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

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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,S1,S2] 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 studies[7,S4] 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 ng/ml, respectively. The median lymphocyte count was 0.62 $\times 10^9$/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,S5] 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,S6-S9]

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

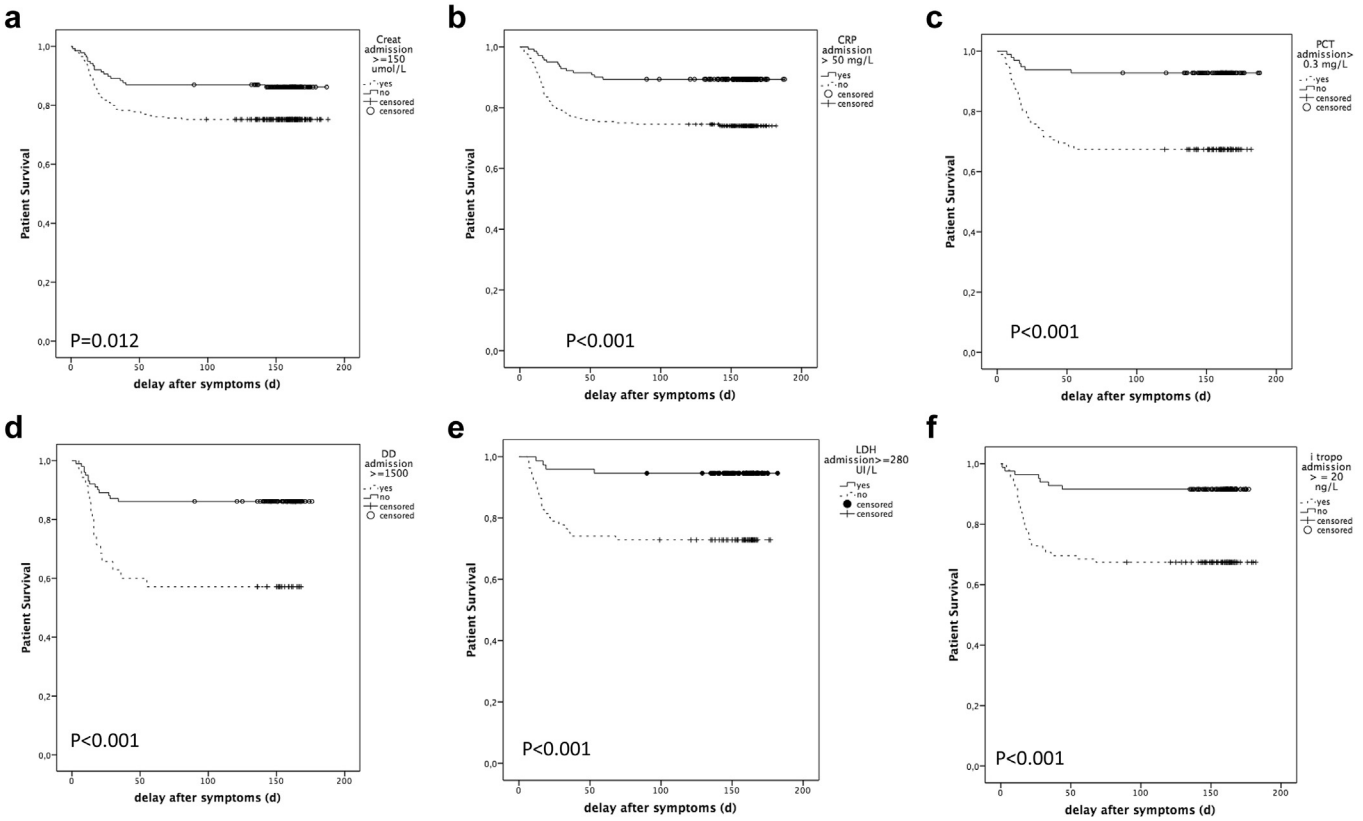

Figure 1. Kaplan–Meier survival plots (after the first day of COVID-19 symptoms) for kidney transplant recipients with COVID-19, stratified according to biomarker levels at the time of diagnosis or hospital admission. (a) Survival curves according to serum creatinine (Screat) levels (> vs. ≤150 umol/l, $P = 0.012$); (b) survival curves according to C-reactive protein (CRP) levels (>vs. ≤50 mg/l, $P < 0.001$); (c) survival curves according to procalcitonin (PCT) levels (>vs. ≤0.3 mg/l, $P < 0.001$); (d) survival curves according to D-dimer levels (> vs. ≤1500 UI/l, $P < .001$); (e) survival curves according lactate dehydrogenase (LDH) levels (>vs. ≤280 UI/l, $P < .001$); and (f) survival curves according to hs-troponin I (tropo) levels (>vs. ≤20 ng/l, $P < 0.001$).

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 macrovascular thrombosis, endothelial dysfunction, and myocardial injury caused by direct SARS-CoV-2 invasion into cardiomyocytes.[S10,S11] The complex interplay between the disproportionate hyperinflammatory reaction occurring in severe COVID-19 and the severity of cardiac injury deserves further scrutiny.[9]

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.[5,S3] However, published studies did not provide specific data for KTRs. Elevated D-dimer

Table 1. Univariate and multivariate analyses showing hazard ratios for COVID-19–related death in kidney transplant recipients (n = 491) according to age, cardiovascular history, and different biomarkers measured at the time of diagnosis or on patient admission

	Univariate analysis				Multivariate analysis			
Variable	HR	95% CI	*P*	*P*[a]	HR	95% CI	*P*	*P*[a]
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	1.89	1.31-2.72	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;
[a]*P* value after bootstrap resampling for internal validation.

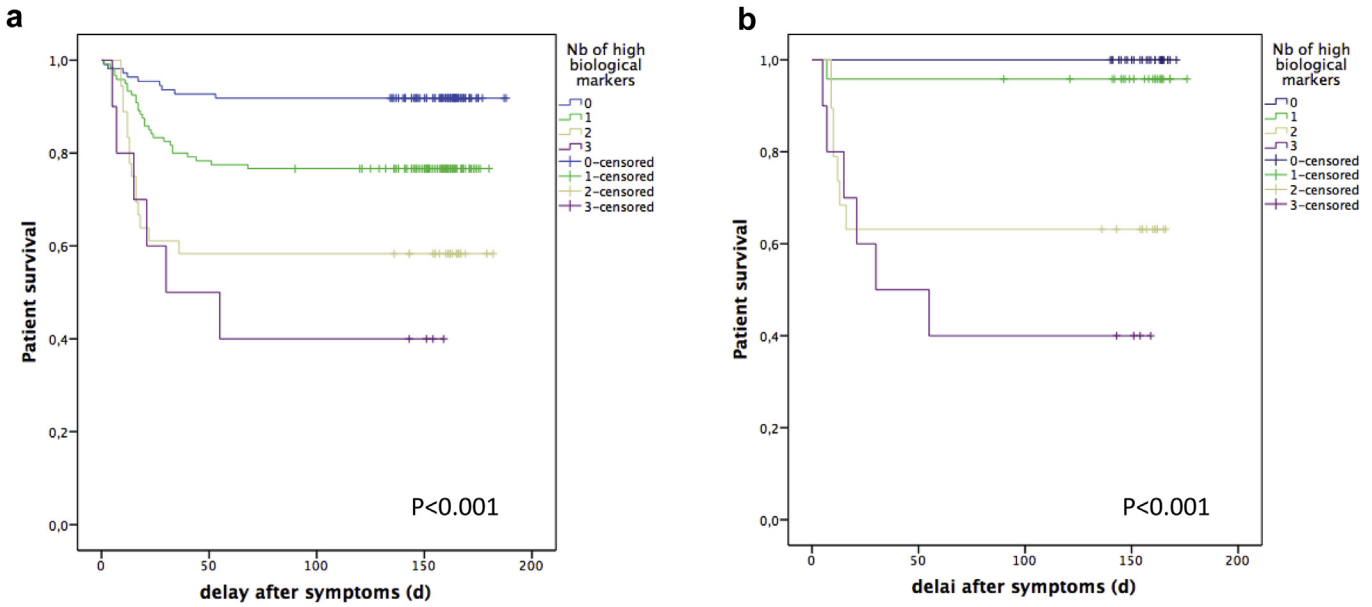

Figure 2. Kaplan–Meier survival plots for kidney transplant recipients with COVID-19, stratified according to the number of biomarkers above the optimal cut-off value at the time of diagnosis or hospital admission. (a) Patients with at least 1 available biomarker (n = 276, $P < 0.001$); (b) patients for whom all 3 biomarkers were available (n = 80, $P < 0.001$).

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%.[S6] 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.[S6] 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.[S12] 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.[S13] 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

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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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