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Clinical Utility of Biochemical Markers for the Prediction of COVID-19–Related Mortality in Kidney Transplant Recipients

Sophie Caillard1, Nathalie Chavarot2, Hélène Francois3, Marie Matignon4, Renaud Snanoudj5, Jérôme Tourret6, Clarisse Greze7, Olivier Thaunat8, Luc Frimat9, Pierre François Westeel10, Philippe Gatault11, Christophe Masset12, Gilles Blancho12, Tristan Legris13, Valérie Moal13, Nassim Kamar14, Mariam Jdidou15, Charlotte Colosio16, Christiane Mousson17, Valentin Goutadier18, Antoine Sicard19, Dominique Bertrand20, Jamal Bamouli21, Paolo Malvezi22, Lionel Couzi23, Jonathan M. Chemouny24, Agnès Duveau25, Christophe Mariat26, Jean-Philippe Rerolle27, Antoine Thierry28, Nicolas Bouvier29, Dany Anglicheau2, Yannick Le Meur30 and Marc Hazzan31; on behalf of the French SOT COVID Registry22

1Department of Nephrology and Transplantation, Strasbourg University Hospital, INSERM, Strasbourg, France; 2Department of Nephrology and Transplantation Adults, Hôpital Universitaire Necker – APHP Centre – Université de Paris INEM INSERM U 1151 – CNRS UMR 8253, Paris, France; 3Department of Transplantation, Nephrology and Clinical Immunology, Hôpital Edouard Herriot, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France; 4Department of Nephrology, University of Lorraine, CHRU-Nancy, Vandoeuvre, France; 5Nephrology, Renal Transplantation and General Medicine, CHU de Dijon, Dijon, France; 6Department of Nephrology and Renal Transplantation Department, AP-HP (Assistance Publique-Hôpitaux de Paris), Hôpital Tenon, Paris, France; 7Nephrology and Renal Transplantation Department, AP-HP (Assistance Publique-Hôpitaux de Paris), Institut Francilien de Recherche en Néphrologie et Transplantation (IFRNT), Groupe Hospitalier Henri-Mondor/Albert-Chenevier, Université Paris-Est Créteil (UPEC), DHU (Département Hospitalo-Universitaire) VIC (Virus-Immunité-Cancer), IMRB (Institut Mondor de Recherche Biomédicale), Equipe 21, INSERM U 955, Créteil, France; 8Nephrology and Renal Transplantation Department, Hôpital Foch, Paris, France; 9Nephrology and Renal Transplantation Department, AP-HP (Assistance Publique-Hôpitaux de Paris), Hôpital la Pitié Salpêtrière, Paris, France; 10Department of Nephrology and Transplantation, Hôpital Bichat, Paris, France; 11Department of Nephrology and Transplantation, Hôpital Conception, Marseille, France; 12Department of Nephrology and Transplantation, Centre Hospitalier Universitaire de Nantes, Nantes, France; 13Centre de Néphrologie et Transplantation Rénale, Aix Marseille Université, Hôpitaux Universitaires de Marseille, Hôtel Conception, Marseille, France; 14Department of Nephrology and Transplantation, University of Rouen, Rouen, France; 15Department of Nephrology and Transplantation, Hôpital Tenon, Paris, France; 16Department of Nephrology and Transplantation, Hôpital Foch, Paris, France; 17Department of Nephrology and Transplantation, AP-HP (Assistance Publique-Hôpitaux de Paris), Hôpital Bicêtre, Le Kremlin-Bicêtre, France; 18Department of Nephrology and Transplantation, University of Poitiers, Poitiers, France; 19Department of Nephrology and Transplantation, Hôpital la Pitié-Salpêtrière, Paris, France; 20Department of Nephrology and Transplantation, University of Angers, Angers, France; 21Department of Nephrology and Transplantation, University of Limoges, Limoges, France; 22Department of Nephrology and Transplantation, University of Caen, Caen, France; 23Department of Nephrology, CHU de Brest, UMR1227, Lymphocytes B et Autoimmunité, Université de Brest, Inserm, Labex IGO, Brest, France; 24Department of Nephrology and Transplantation, University of Rennes, CHU Rennes, Inserm, EHESP, IRSET (Institut de Recherche en Santé, Environnement et Travail) – UMR_S 1085, CIC-P 1414, Rennes, France; 25Department of Nephrology and Transplantation, University of Toulouse, Toulouse, France; 26Department of Nephrology and Transplantation, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; 27Department of Nephrology, University of Bordeaux, Bordeaux, France; 28Department of Nephrology and Transplantation, University of Bordeaux, Bordeaux, France; 29Department of Nephrology and Transplantation, University of Poitiers, Poitiers, France; 30Department of Nephrology and Transplantation, University of Caen, Caen, France; 31Department of Nephrology, CHU de Brest, UMR1227, Lymphocytes B et Autoimmunité, Université de Brest, Inserm, Labex IGO, Brest, France; and 32Department of Nephrology and Transplantation, University of Lille, Lille, France

Correspondence: Sophie Caillard, Department of Nephrology and Transplantation, Strasbourg University Hospital, 1 place de l’hôpital, 67091 Strasbourg Cedex, France. E-mail: Sophie.caillard@chru-strasbourg.fr

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Coronavirus disease–2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a significant threat for patients with pre-existing renal disease, including kidney transplant recipients (KTRs).1-3,51,52 Although there is ample literature to suggest a role for kidney impairment in the
severity of COVID-19, its clinical course in KTRs can vary widely, from minimal symptoms to life-threatening illness.

Much of the recent focus in COVID-19 research has revolved around predictors of death and severe disease. Several studies in the adult general population have found an association between elevation of cardiac injury, coagulation, and inflammatory biomarkers and COVID-19–related mortality.4-6,S3

Nevertheless, only a limited number of single-center studies7-9 have specifically explored the clinical utility of circulating biomarkers for the prediction of COVID-19–related mortality in solid organ transplant recipients (see Azzi et al.8 for a recent review). By taking advantage of data from a French nationwide registry of KTRs with COVID-19, we sought to investigate the prognostic significance of increased biomarkers of cardiac injury, coagulation, and inflammation in this population.

RESULTS
Patient Characteristics
The study sample consisted of 494 KTRs who were included in the French SOT COVID registry during the first wave of the pandemic. A total of 411 patients were admitted to hospital, whereas the remaining 83 were managed at home. The baseline characteristics of the study patients are shown in Supplementary Table S1. The median age was 61 years (interquartile range [IQR] = 52–69 years), and two-thirds were men. SARS-CoV-2 infection was diagnosed after a median of 6 years from kidney transplantation. The median interval between symptom onset and hospital admission was 5 days (IQR = 3–8 days). The most common symptom was fever (73%), followed by cough (63%), dyspnea (45%), diarrhea (33%), and anosmia (16%). Supplementary Table S2 summarizes the clinical management and the evolution of disease over time. The 60-day overall survival rate in the entire study cohort was 80% (Supplementary Figure S1).

Biochemical Markers
The median levels of CRP and procalcitonin were 63 mg/l and 0.29 mg/ml, respectively. The median lymphocyte count was 0.62 × 10^9/l, whereas thrombocytopenia was identified in 94 (29%) patients. The median concentrations of hs-troponin I, lactate dehydrogenase (LDH), and D-dimer were 22 ng/l, 288 UI/l, and 927 µg/l, respectively (Supplementary Table S2). After setting the maximum point of the Youden index on the receiver operating characteristic (ROC) curve as the optimal cut-off value for each biomarker, we found that patients with serum creatinine >150 µmol/l, CRP >50 mg/l, procalcitonin >0.3 mg/l, hs-troponin I >20 ng/l, LDH >280 UI/l, and D-dimer >1500 UI/l were at an increased risk for COVID-19–related mortality (Supplementary Figure S2). Cumulative patient survival was significantly lower in KTRs who showed increased concentrations of these biomarkers at the time of hospital admission or diagnosis (Figure 1).

Survival curves according to different cut-off points for each biomarker of interest are shown in Supplementary Figure S3. The hazard ratios for mortality according to each clinical and laboratory variable of interest are shown in Table 1. On multivariate analysis, procalcitonin and troponin I retained their independent association with mortality. The results of correlation analyses between different biomarkers are summarized in Supplementary Table S3. In the subgroup of patients (n = 276) who had at least 1 available biomarker, the combination of a marker of inflammation (procalcitonin), thrombosis (D-dimer), and cell lysis (hs-troponin I) was highly predictive of COVID-19–related mortality. Specifically, the 60-day survival rate was as high as 92% in patients (n = 110) without elevation of any of the 3 markers, whereas it declined to 77% in those (n = 120) who had at least 1 elevated biomarker. Less favorable outcomes were observed in patients (n = 36) with 2 (60-day survival rate, 58%) and 3 (n = 10) elevated biomarkers (60-day survival rate, 40%) (Figure 2a). On analyzing the subgroup of patients for which all 3 biomarkers were available on admission (n = 80), similar results were observed (Figure 2b).

DISCUSSION
In this study comprising 494 KTRs, we found that elevations of markers of inflammation, cardiac injury, and thrombosis were significantly associated with an increased risk of COVID-19–related mortality.

Growing evidence indicates that inflammatory mediators are paramount in determining the severity of COVID-19, with poor outcomes frequently resulting from a massive release of proinflammatory cytokines, also known as “cytokine storm.”6,9 Notably, the optimal cut-off values for serum CRP (50 mg/l) and procalcitonin (0.3 mg/l) levels identified in our study are consistent with those reported in previous investigations.7-9

On analyzing the survival figures of our KTRs, we found that individuals with elevated levels of circulating hs-troponin I, a well-known biomarker of myocardial injury, were at an increased risk for COVID-19-related mortality. Li et al.9 published a population-based study of 2068 patients with laboratory-confirmed COVID-19, of whom 8.8% had elevated hs-troponin I; the prevalence rate increased to
30% in critically ill patients, who experienced a mortality rate of 38%. An increase in the mortality rates among patients with COVID-19 and elevated hs-troponin I supports the utility of this biomarker for prognostic stratification. The mechanisms of cardiac involvement in COVID-19 include, but are not limited to, the following: cytokine-mediated cardiac tissue damage, an imbalance between oxygen supply and demand, ischemic injury due to micro- and/or macro-vascular thrombosis, endothelial dysfunction, and myocardial injury caused by direct SARS-CoV-2 invasion into cardiomyocytes. The complex interplay between the disproportionate hyper-inflammatory reaction occurring in severe COVID-19 and the severity of cardiac injury deserves further scrutiny.

Finally, our results add to the growing literature indicating that D-dimer concentrations may be a useful laboratory parameter that should be taken into account for prognostic stratification of patients with COVID-19. However, published studies did not provide specific data for KTRs. Elevated D-dimer

| Variable | Univariate HR | 95% CI | P | P* | Multivariate HR | 95% CI | P | P* |
|----------|---------------|--------|----|----|----------------|--------|----|----|
| Age >60 yr | 3.64 | 2.23-5.94 | <0.001 | 0.001 | 7.33 | 1.91-28.1 | 0.004 | 0.004 |
| CV history | 1.25 | 1.03-1.52 | 0.027 | 0.036 | | | | |
| SCr >150 μmol/l | 1.39 | 1.07-1.78 | 0.014 | 0.009 | | | | |
| PCT >0.3 mg/l | 2.28 | 1.51-3.64 | <0.001 | 0.001 | 3.73 | 1.53-9.13 | 0.004 | 0.001 |
| DD >1500 UI/l | 1.69 | 1.31-2.27 | 0.001 | 0.001 | | | | |
| hs-Troponin I >20 ng/l | 2.11 | 1.39-3.19 | <0.001 | 0.001 | 2.91 | 1.02-8.34 | 0.047 | 0.022 |

CI, confidence interval; CV, cardiovascular; DD, D-dimer; HR, hazard ratio; hs, high-sensitivity; PCT, procalcitonin; SCr, serum creatinine; *P value after bootstrap resampling for internal validation.
levels reflect a hypercoagulability state that may increase the risk of venous thromboembolic disease. A large multicenter study involving 400 hospitalized patients with COVID-19 who received prophylactic anticoagulation reported an incidence rate of thrombotic complications of 9.5%. The final multivariable analysis showed an increased risk of thrombotic complications during hospitalization (adjusted odds ratio, 6.8) for patients with D-dimer levels >2500 ng/ml on admission. In a French study, patients with D-dimer levels >2590 ng/ml were found to have a 17-fold increase in the adjusted risk of pulmonary embolism. Although the rate of thrombotic events observed in our KTRs was relatively low (7.5%), screening of venous thromboembolic disease was not systematically performed.

Several caveats of our investigation need to be considered. First, the retrospective nature of the study could be associated with information bias, and some biomarker values were missing. Second, although we analyzed serum levels of hs-troponin I as a biomarker of cardiac injury, the use of transthoracic echocardiography and electrocardiography might have improved the power of the study in terms of identifying myocardial dysfunction. Finally, we had no systematic screening of vascular thrombosis or pulmonary embolism. Despite these limitations, our data represent a promising step in understanding the value of several biochemical markers for predicting COVID-19–related mortality in KTRs. In addition, the current study is one of the largest to date specifically focusing on this clinical issue in a frail population under immunosuppressive therapy.

In conclusion, our study findings indicated that, in KTRs with COVID-19, elevations in biochemical markers of inflammation, cardiac injury, and coagulation are associated with less favorable survival figures. If independently validated, the use of biomarkers may help to guide therapeutic decision making in transplant patients.

DISCLOSURE
All the authors declared no competing interests.

APPENDIX
*The French SOT COVID Registry Collaborators are as follows: Sophie Caillard, Bruno Moulin, Service de Néphrologie et Transplantation, Hôpitaux Universitaires de Strasbourg, Strasbourg; Samira Fafi-Kremer, Laboratoire de Virologie, Hôpitaux Universitaires de Strasbourg, Strasbourg; Marc Hazzan, Service de Néphrologie, Hôpital Huriez, Lille; Dany Anglicheau, Service de Néphrologie et Transplantation Adultes, AP-HP, Hôpital Necker, Paris; Alexandre Hertig, Jérôme Tourret, Benoit Barrou, Service de Néphrologie, AP-HP, Hôpital La Pitié Salpêtrière, Paris; Emmanuel Morelon, Olivier Thaunat, Service de Néphrologie, Hôpital Edouard Herriot, Lyon; Lionel Couzi, Pierre Merville, Service de Néphrologie–Transplantation–Dialyse, Hôpital Pellegrin, Bordeaux; Valérie Moal, Tristan Legris, Service de Néphrologie et Transplantation, AP-HM, Hôpital de la Conception, Marseille; Pierre-François Westeel, Maïté Jaureguy, Service de Néphrologie, CHU Amiens Picardie, Amiens; Luc Frimat, Service de Néphrologie, CHRU Nancy, Vandoeuvre; Didier...
Ducloux, Jamal Bamouilid, Service de Néphrologie, Hôpital Jean-Minjoz, Besançon; Dominique Bertrand, Service de Néphrologie, CHU de Rouen, Rouen; Michel Tsimaratos, Florentine Garaix-Gilardo, Service de Pédiatrie Multidisciplinaire, Hôpital La Timone, Marseille; Jérôme Dumortier, Service d’Hépato-Gastroentérologie, Hôpital Edouard Herriot, Lyon; Sacha Mussot, Antoine Roux, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson; Laurent Sebbag, Service d’Insuffisance Cardiaque, Hôpital Louis Pradel, Bron; Yannick Le Meur, Service de Néphrologie, Hôpital de la Cavale Blanche, Brest; Gilles Blancho, Christophe Masset, Service de Néphrologie–Transplantation, Hôtel Dieu, Nantes; Nassim Kamar, Service de Néphrologie et Transplantation, AP-HP, Hôpital Tenon, Paris; Nicolas Bouvier, Service de Néphrologie, Dialyse, Transplantation Rénale, CHU, Caen; Christiane Mousson, Service de Néphrologie, Dijon; Matthias Buchler, Philippe Gatault, Service de Néphrologie, Tours; Jean-François Augusto, Agnès Duveau, Service de Néphrologie, Dialyse, Transplantation, CHU Angers, Angers; Cécile Vigneau, Marie-Christine Morin, Jonathan Chemouny, Elena Saliba, Service d’Hépatologie, Centre hépato-biliaire Paul Brousse, Villejuif, France.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Table S1. Baseline characteristics of kidney transplant recipients with COVID-19

Table S2. Laboratory data, management of immunosuppression, treatment modalities, and outcomes of kidney transplant recipients with COVID-19

Table S3. Spearman correlation coefficients between baseline patient characteristics and biomarker levels measured at the time of diagnosis or on admission

Figure S1. Kaplan–Meier survival plot of kidney transplant recipients hospitalized with COVID-19.

Figure S2. Receiver operating characteristic curve analysis of COVID-19–related mortality.

Figure S3. Kaplan–Meier survival plots for kidney transplant recipients with COVID-19.

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