpha = 0.05$. Sensitivity analyses were done including only patients who had their CNI or antimetabolite changed before the biomarkers being collected.

A separate model was constructed to test the main effects of CNI (no change vs decreased or discontinued) and pulmonary manifestations (present vs absent), plus the interaction term of the 2 variables in the logistic regression model for the composite outcome.

RESULTS

Baseline Characteristics

Fifty-nine patients with functioning kidney allografts who tested positive for SARS-CoV-2 by PCR testing were included in the analysis. The clinical features, baseline characteristics, and laboratory values at the time of diagnosis are outlined in Table 1 based on the presence or absence of pulmonary manifestations. Comparisons based on allograft donor type can be found in Table 2. The mean age of the patients was 50.5 ± 15.4 years. Of the entire cohort, 35, 59.3%, were men, 13, 22%, were black, and 36, 61%, were Hispanic. Forty six, 78%, of the individuals had received a deceased donor transplant. Of the cohort, 29, 50%, had a baseline eGFR <60 mL/min/1.73 m^2, 52, 88.1%, had underlying hypertension, and 33, 55.9%, had diabetes mellitus. At baseline, 55, 93.2%, were being treated with CNI and 48, 81.4%, with an antimetabolite agent. Six of the 59 (10.2%) individuals had been treated for an episode of acute rejection in the 12 months before diagnosis with COVID-19, consisting of IV immunoglobulin, thymoglobulin, rituximab, steroids, and plasmapheresis.

Those with pulmonary manifestations of COVID-19 were older than those without pulmonary manifestations, with a mean age of 53.8 ± 14.7 years vs 44 ±14.3 years ($P = .02$), had more underlying cardiovascular disease (22.2% vs 0%; $P = .02$), and were more likely to have been treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at baseline (40.9% vs 77.8%; $P = .005$) (Table 1). Peak levels of alanine transaminase and aspartate aminotransferase were significantly higher in those with pulmonary manifestations than in those without. Peak plasma levels of hs-CRP (median, 171 mg/L; IQR, 101-350 vs median, 22 mg/L; IQR, 15-101; $P = .005$), as well as initial ferritin levels (median, 258.5 mg/L; IQR, 692-1834.8 vs median, 262 mg/L; IQR, 95-1199; $P = .024$) were also significantly higher in those with pulmonary manifestations (Table 1).

Treatments and Outcomes

COVID-19−related treatments received by participants and outcomes are shown in Table 3. Treatments and outcomes based on allograft donor type are shown in Table 4. There were 31 composite events, including 12 deaths (20.3%), 13 ICU admissions (22%), and 29 experiencing AKI (55.8%) (Table 3). Overall, 43 of 59 (72.9%) patients required hospitalization and of those, 28 (65.1%) met criteria for AKI. Ten of the 28 with AKI (34.5%) required RRT. Of the 29 patients with AKI, 10 died, 1 initiated maintenance hemodialysis, and 1 did not have a serum creatinine at 90-day follow-up. Therefore, follow-up serum creatinine values were available for 28 patients with AKI, and 13 (46.4%) recovered kidney function.

Those with pulmonary manifestations were more likely to be treated with high-dose steroids, remdesivir, anticoagulation, and vasopressors (Table 3). There was a trend toward a higher rate of AKI in patients with pulmonary manifestations vs those without (63%, 22 vs 41%, 7), which was not statistically significant. However, those with no pulmonary manifestations and AKI were more likely to recover renal function (100% vs 29%; $P = .001$).

Immunosuppression Management and Inflammatory Biomarkers

Table 5 outlines changes to participants' baseline immunosuppression regimen during COVID-19 illness, classified by presence or absence of pulmonary manifestations. Immunosuppression changes classified by donor type can be seen in Table 6. Two-level comparisons based on no change to regimen vs dose decreased or medication discontinued can be seen in Table 7. Of those on an antimetabolite-containing regimen, 87.5% (n = 42) had the antimetabolite either discontinued or the dose decreased during COVID-19 illness. Of those on a regimen with a CNI at

Table 1. Baseline Characteristics

Characteristic	All Participants	No pulmonary Manifestations	Pulmonary Manifestations	*P* Value*
Demographic characteristics				
Age, y, mean (SD)	50.5 (15.4) N = 59	44.0 (14.3) n = 22	53.8 (14.7) n = 36	.022
Men	35/59 (59.3)	13/22 (40.9)	21/36 (41.7)	.955
Race				
White	7/59 (11.9)	2/22 (9.1)	5/36 (13.9)	.438
Black	13/59 (22.0)	7/22 (31.8)	6/36 (16.7)	
Other races	39/59 (66.1)	13/22 (59.1)	25/36 (69.4)	
Hispanic ethnicity	36/59 (61.0)	13/22 (59.1)	22/36 (61.1)	.879
Insurance status				
None	4/59 (6.8)	3/22 (13.6)	1/36 (2.8)	.275
Dallas county	21/59 (35.6)	9/22 (40.9)	12/36 (33.3)	
Medicare	21/59 (35.6)	5/22 (22.7)	15/36 (41.7)	
Private (1 mild-condition, 3 severe-condition patients were double counted in Medicare and private)	17/59 (28.8)	6/22 (27.3)	11/36 (30.6)	
Type of transplant				
Deceased donor	46/59 (78.0)	18/22 (81.8)	27/36 (75)	.747
Living donor	13/59 (22.0)	4/22 (18.2)	9/36 (25)	
Time since transplant, medium (IQR), mo	73.1 (41.3-115.7)	66.5 (48.8-98.7)	81.7 (30.5-115.4)	.724
Time since transplant <6 mo	4/59 (6.8)	1/22 (4.5)	3/36 (8.3)	> .99
Multiorgan transplants†	2/59 (3.4)	2/22 (9.1)	0/36 (0)	> .99
Medical comorbidities				
eGFR <60 mL/min/1.73 m^2	29/58 (50)	11/22 (50.0)	18/35 (51.4)	.916
eGFR, mL/min/1.73m^2, median (IQR)	60 (45.8-60.0) N = 58	58 (51.5-60.0) n = 22	60 (41.0-60.0) n = 35	.439
Hypertension	52/59 (88.1)	17/22 (77.3)	34/36 (94.4)	.092
Diabetes mellitus	33/59 (55.9)	11/22 (50.0)	21/36 (58.3)	.536
Cardiovascular disease‡	8/59 (13.6)	0/22 (0)	8/36 (22.2)	.019
Peripheral vascular disease	4/58 (6.9)	0/22 (0)	3/36 (8.6)	.276
Lung disease	2/59 (3.4)	1/22 (4.5)	1/36 (2.87)	> .99
Cancer§	5/59 (8.5)	1/22 (4.5)	3/36 (8.3)	> .99
Smoker	13/59 (22.0)	3/22 (13.6)	10/36 (27.8)	.332
Obesity	28/59 (47.4)	12/22 (54.5)	15/36 (41.7)	.340
ACEI or ARB use	37/58 (63.8)	9/22 (40.9)	28/36 (77.8)	.005
Treatment for rejection in <1 y	6/59 (10.2)	2/22 (9.1)	4/36 (11.1)	> .99
Immunosuppressant medications				
Azathioprine	6/59 (10.2)	2/22 (9.1)	4/36 (11.1)	> .99
MMF	42/59 (71.2)	17/22 (77.3)	25/36 (69.4)	.517
CNI	55/59 (93.2)	21/22 (95.4)	34/36 (94.4)	> .99
Prednisone	57/59 (96.6)	22/22 (100)	34/36 (94.4)	.521
MTOR-I	5/59 (8.5)	2/22 (9.1)	2/36 (5.6)	.630
Belatacept	2/59 (3.4)	0/22 (0)	2/36 (5.6)	.521
Antimetabolite‖	48/59 (81.4)	18/22 (81.8)	30/36 (83.3)	> .99
Laboratory values				
Baseline serum creatinine, mg/dL, median (IQR)	1.2 (1.0-1.6) N = 59	1.2 (1.0-1.5) n = 22	1.2 (0.9-1.7) n = 36	.828
ALT, U/L, median (IQR)	18.0 (13.8-25.0) N = 48	18.0 (13.0-21.0) n = 13	19.0 (15.5-25.0) n = 35	.236
AST, U/L, median (IQR)	27.5 (21.5-39.2) N = 48	22.0 (19.0-26.0) n = 13	30.0 (23.0-40.5) n = 35	.040
Hemoglobin, g/dL, mean (SD)	12.0 (2.1) N = 52	12.4 (1.8) n = 16	11.9 (2.2) n = 36	.366
White blood cell count, X 10^9/L, median (IQR)	6.0 (4.7-8.1) N = 52	6.2 (5.1-8.2) n = 16	5.9 (4.4-7.6) n = 36	.586
Platelet count, median (IQR), X 10^9/L, median (IQR)	177.5 (146.8-226.5) N = 52	203 (154.0-226.5) n = 16	174 (145.2-228.2) n = 36	.537
hs-CRP, mg/L, median (IQR)	74.6 (31.5-116.1) N = 40	22.0 (10-72.6) n = 7	81.0 (52.0-117.0) n = 33	.059

(*continued*)

Table 1 (*Continued*)

Characteristic	All Participants	No pulmonary Manifestations	Pulmonary Manifestations	*P* Value*
Ferritin, ng/mL, median (IQR)	1199.0(519.0-1787.0) N = 41	262 (95-1199) n = 9	1258.5 (692-1834.8) n = 32	.024

Data expressed as n/N (%) unless otherwise noted. Variability in n is based on available information.

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CABG, coronary artery bypass graft; CAD, coronary artery disease; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; MMF, mycophenolate mofetil; PCI, percutaneous coronary intervention; SD, standard deviation.

* *P* value for comparisons between categorical variables: if n <5, Fisher exact test was used; otherwise, Pearson χ^2 test was used. For continuous variables, unpaired *t* test (parametric) was applied to normally distributed data and Mann-Whitney U test (nonparametric) was applied to not normally distributed data.

† One patient had a simultaneous kidney and pancreas transplant; 1 patient had a liver transplant after kidney transplant.

‡ Cardiovascular disease refers to CAD, PCI, and CABG.

§ Includes current or past history.

‖ Antimetabolite includes MMF, azathioprine, and leflunomide.

Table 2. Baseline Characteristics and Laboratory Data During Illness According to Donor Type

Characteristic	All Participants	Living Donor	Deceased Donor	*P* Value*
Demographic characteristics				
Age, y, mean (SD)	50.5/59(15.4)	49.6/13 (15.8)	50/46 (15.4)	.891
Men	35/59 (59.3)	9/13 (69.2)	26/46 (56.5)	.529
Race				
White	7/59 (11.9)	1/13 (7.7)	6/46 (13.0)	.048
Black	13/59 (22.0)	0/13 (0)	13/46 (28.3)	
Other races	39/59 (66.1)	12/13 (92.3)	27/46 (58.7)	
Hispanic ethnicity	36/59 (61.0)	11/13 (84.6)	25/46 (54.3)	.059
Insurance status				
None	4/59 (6.8)	0/13 (0)	4/46 (8.7)	.769
Dallas county	21/59 (35.6)	5/13 (38.5)	16/46 (34.8)	
Medicare	21/59 (35.6)	4/13 (30.8)	17/46 (37)	
Private (1 living donor, 3 deceased donor patients were double counted in Medicare and private)	17/59 (28.8)	5/13 (38.5)	12/46 (26.1)	
Type of transplant				
Deceased donor	46/59 (78.0)			
Living donor	13/59 (22.0)			
Time since transplant, median (IQR), mo	73.1 (41.3-115.7)	89.3 (52.8-107.6)	72.6 (39.7-116.7)	.583
Time since transplant <6 mo	4/59 (6.8)	0/13 (0)	4/46 (8.7)	.566
Multiorgan transplants†	2/59 (3.4)	0/13 (0)	2/46 (4.3)	> .99
Medical comorbidities				
eGFR <60 mL/min/1.73 m^2	29/58 (50)	4/13 (30.8)	25/45 (55.6)	.207
eGFR, mL/min/1.73m^2, median (IQR)	60 (45.8-60.0) N = 58	60 (54.0-60.0) n = 13	56 (45.0-60.0) n = 45	.269
Hypertension	52/59 (88.1)	10/13 (76.9)	42/46 (91.3)	.017
Diabetes mellitus	33/59 (55.9)	7/13 (53.8)	26/46 (56.5)	.864
Cardiovascular disease†	8/59 (13.6)	2/13 (15.4)	6/46 (13.0)	> .99
Peripheral vascular disease	4/58 (6.9)	2/13 (15.4)	2/45 (4.4)	.214
Lung disease	2/59 (3.4)	0/13 (0)	2/46 (4.3)	> .99
Cancer	5/59 (8.5)	0/13 (0)	5/46 (10.9)	.576
Smoker	13/59 (22)	2/13 (15.4)	11/46 (23.9)	.712
Obesity	28/59 (47.4)	4/13 (30.8)	24/46 (52.2)	.218
ACEI or ARB use	37/58 (63.8)	7/13 (53.8)	30/45 (66.7)	.397
Immunosuppressant medications				
Azathioprine	6/59 (10.2)	1/13 (7.7)	5/46 (10.9)	> .99
MMF	42/59 (71.2)	11/13 (84.6)	31/46 (67.4)	.310
CNI	55/59 (93.2)	13/13 (100)	42/46 (91.3)	.566
Prednisone	57/59 (96.6)	12/13 (92.3)	45/46 (97.8)	.395

(*continued*)

Table 2 (*Continued*)

Characteristic	All Participants	Living Donor	Deceased Donor	*P* Value*
MTOR-I	5/59 (8.5)	0/13 (0)	5/46 (10.9)	.576
Belatacept	2/59 (3.4)	0/13 (0)	2/46 (4.3)	> .99
Antimetabolite§	48/59 (81.4)	13/13 (100)	35/46 (76.1)	.100
Laboratory values				
Baseline serum creatinine, mg/dL, median (IQR)	1.2 (1.0-1.6) N = 59	1.0 (0.9-1.3) n = 13	1.0 (1.0-1.7) n = 46	.183
ALT initial, U/L, median (IQR)	18.0 (13.8-25.0) N = 48	21.0 (13.0-31.0) n = 11	18 (14.0-22.0) n = 37	.533
ALT peak, U/L, median (IQR)	29.5 (20.0-63.8) N = 44	56.0 (22.0-88.0) n = 9	29.0 (20.0-52.5) n = 35	.221
AST initial, U/L, median (IQR)	27.5 (21.5-39.2) N = 48	27.0 (19.5-34.0) n = 11	28.0 (22.0-40.0) n = 37	.589
AST peak, U/L, median (IQR)	44.0 (27.0-95.2) N = 44	71.0 (27.0-101.0) n = 9	44.0 (27.5-82.0) n = 35	.705
Hemoglobin, , initial, g/dL,mean (SD),	12.0 (2.1) N = 52	12.1 (1.1) n = 11	12.0 (2.3) n = 41	.871 (t)
Hemoglobin, lowest, g/dL, mean (SD)	9.8 (2.6) N = 44	8.4 (2.3) n = 7	10.0 (2.6) n = 37	.127
White blood cell count, initial, X 10^9/L, median (IQR)	6.0 (4.7-8.1) N = 52	5.2 (4.5-8.1) n = 11	6.0 (4.7-7.7) n = 41	.606
White blood cell count, peak, X 10^9/L, median (IQR)	9.5 (5.9-18.7) N = 43	22.9 (10.4-44.6) n = 7	8.4 (5.7-14.5) n = 36	.103
Platelet count, initial, X 10^9/L, median (IQR)	177.5 (146.8-226.5) N = 52	209.0 (175.0-237.0) n = 11	162.0 (146.0-226.0) n = 41	.282
Platelet count, lowest, X 10^9/L, median (IQR)	144.0 (90.8-186.5) N = 44	105.0 (68.0-177.0) n = 7	146.0 (102.0-188.0) n = 37	.278 (t)
hs-CRP, initial, mg/L, median (IQR)	74.6 (31.5-116.1) N = 40	65.0 (52.0-93.0) n = 9	80.0 (25.0-117.3) n = 31	> .99
hs-CRP, peak, mg/L, median (IQR)	145.0 (80.0-344.0) N = 37	233.0 (142.0-371.0) n = 7	133.0 (69.8-326.2) n = 30	.108
hs-CRP, final, mg/L, median (IQR)	67.0 (22.0-120.0) N = 37	80.0 (34.0-165.5) n = 7	66.0 (22.4-111.5) n = 30	.877
Ferritin, initial, ng/mL, median (IQR)	1199.0(519.0-1787.0) N = 41	1265.0 (716.0-1686.0) n = 9	1136.0 (351.8-1788.2) n = 32	.581
Ferritin, peak, ng/mL, median (IQR)	2559.0 (1125.5-6568.5) N = 23	14188.5 (1969.2-44559.2) n = 4	2559.0 (1125.5-4941.5) n = 19	.351
Ferritin, final, ng/mL, median (IQR)	1804.0(998.5-3198.5) N = 23	1823.0 (1256.8-26723.5) n = 4	1804.0 (908.5-3198.5) n = 19	.656
LDH, initial, U/L, median (IQR)	294.0 (237.2-372.0) N = 28	267.0 (250.0-360.0) n = 5	300.0 (236.0-380.0) n = 23	> .99
LDH, peak, U/L, median (IQR)	423.0(265.5-755.2) N = 20	801.0 (534.0-10400.5) n = 3	412.0 (261.0-553.0) n = 17	.428
D-dimer, initial, mg/L, median (IQR)	0.9 (0.6-1.6) N = 35	0.9 (0.6-0.9) n = 9	1.0 (0.6-1.6) n = 26	.396
D-dimer, peak, mg/L, median (IQR)	1.6 (0.8-6.3) N = 31	1.5 (0.8-4.2) n = 7	1.9 (0.9-6.9) n = 24	.603

Data expressed as n/N (%) unless otherwise noted.

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CABG, coronary artery bypass graft; CAD, coronary artery disease; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; PCI, percutaneous coronary intervention; SD, standard deviation.

* *P* value for comparisons between categorical variables: if n <5, Fisher's exact test was used; otherwise, Pearson χ^2 test was used. For continuous variables, unpaired *t* test (parametric) was applied to normally distributed data and Mann-Whitney U test (nonparametric) was applied to not normally distributed data.

† One patient had a simultaneous kidney and pancreas transplant; 1 patient had a liver transplant after kidney transplant.

‡ Cardiovascular disease refers to CAD, PCI, and CABG.

§ Antimetabolite includes MMF, azathioprine, and leflunomide.

Table 3. COVID-19–Related Treatments and Outcomes Based on COVID Pulmonary Manifestations

Variablen (%)	All Participants, n/N (%)	No pulmonary Manifestations, n/N (%)	Pulmonary Manifestations, n/N (%)	*P* Value*
COVID-19–related treatments				
High-dose steroids†	19/58 (32.8)	0/22 (0)	19/35 (52.8)	< .001
Remdesivir	15/58 (25.9)	0/22 (0)	15/36 (41.7)	< .001
Tocilizumab	2/58 (3.4)	0/22 (0)	2/36 (5.6)	.521
Convalescent plasma	9/58 (15.5)	1/22 (4.5)	8/36 (22.2)	.133
Azithromycin	3/58 (5.2)	1/22 (4.5)	2/36 (5.6)	> .99
Hydroxychloroquine	3/58 (5.2)	1/22 (4.5)	2/36 (5.6)	> .99
Anticoagulation	38/58 (65.5)	8/22 (36.4)	30/36 (83.3)	< .001
Supplemental oxygen	24/58 (41.4)	0/22 (0)	24/36 (66.7)	< .001
Hospitalized	43/59 (72.9)	10/22 (45.4)	33/36 (91.7)	< .001
Mechanical ventilation	12/58 (20.7)	0/22 (0)	12/36 (33.3)	.002
Vasopressors	12/58 (20.7)	0/22 (0)	12/36 (33.3)	.002
Endpoints				
All AKI‡	29/52 (55.8)	7/17 (41.2)	22/35 (62.8)	.140
AKI, hospitalized	28/43 (65.1)	6/10 (60)	22/33 (66.7)	.719
AKI, present on admit (among hospitalized)	23/43 (53.5)	5/10 (50)	18/33 (54.5)	.801
AKI, during admission (among hospitalized)	7/42 (16.7)	1/9 (11.1)	6/33 (18.2)	> .99
AKI requiring RRT (among all AKI)	10/28 (34.5)	1/7 (14.3)	9/22 (40.9)	.367
AKI recovered§ (among all AKI)	13/28 (46.4)	7/7 (100)	6/21 (28.6)	.001
AKI-RRT during hospitalization	10/43 (23.3)	1/10 (10.0)	9/33 (27.3)	.407
Intensive care unit	13/59 (22.0)	1/22 (4.5)	12/36 (33.3)	.011
Death‖	12/59 (20.3)	0/22 (0)	11/36 (30.6)	.004
Composite event¶	31/59 (52.5)	7/22 (31.8)	23/36 (63.9)	.018

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IV, intravenous; POA, present on admission; RRT, renal replacement therapy; SCr, serum creatinine.

* *P* value for comparisons between categorical variables: if n < 5, Fisher's exact test was used; otherwise, Pearson χ^2 test was used.

† High-dose steroids included IV hydrocortisone, IV dexamethasone, and IV methylprednisolone.

‡ Of the 59 patients, 7 did not have SCr values, so AKI could not be ascertained. Two patients had an AKI POA but recovered and subsequently developed another AKI while admitted, 1 patient had an AKI but was not admitted to the hospital.

§ Defined as a decrease in the SCr to within 10% of the baseline SCr value within 90 days after positive severe acute respiratory syndrome coronavirus 2 test. Of the 29 patients with AKI, 10 died, 1 initiated maintenance hemodialysis, and 1 did not have a SCr at 30- or 90-day follow-up and was excluded.

‖ One patient died at home, limited information on manifestations, included in no pulmonary manifestations group.

¶ Experienced AKI, admitted to ICU, or died.

baseline, 60% (n = 33) discontinued or the dose was decreased. Seventy-five percent (n = 42) of patients on maintenance glucocorticoids had these continued and 19.7% (n = 11) had these discontinued or the dose decreased (Table 5). Those with pulmonary manifestations were more likely than those without to have baseline CNI, anti-metabolite, or prednisone dose either discontinued or decreased.

Figure 1 shows comparisons in inflammatory marker levels between patients in whom CNIs were continued at the same dose vs in those where the CNI was stopped or the dose was decreased. Patients who stopped CNI drugs showed significantly higher peak hs-CRP than those who were maintained on the baseline dose (median, 344; IQR, 145-374 mg/L vs median, 41; IQR, 22-116 mg/dL; *P* = .032) (Fig 1B). Initial ferritin levels were also found to be higher in those who had CNI drug decreased or discontinued compared with those who were on the same dose (median, 1271; IQR, 839-1932 vs median, 283; IQR, 124-569 ng/mL; *P* = .0002) (Fig 1C). There was also a significantly higher peak WBC in patients who had their CNI discontinued vs those who were maintained at the same dose (median, 19.1; IQR, 15.2-40.9 vs median, 6.3; IQR, 4.7-8.2 X 10^9/L; *P* = .002) (Fig 1F). The results of the sensitivity analysis performed on only those patients who had CNI dosage adjusted before obtaining inflammatory biomarkers are depicted in Fig 2. Of those patients whose CNI regimen was altered before biomarkers being obtained, the peak CRP was significantly higher if CNI was discontinued or the dose changed compared with those who maintained dosing (median, 206; IQR, 105-375 vs median, 42; IQR, 22-116 mg/L; *P* = .02) (Fig 2A). Results for ferritin and WBC showed the same conclusion as found in the full cohort (Fig 2C-F).

No significant differences in hs-CRP, ferritin, or WBC were found between patients whose antimetabolite medications were maintained vs those whose medications were discontinued or whose dose was changed during COVID-19 illness (Fig 3). These results were confirmed in a sensitivity analysis using only those patients whose regimen was changed before biomarkers being obtained (data not shown). When the delta initial-to-peak change (peak minus initial value) in levels of hs-CRP, WBC, and ferritin were compared by regimen change,

Table 4. COVID-19–Related Treatments and Outcomes Based on Donor Type

Variable, n (%)	All Participants, n/N (%)	Living Donor, n/N (%)	Deceased Donor, n/N (%)	*P* Value*
COVID-19–related treatments				
High-dose steroids	19/58 (32.8)	5/13 (38.5)	14/45 (31.1)	.619
Remdesivir	15/58 (25.9)	4/13 (30.8)	11/45 (24.4)	.724
IL-6 inhibitors	2/58 (3.4)	1/13 (7.7)	1/45 (2.2)	.401
Convalescent plasma	9/58 (15.5)	3/13 (23.1)	6/45 (13.3)	.404
Azithromycin	3/58 (5.2)	1/13 (7.7)	2/45 (4.4)	.540
Hydroxychloroquine	3/58 (5.2)	0/13 (0)	3/45 (6.7)	> .99
Anticoagulation	38/58 (65.5)	7/13 (53.8)	31/45 (68.9)	.315
Supplemental oxygen	24/58 (41.4)	5/13 (38.5)	19/45 (42.2)	.808
Hospitalized	43/59 (72.9)	8/13 (61.5)	35/46 (76.1)	.297
Intensive care unit	13/59 (22)	4/13 (30.8)	9/46 (19.6)	.455
Mechanical ventilation	12/58 (20.7)	4/13 (30.8)	8/45 (17.8)	.437
Vasopressors	12/58 (20.7)	4/13 (30.8)	8/45 (17.8)	.437
Endpoints				
All AKI†	29/52 (55.8)	7/11 (63.6)	22/41 (53.6)	.735
AKI, hospitalized	28/43 (65.1)	7/8 (87.5)	21/35 (60.0)	.226
AKI POA (among hospitalized)	23/43 (53.5)	6/8 (75.0)	17/35 (47.6)	.250
AKI, during admission (among hospitalized)	7/42 (16.7)	2/8 (25.0)	5/34 (14.7)	.601
AKI requiring RRT (among all AKI)	10/28 (34.5)	2/7 (28.6)	8/21 (36.4)	> .99
AKI recovered‡ (among all AKI)	13/28 (46.4)	1/7 (14.3)	12/21 (57.1)	.084
AKI-RRT during hospitalization	10/43 (23.3)	2/8 (25)	8/35 (22.8)	> .99
Death	12/59 (20.3)	3/13 (23.1)	9/46 (19.6)	.716
Composite event§	31/59 (52.5)	7/13 (53.8)	24/46 (52.2)	.915

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; IL, interleukin; POA, present on admission; RRT, renal replacement therapy; SCr, serum creatinine.

* *P* value for comparisons between categorical variables: if n < 5, Fisher's exact test was used; otherwise, Pearson χ^2 test was used.

†Of the 59 total patients, 7 did not have SCr values, so AKI could not be ascertained. Two patients had an AKI POA but recovered and subsequently developed another AKI while admitted; 1 patient had an AKI but was not admitted to the hospital.

‡ Defined as a decrease in the SCr to within 10% of the baseline SCr value within 90 days after positive severe acute respiratory syndrome coronavirus 2 test. Of the 29 patients with AKI, 10 died, 1 initiated maintenance hemodialysis, and 1 did not have a SCr at 30- or 90-day follow-up and was excluded.

§ Experienced AKI, admitted to ICU, or died.

there was a statistically significant delta increase from initial to peak values in CRP and WBC in those who had CNI discontinued or dose changed (Fig 4A, E). There were no significant initial-to-peak delta changes in levels of inflammatory markers between patients whose antimetabolite drug was discontinued or decreased compared with those maintained on the same dose (Fig 4B, D, F).

In participants with no evidence of pulmonary manifestations, no significant differences were found in hs-CRP, ferritin, or WBC based on changes to CNI regimen (Fig 5A, 5C, 5E). In patients with presence of pulmonary manifestations, compared with patients maintained on the same CNI dose, those who had CNI dose decreased or discontinued had significantly higher initial ferritin levels (median, 1347; IQR, 839-1963 vs median, 519; IQR, 303-585 ng/mL; $P = .005$) and peak WBC (median, 13.3; IQR, 6.6-23.3 vs median, 7.5; IQR, 4.4-8.2 X 10^9/L; $P = .04$) (Fig 5D, F).

Factors Associated With the Composite Event

Univarible analyses revealed that eGFR <60 mL/min/1.73 m^2, peak hs-CRP, final hs-CRP, peak WBC, and decreased dose or discontinuation of CNI were significantly associated with the composite event (Table 8). A multivariable backward variable selection model was constructed that included age, eGFR <60 mL/min/1.73 m^2, peak hs-CRP, peak WBC, and decreased or discontinued CNI. In this final model, factors associated with the composite event included eGFR <60 mL/min/1.73 m^2, with an adjusted OR of 11.18 (95% CI, 1.58-79), and peak hs-CRP, with an adjusted OR of 1.01 (95% CI, 1.00-1.02) per unit increase in hs-CRP. The area under the curve of the model was 0.887. The critical value cutoff of hs-CRP associated with an adverse event was 171 mg/L with an area under the curve of 0.79, sensitivity 0.62, specificity 1, positive predictive value 1, negative predictive value 0.52, positive likelihood ratio ∞, negative likelihood ratio 0.39 ($P = .02$). The interaction of CNI (no change vs decreased or discontinued) × pulmonary manifestations (present vs absent) was not statistically significant in the multivariable logistic regression model for the composite outcome ($P = .92$ for interaction term).

DISCUSSION

In this analysis, we observed that mortality among KTRs with COVID-19 was 20% and that most of the infected patients required hospitalization, whereas 22% required admission to the ICU, with 22% requiring mechanical ventilation. More than half (56%) developed an AKI, whereas about 17% developed

Table 5. Immunosuppression Regimen and Modifications by COVID-19 Pulmonary Manifestations

Medication		All Participants, n/N (%)	No Pulmonary Manifestations, n/N (%)	Pulmonary Manifestations, n/N (%)	*P* Value
Azathioprine	No change	1/6 (16.7)	1/2 (50)	0/4 (0)	.067
	Dose increased	0/6 (0)	0/2 (0)	0/4 (0)	
	Dose decreased	1/6 (16.7)	1/2 (50)	0/4 (0)	
	Discontinued	4/6 (66.7)	0/2 (0)	4/4 (100)	
	Not prescribed at baseline	52/58 (89.6)	20/22 (90)	32/36 (88.9)	> .99
MMF	No change	6/42 (14.3)	4/17 (23.5)	2/25 (8)	.009
	Dose increased	0/42 (0)	0/17 (0)	0/25 (0)	
	Dose decreased	14/42 (33.3)	9/17 (52.9)	5/25 (20.0)	
	Discontinued	22/42 (52.4)	4/17 (23.5)	18/25 (72.0)	
	Not prescribed at baseline	16/58 (27.6)	5/22 (22.7)	11/36 (30.6)	.517
CNI	No change	22/55 (40.0)	15/21 (71.4)	7/34 (20.6)	< .001
	Dose increased	0/55 (0)	0/21 (0)	0/34 (0)	
	Dose decreased	22/55 (40.0)	6/21 (28.6)	16/34 (47.0)	
	Discontinued	11/55 (20.0)	0/21 (0)	11/34 (32.4)	
	Not prescribed at baseline	3/58 (5.2)	1/22 (4.5)	2/36 (5.6)	> .99
Prednisone*	No change	42/56 (75)	21/22 (95.4)	21/34 (61.8)	.005
	Dose increased	3/56 (5.4)	0/22 (0)	3/34 (8.9)	
	Dose decreased	2/56 (3.6)	1/22 (4.5)	1/34 (2.9)	
	Discontinued	9/56 (16.1)	0/22 (0)	9/34 (26.5)	
	Not prescribed at baseline	2/58 (3.4)	0/22 (0)	2/36 (5.6)	.521
MTOR-I	No change	2/4 (50)	2/2 (100)	0/2 (0)	.333
	Dose increased	0/4 (0)	0/2 (0)	0/2 (0)	
	Dose decreased	2/4 (50)	0/2 (0)	2/2 (100)	
	Discontinued	0/4 (0)	0/2 (0)	0/2 (0)	
	Not prescribed at baseline	54/58 (93.1)	20/22 (90.0)	34/36 (94.4)	.630
Belatacept	No change	1/2 (50.0)	0/0 (0)	1/2 (50)	> .99
	Dose increased	0/2 (0)	0/0 (0)	0/2 (0)	
	Dose decreased	0/2 (0)	0/0 (0)	0/2 (0)	
	Discontinued	1/2 (50.0)	0/0 (0)	1/2 (50)	
	Not prescribed at baseline	56/58 (96.6)	22/22 (100)	34/36 (94.4)	> .99
Antimetabolite†	No change	6/48 (12.5)	4/18 (22.2)	2/30 (6.7)	< .001
	Dose increased	0/48 (0)	0/18 (0)	0/30 (0)	
	Dose decreased	15/48 (31.2)	10/18 (55.6)	5/30 (16.7)	
	Discontinued	27/48 (56.2)	4/18 (22.2)	23/30 (76.7)	
	Not prescribed at baseline	10/58 (17.2)	4/22 (18.2)	6/36 (16.7)	> .99

CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; MMF, mycophenolate mofetil; MTOR-I, mammalian target of rapamycin inhibitor.

* Prednisone refers to oral prednisone.

† Antimetabolite includes MMF, azathioprine, and leflunomide.

an AKI requiring RRT. All patients with AKI but without pulmonary manifestations recovered renal function to 10% of their baseline at follow-up. Importantly, a baseline eGFR <60 mL/min/1.73 m^2 and peak hs-CRP during hospitalization were independently associated with worse outcomes. To our knowledge, this was the first study to show a possible association between reduction or discontinuation of baseline CNI regimen and an increase in inflammatory biomarkers. Patients with pulmonary manifestations of COVID-19 had a greater increase in inflammatory biomarkers and were more likely to have their immunosuppression regimen changed than those without.

The mortality rate of 1 in 5 KTRs infected with COVID-19 falls in a similar range as that reported by other US transplant centers. Earlier reports, with small number of patients, showed extremely variable mortality rates, ranging from 0% to 60% [2-4,7,9,16,17]. Larger studies have showed mortality rates similar to our findings. Azzi et al. found a death rate of 20.5% in all-comers and 37.8% in those transplant patients who required hospital admission [6]. Two large European studies showed 28-day mortality rates of 19.9% and 22.8%, respectively [5,18]. Many initial studies did not comment on AKI rates among transplant patients, and the rates of AKI requiring RRT are reported in only a handful of studies, with larger cohorts reporting rates lower than ours [5,6]. Given that AKI is an important prognosticator in transplant recipients, we included it as part of the composite outcome. The rate of AKI in the present cohort appears higher than in initial reports involving smaller groups of transplant patients; these earlier findings described rates of AKI ranging from 20% to 50% [4,9,16,17]. This may be due to different ways of defining AKI. Our definition was robust in that we used the Kidney Disease: Improving Global Outcomes guideline standard. Half of our cohort had eGFR <60 mL/min at presentation; underlying chronic kidney disease, especially in a hospitalized setting, is a well-recognized AKI risk factor [19].

There are presently no standardized guidelines for the management of immunosuppression in KTRs with COVID-19;

Table 6. Immunosuppression Regimen and Modifications by Donor Type

Medication		All Participants, n/N (%)	Living Donor, n/N (%)	Deceased Donor, n/N (%)	*P* Value
Azathioprine	No change	1/6 (16.7)	0/1 (0)	1/5 (20)	> .99
	Dose increased	0/6 (0)	0/1 (0)	0/5 (0)	
	Dose decreased	1/6 (16.7)	0/1 (0)	1/5 (20.0)	
	Discontinued	4/6 (66.7)	1/1 (100)	3/5 (60.0)	
	Not prescribed at baseline	53/59 (89.8)	12/13 (92.3)	41/46 (89.1)	> .99
MMF	No change	6/42 (14.3)	3/11 (27.3)	3/31 (9.7)	.247
	Dose increased	0/42 (0)	0/11 (0)	0/31 (0)	
	Dose decreased	14/42 (33.3)	2/11 (18.2)	12/31 (38.7)	
	Discontinued	22/42 (52.4)	6/11 (54.5)	16/31 (51.6)	
	Not prescribed at baseline	17/59 (28.8)	2/13 (4.6)	15/46 (32.6)	.31
CNI	No change	22/55 (40.0)	6/13 (46.2)	16/42 (38.1)	.466
	Dose increased	0/55 (0)	0/13 (0)	0/42 (0)	
	Dose decreased	22/55 (40.0)	6/13 (46.2)	16/42 (38.1)	
	Discontinued	11/55 (20.0)	1/13 (7.7)	10/42 (23.8)	
	Not prescribed at baseline	4/59 (6.8)	0/13 (0)	4/46 (8.7)	.566
Prednisone*	No change	43/57 (75.4)	9/12 (75)	34/45 (75.6)	.415
	Dose increased	3/57 (5.3)	1/12 (8.3)	2/45 (4.4)	
	Dose decreased	2/57 (3.5)	0/12 (0)	2/45 (4.4)	
	Discontinued	9/57 (15.8)	2/12 (16.7)	7/45 (15.6)	
	Not prescribed at baseline	2/59 (3.4)	1/13 (7.7)	1/46 (2.2)	.395
MTOR-I	No change	3/5 (60.0)	0/0 (0)	3/5 (60.0)	> .99
	Dose increased	0/5 (0)	0/0 (0)	0/5 (0)	
	Dose decreased	2/5 (40.0)	0/0 (0)	2/5 (40.0)	
	Discontinued	0/5 (0)	0/0 (0)	0/5 (0)	
	Not prescribed at baseline	54/59 (91.5)	13/13 (100)	41/46 (89.1)	.576
Belatacept	No change	1/2 (50.0)	0/0 (0)	1/2 (50)	> .99
	Dose increased	0/2 (0)	0/0 (0)	0/2 (0)	
	Dose decreased	0/2 (0)	0/0 (0)	0/2 (0)	
	Discontinued	1/2 (50.0)	0/0 (0)	1/2 (50.0)	
	Not prescribed at baseline	57/59 (96.6)	13/13 (100)	44/46 (95.7)	> .99
Antimetabolite†	No change	6/48 (12.5)	3/13 (23.1)	3/35 (8.6)	.195
	Dose increased	0/48 (0)	0/13 (0)	0/35 (0)	
	Dose decreased	15/48 (31.2)	2/13 (15.4)	13/35 (37.1)	
	Discontinued	27/48 (56.2)	8/13 (61.5)	19/35 (54.3)	
	Not prescribed at baseline	11/59 (18.6)	0/13 (0)	11/46 (23.9)	0.1

CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTOR-I, mammalian target of rapamycin inhibitor.
* Prednisone refers to oral prednisone.
† Antimetabolite includes MMF, azathioprine, and leflunomide.

Table 7. Immunosuppression Regimen and Modifications: 2 Levels by COVID-19 Pulmonary Manifestations

Medication		All Participants, n/N (%)	No Pulmonary Manifestations, n/N (%)	Pulmonary Manifestations, n/N (%)	*P* Value
Azathioprine	No change	1/6 (16.7)	1/2 (50.0)	0/4 (0)	.333
	Dose decreased/discontinued	5/6 (83.3)	1/2 (50.0)	4/4 (100)	
MMF	No change	6/42 (14.3)	4/17 (23.5)	2/25 (8)	.202
	Dose decreased/discontinued	36/42 (85.7)	13/17 (76.5)	23/25 (92.0)	
CNI	No change	22/55 (40.0)	15/21 (71.4)	7/34 (20.6)	<.001
	Dose decreased/discontinued	33/55 (60.0)	6/21 (28.6)	27/34 (79.4)	
Prednisone*	No change	42/56 (75)	21/22 (95.4)	21/34 (61.8)	.017
	Dose decreased/discontinued	11/56 (19.7)	1/22 (4.5)	10/34 (29.4)	
MTOR-I	No change	2/4 (50.0)	2/2 (100)	0/2 (0)	.333
	Dose decreased/discontinued	2/4 (50.0)	0/2 (0)	2/2 (100)	
Belatacept	No change	1/2 (50.0)	0/0 (0)	1/2 (50)	> .99
	Dose decreased/discontinued	1/2 (50.0)	0/0 (0)	1/2 (50)	
Antimetabolite†	No change	6/48 (12.5)	4/18 (22.2)	2/30 (6.7)	.179
	Dose decreased/discontinued	42/48 (87.5)	14/18 (77.8)	28/30 (93.3)	

CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; MMF, mycophenolate mofetil; MTOR-I, mammalian target of rapamycin inhibitor.
* Prednisone refers to oral prednisone.
† Antimetabolite includes MMF, azathioprine, and leflunomide.

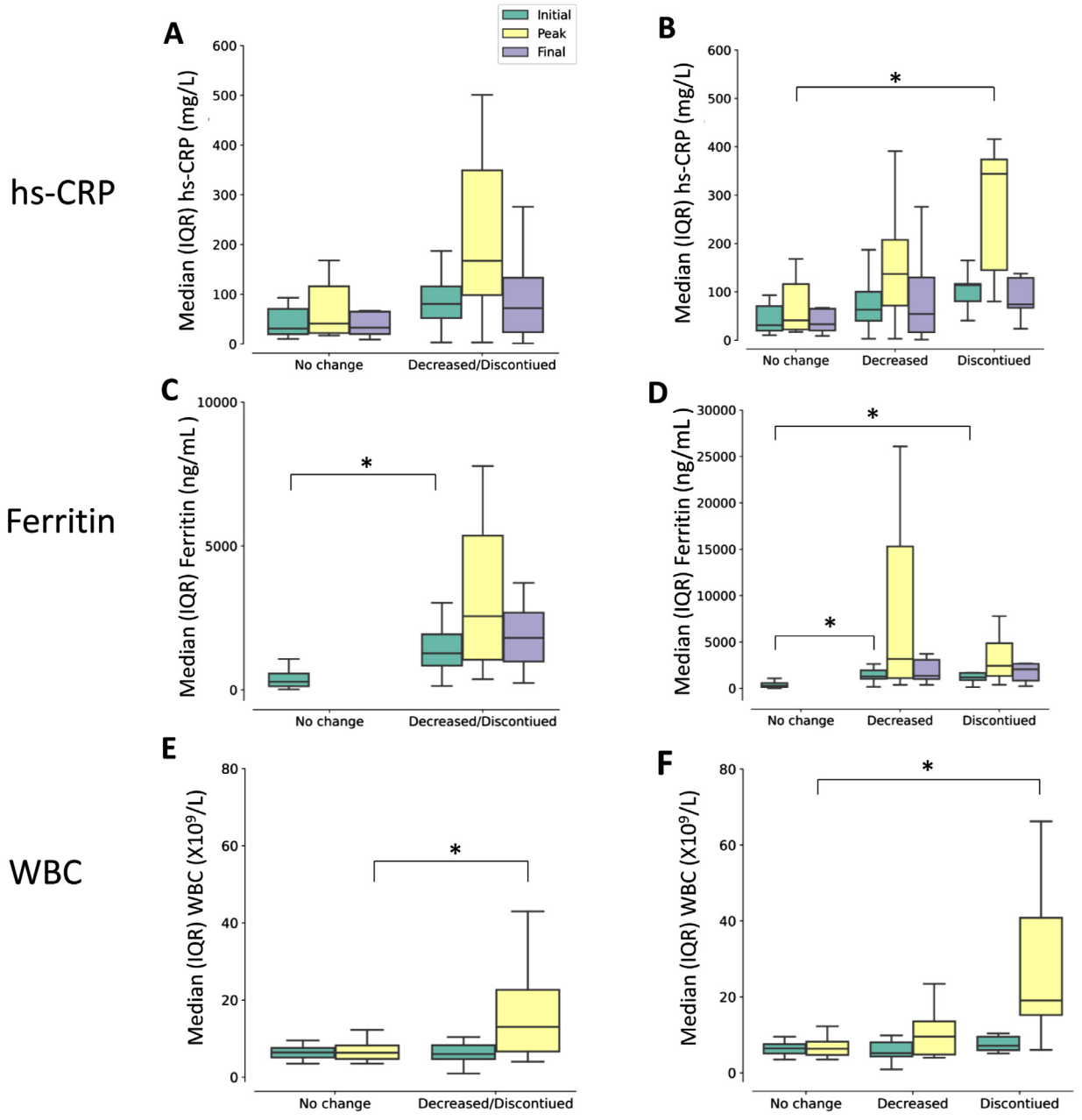

Fig 1. Associations of inflammatory biomarkers and changes in CNI regimen. (**A**) Initial, peak, and final hs-CRP level in unchanged CNI compared with decreased or discontinued CNI. (**B**) Initial, peak, and final hs-CRP in unchanged CNI compared with both decreased and discontinued CNI. (**C**) Initial ferritin level in unchanged CNI compared with decreased or discontinued CNI. (**D**) Initial ferritin in unchanged CNI compared with both decreased and discontinued CNI. Comparisons between peak and final ferritin unable to be made due to small number of available values in no-change group. (**E**) Initial and peak WBC in unchanged CNI compared with decreased or discontinued CNI. (**F**) Initial and peak WBC in unchanged CNI compared with both decreased and discontinued CNI. CNI, calcineurin inhibitor; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell. *Significant $P < .05$.

however, most groups recommend reducing or stopping the antimetabolite in hospitalized patients [5,16,20]. Two other studies have evaluated changes in immunosuppression regimen and also assessed association of hs-CRP with COVID-19 disease severity, but none have investigated whether immunosuppression changes were associated with changes in hs-CRP or other inflammatory biomarkers [5,6]. Few studies with larger samples lacked granular data to make such comparisons [18] or used only univariate models [6]. By comparing changes in inflammatory markers as they correlate with CNI

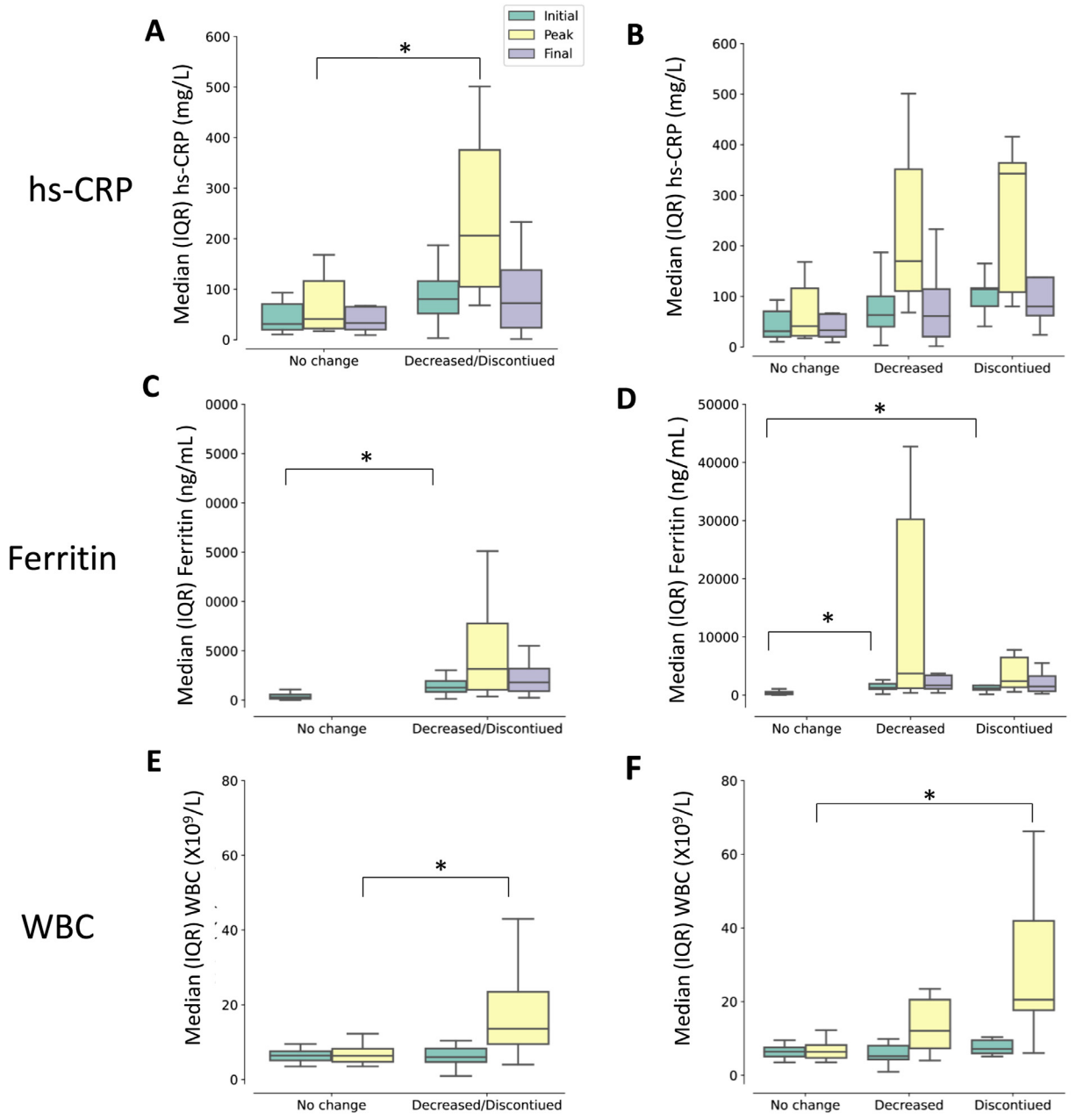

Fig 2. Sensitivity analysis using only patients whose CNI was changed before biomarker laboratory results compared with patients with no changes in CNI dosing. (**A**) Initial, peak, and final hs-CRP levels in unchanged CNI compared with decreased or discontinued CNI. (**B**) Initial, peak, and final hs-CRP in unchanged CNI compared with both decreased and discontinued CNI. (**C**) Initial ferritin level in unchanged CNI compared with decreased or discontinued CNI. (**D**) Initial ferritin in unchanged CNI compared with both decreased and discontinued CNI. Comparisons between peak and final ferritin unable to be made owing to small number of available values in no -change group. (**E**) Initial and peak WBC in unchanged CNI compared with decreased or discontinued CNI. (**F**) Initial and peak WBC in unchanged CNI compared with both decreased and discontinued CNI. CNI, calcineurin inhibitor; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell. *Significant $P < .05$.

dosing changes, we observed patients, with discontinued or decreased CNI dosing, having higher levels of inflammatory markers when compared with those who had their baseline CNI dose continued. Interestingly, we found no changes to inflammatory markers with reduction or discontinuation of antimetabolites, perhaps suggesting a stronger association of CNI reduction to COVID-19 cytokine milieu. However, nearly 85% of the cohort had their antimetabolite reduced or stopped

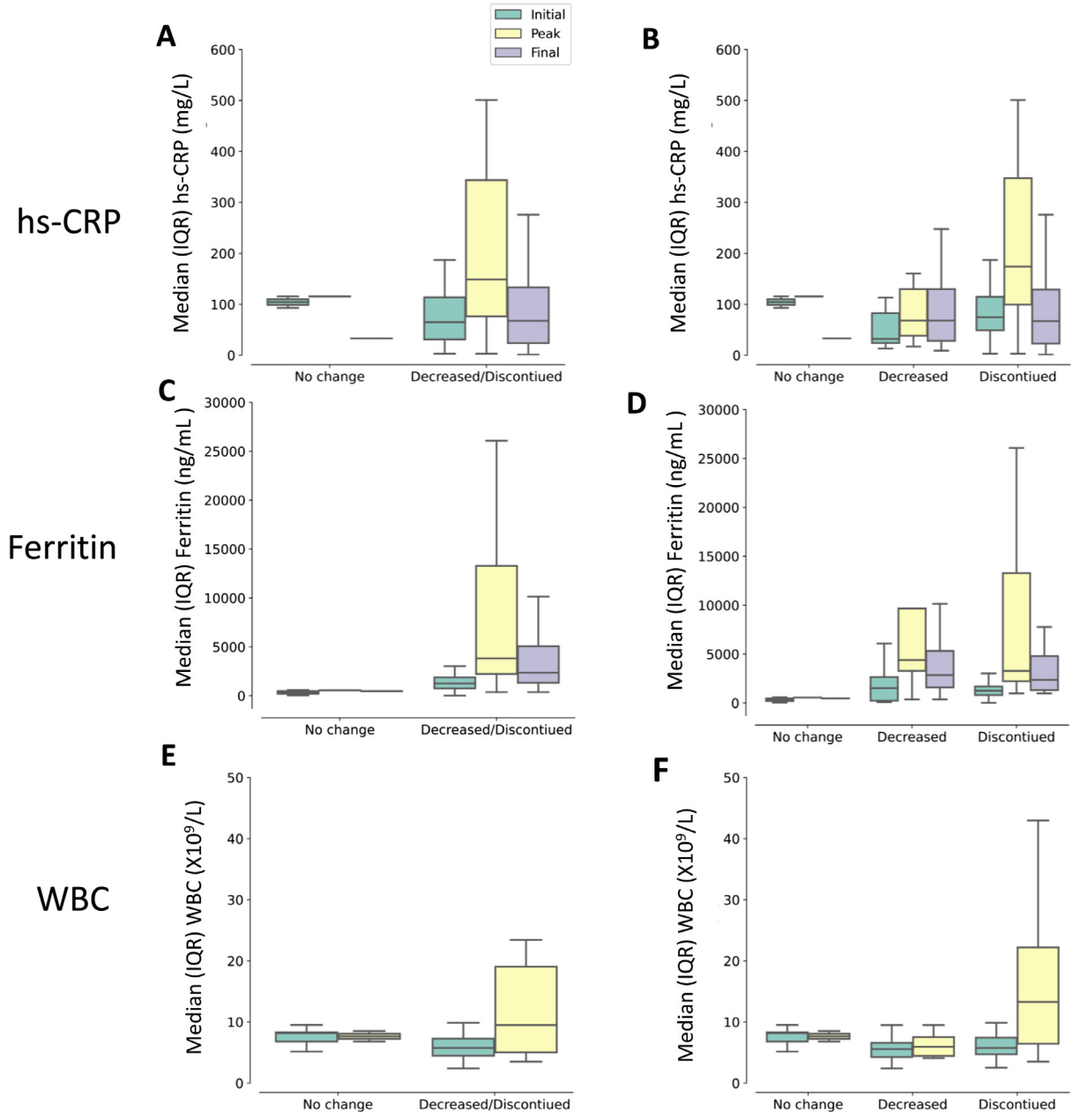

Fig 3. Associations of inflammatory biomarkers and changes in antimetabolite regimen. (**A**) Initial, peak, and final CRP levels in unchanged antimetabolite compared with decreased or discontinued antimetabolite. (**B**) Initial, peak, and final CRP levels in unchanged antimetabolite compared with both decreased and discontinued antimetabolite. (**C**) Initial, peak, and final ferritin levels in unchanged antimetabolite compared with decreased or discontinued antimetabolite. (**D**) Initial, peak, and final ferritin levels in unchanged antimetabolite compared with both decreased and discontinued antimetabolite. (**E**) Initial and peak WBC in unchanged antimetabolite compared with decreased or discontinued antimetabolite. (**F**) Initial and peak WBC in unchanged antimetabolite compared with both decreased and discontinued antimetabolite. No $P < .05$ found. CRP, C-reactive protein; WBC, white blood cell.

regardless of the severity of illness, conceivably masking any effect of reduction on inflammatory markers. Those patients with pulmonary manifestations of COVID were more likely to have higher levels of inflammatory markers and to have their baseline CNI decreased or discontinued. This may be an indication bias, such that providers were more likely to decrease the dose or discontinue immunosuppressant medications in sicker patients. However, our sensitivity analysis including only patients in whom the change in immunosuppressive medications took place before inflammatory markers were measured

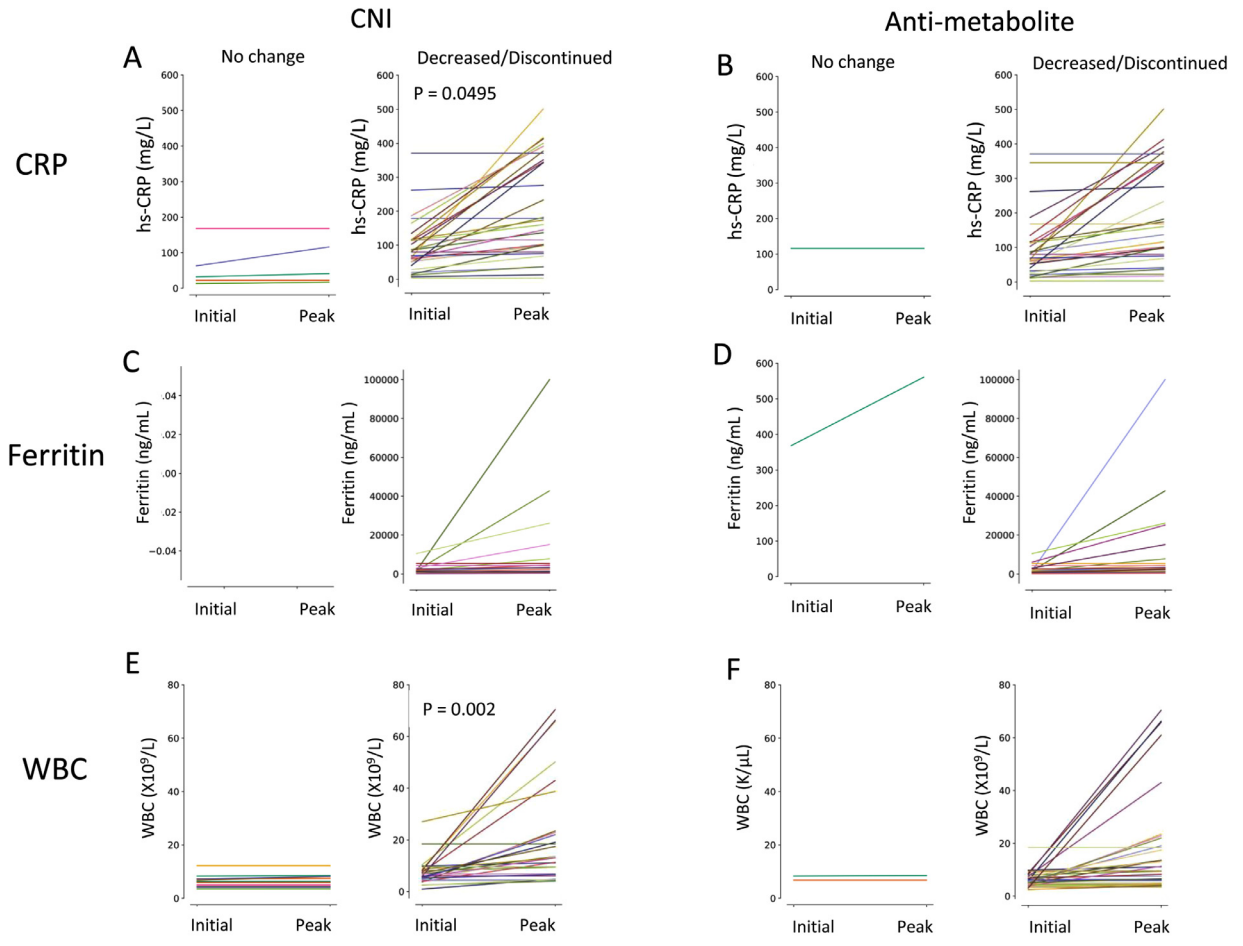

Fig 4. Comparisons of Δ change (peak value minus initial value) of inflammatory biomarkers and changes in immunosuppression regimen. (**A**) Δ change of hs-CRP for patients with unchanged CNI and those whose CNI was decreased or discontinued. (**B**) Δ change of hs-CRP for patients with unchanged antimetabolite and those whose antimetabolite was decreased or discontinued. (**C**) Δ change of ferritin for patients with unchanged CNI and those whose CNI was decreased or discontinued. (**D**) Δ change of ferritin for patients with unchanged antimetabolite and those whose antimetabolite was decreased or discontinued. (**E**) Δ change of WBC for patients with unchanged CNI and those whose CNI was decreased or discontinued. (**F**) Δ change of ferritin for patients with unchanged antimetabolite and those whose antimetabolite was decreased or discontinued. Significant $P < .05$ are indicated on the corresponding figure. Each line represents 1 individual. Δ change of ferritin unable to be determined in any patients with no change to CNI owing to unavailable values. CNI, calcineurin inhibitor; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell.

suggests that indication bias may not account for the entire relationship.

We showed that CNI dose reduction or discontinuation, when compared with dose maintenance, was associated with an increase in hs-CRP, ferritin, and WBC, and that hs-CRP was independently associated with worse outcomes. These findings are hypothesis-generating and need confirmation in larger studies; a potential explanation could be that continuation of CNI ameliorated the COVID-19–induced host inflammatory response, manifested as a cytokine storm that may play an important role in the pathophysiology of multiorgan failure. Progression of COVID-19 lung infection has been described in distinct phases. The initial phase comprises of increasing COVID-19 disease severity, subsequently followed by a decline in viral response, and lastly, an enhanced host inflammatory response. In this final phase, seemingly uninhibited, systemic microvascular inflammation via production of multiple cytokines and inflammatory biomarkers such as hs-CRP can lead to multiorgan failure, including AKI [11,20]. Remy et al. proposed that COVID-19 viral injury occurs because of an impaired immune system response secondary to an immunocompromised state. Elevation of certain inflammatory markers has thereby been thought to be due to cellular injury of pulmonary epithelial cells [21]. Alternatively, the majority of groups have concluded that immunosuppression curbs the profound cytokine surge of COVID-19 [10,21,22]. Other supporting evidence includes in

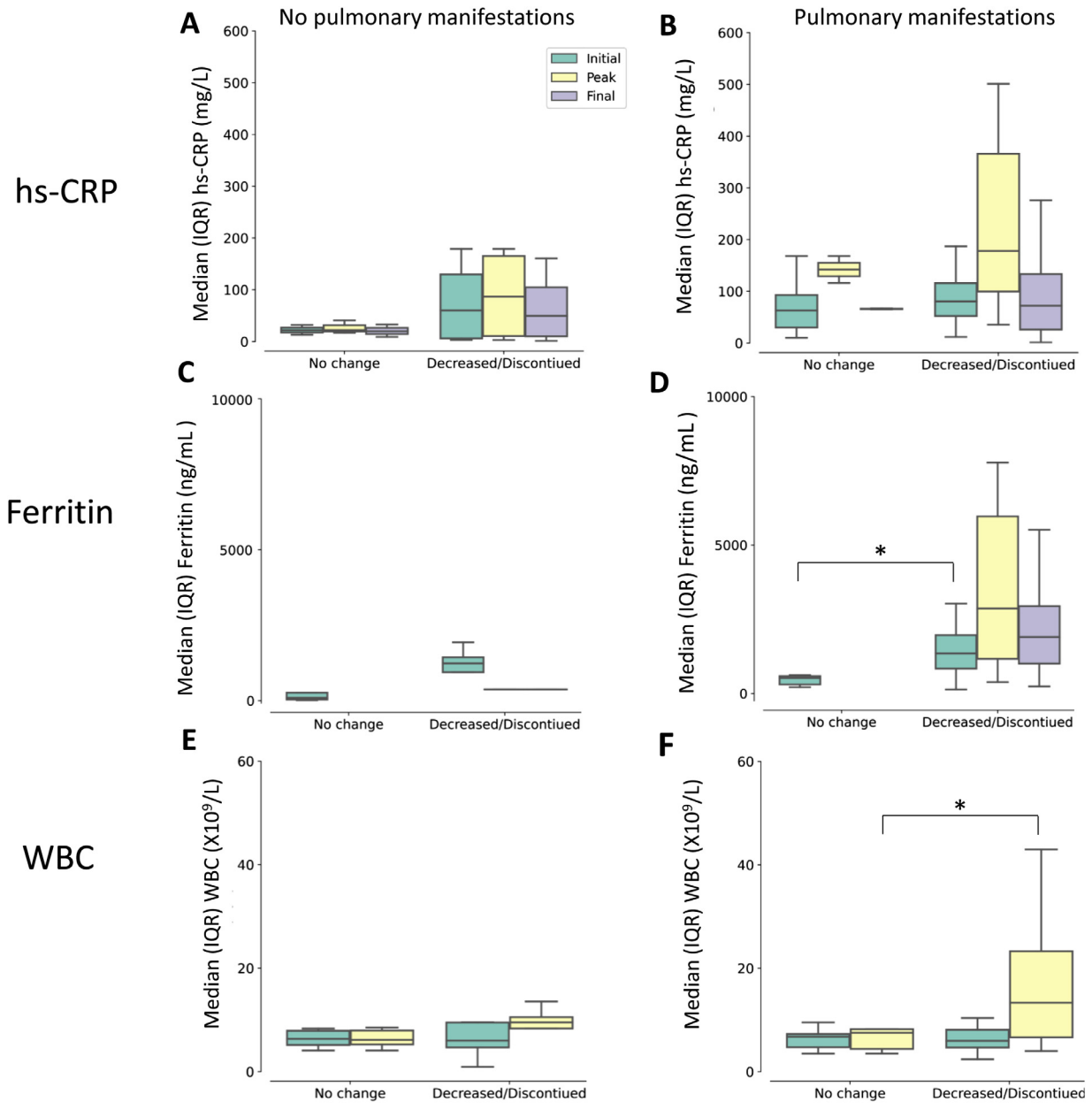

Fig 5. Associations of inflammatory biomarkers and change in CNI regimen in patients with absence of pulmonary manifestations and those with the presence of pulmonary manifestations. (**A**) Initial, peak, and final hs-CRP levels in unchanged CNI compared with decreased or discontinued CNI in those with no pulmonary manifestations. (**B**) Initial, peak, and final hs-CRP levels in unchanged CNI compared with decreased or discontinued CNI in those with pulmonary manifestations. (**C**) Initial ferritin level in unchanged CNI compared with decreased or discontinued CNI in those with no pulmonary manifestations. Peak and final ferritin levels unable to be compared due to small number of available values in both groups. (**D**) Initial ferritin level in unchanged CNI compared with CNI decreased or discontinued in those with pulmonary manifestations. Peak and final ferritin levels unable to be compared due to small number of available values in no change group. (**E**) Initial and peak WBC in unchanged CNI compared with decreased or discontinued CNI in those with no pulmonary manifestations. (**F**) Initial and peak WBC in unchanged CNI compared with decreased or discontinued CNI in those with pulmonary manifestations. CNI, calcineurin inhibitor; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell. *Significant $P <$ .05.

Table 8. Univariable and Multivariable Logistic Regression Models Using a Composite Event of AKI, ICU Admission, or Death. Total Number of Events Was 31.

	Univariable		Multivariable	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, per year	1.033 (0.997−1.070)	.075	x	
Female sex	0.476 (0.166−1.369)	.169		
African race	1.069 (0.311−3.675)	.915		
Diabetes	2.098 (0.738−5.968)	.165		
eGFR <60 mL/min/1.73m^2	5.833 (1.880−18.099)	**.002***	11.176 (1.581−79.001)	**.016**†
<1 y since transplant	0.414 (0.070−2.457)	.332		
Antimetabolite	1.841 (0.461−7.352)	.388		
Insurance	1.038 (0.369−2.920)	.943		
hs-CRP, initial, mg/L	1.011 (0.998−1.024)	.103		
hs-CRP, peak, mg/L	1.011 (1.002, 1.021)	**.019**†	1.010 (1.000−1.02)	**.049**†
hs-CRP, final, mg/L	1.023 (1.000−1.047)	**.046**†		
WBC, nadir, X 10^9/L	1.106 (0.767−1.595)	.591		
WBC, peak, X 10^9/L	1.173 (1.006−1.368)	**.041**†	x	
CNI decreased/discontinued	4.286 (1.353−13.572)	**.013**†	x	
Presence of pulmonary manifestations‡	3.791 (1.230−11.687)	**.020**†	x	

Age, eGFR <60, peak hs-CRP, peak WBC, CNI decreased/discontinued CNI, and COVID-19 pulmonary manifestations were included in the multivariate backward variable selection; AKI, acute kidney injury; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ICU, intensive care unit; WBC, white blood cell.

* $P < .01$.

† $P < .05$.

‡ Defined as requiring any form of supplemental oxygen, mechanical ventilation, or a pulmonary infiltrate noted on chest x-ray.

vitro data suggesting that CNIs at low levels inhibit growth of other coronaviruses; genome analysis show cyclophilin proteins and tacrolimus binding proteins interacting with SARS-CoV proteins with knock out of the latter in tacrolimus-treated patients inhibiting the virus replication [23-25]. The present findings suggest a potential role for continuation of at least low-dose CNI in KTRs in whom the cytokine surge seemingly predicts a worse outcome. We showed that CNI reduction or discontinuation was associated with increase in hs-CRP, ferritin, and WBC when compared with no change in CNI, and that hs-CRP was independently associated with worse outcomes. These findings, however, are hypothesis-generating and need to be confirmed in larger, prospective studies.

Several limitations are worth mentioning. Although we obtained granular data to ascertain associations between immunosuppression changes and inflammatory biomarkers, there is risk for indication bias as sicker patients with higher levels of inflammatory biomarkers at presentation would have had a higher probability to trigger reduction or discontinuation of immunosuppression. A larger sample size would have allowed propensity score analysis to match baseline characteristics of the patients, such as comorbid conditions and markers of illness, to further reduce potential indication bias. Another limitation is interhospital variability in clinical practice patterns as well as rapidly evolving knowledge of COVID-19 in transplant recipients. We were not able to determine whether changes in immunosuppression were driven by severity of COVID-19 illness, drug toxicity, or targeting specific CNI troughs. Future studies controlling for these factors are needed to guide changes in immunosuppression in the setting of COVID-19 infection.

CONCLUSIONS

Kidney transplant patients infected with SARS-CoV-2 have high rates of ICU admissions, AKI, and death. Pulmonary manifestations and reduction or discontinuation in CNI regimen are associated with higher levels of inflammatory biomarkers that seem to correlate with worse outcomes. More studies are needed to determine if this association should drive clinical management in not only KTRs but also that of other solid organs. Peak hs-CRP was higher in patients whose CNI was reduced or discontinued, and this change persisted in those whose regimen was changed before the laboratory results; this strengthens the use of hs-CRP as an important prognostic marker in renal transplant patients infected with SARS-CoV-2. Moreover, our findings may have potential therapeutic implications as ongoing studies look at immunomodulatory agents for potential treatments in COVID-19 disease.

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