

Article

# Impact of Hypertension on COVID-19 Burden in Kidney Transplant Recipients: An Observational Cohort Study

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**Abstract:** Background: COVID-19 severity is determined by cardiometabolic risk factors, which can be further aggravated by chronic immunosuppression in kidney transplant recipients (KTRs). We aimed to verify the main risk factors related to hypertension (HTN) that contribute to COVID-19 progression and mortality in that population. Methods: Retrospective analysis of 300 KTRs from March 2020 to August 2020 in a single center. We compared the main outcomes between HTN ( $n = 225$ ) and non-HTN ( $n = 75$ ), including admission to the intensive care unit (ICU), development of acute kidney injury (AKI), need for invasive mechanical ventilation or oxygen, and mortality. Results: Of the patients in the study, 57.3% were male, 61.3% were white, the mean age was 52.5 years, and 75% had HTN. Pre-existing HTN was independently associated with higher rates of mortality (32.9%, OR = 1.96,  $p = 0.036$ ), transfer to the ICU (50.7%, OR = 1.94,  $p = 0.017$ ), and AKI with hemodialysis (HD) requirement (40.4%, OR = 2.15,  $p = 0.011$ ). In the hypertensive group, age, diabetes mellitus, heart disease, smoking, glycemic control before admission, C-reactive protein, lactate dehydrogenase, lymphocytes, and D-dimer were significantly associated with COVID-19 progression and mortality. Both lower basal and previous estimated glomerular filtration rates posed KTRs with HTN at greater risk for HD requirement. Conclusions: Therefore, the early identification of factors that predict COVID-19 progression and mortality in KTRs affected by COVID-19 contributes to therapeutic decisions, patient flow management, and allocation of resources.

**Keywords:** hypertension; kidney transplant; COVID-19; outcomes



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## 1. Introduction

COVID-19 severity is affected by aging and chronic diseases, such as hypertension (HTN), diabetes mellitus (DM), cardio- and cerebrovascular diseases, obesity, chronic kidney disease (CKD), smoking, neoplasia, and chronic obstructive pulmonary disease (COPD) [1–3]. Particularly, the kidney transplant population, not only due to the presence of multiple comorbidities but also due to chronic immunosuppressive regimen, has a higher risk of COVID-19 progression and mortality [4].

HTN is identified as one of the most prevalent comorbidities in patients with COVID-19 [5]. HTN burden increases with age [6] and is frequently associated with underlying comorbidities [7]. Mechanistically, pre-existing cardiovascular diseases may aggravate COVID-19 by the interaction between the viral spike protein of SARS-CoV-2 and angiotensin-converting enzyme 2, which leads to an imbalance of the renin-angiotensin-aldosterone system (RAAS), increased endothelial cell damage, thromboinflammation, and dysregulated immune response [5,8].

Given the high prevalence of HTN in the kidney transplant population, we aimed to investigate whether kidney transplant recipients (KTRs) with the diagnosis of HTN had a

worse prognosis for COVID-19 when compared to KTRs without HTN in a single center. In addition, we sought to verify the main risk factors associated with COVID-19 outcomes, including mortality, intensive care unit (ICU) admission, need for supplemental oxygen (O<sub>2</sub>), need for invasive mechanical ventilation (IMV), development of acute kidney injury (AKI), and need for hemodialysis (HD).

Early identification of KTRs at high risk of COVID-19 progression provides an effective health system response for disease identification, COVID-19 diagnosis, disease management, monitoring of cases, mortality risk, and resource allocation in future pandemic waves of COVID-19 and other respiratory viruses in general [9,10].

## 2. Material and Methods

### 2.1. Study Design and Setting

We conducted a cohort, cross-sectional, observational study at Hospital do Rim, São Paulo, SP, Brazil. We assessed the medical records of patients who were either hospitalized or non-hospitalized with the diagnosis of COVID-19 during the study period of March to August 2020, corresponding to the first wave of COVID-19 in Brazil. We included only patients in whom SARS-CoV-2 was detected by nasopharyngeal swab RT-PCR (reverse transcriptase-polymerase chain reaction).

The population at risk included 11,875 patients. Of the 590 kidney transplant recipients who were hospitalized, 300 were included in the study. Six were excluded for being a double transplant, four for having lost the graft in the period before COVID-19, four for being a recent transplant and being in delayed graft function at the time of diagnosis of COVID-19, one for not using immunosuppressive drugs due to cancer treatment, one for being underage, and 274 were excluded for missing data due to admission to other services (Figure S1). The Ethics and Research Committee from the Federal University of São Paulo (CAEE35311020.9.0000.8098) approved the study. All the methods were performed following the relevant guidelines and regulations. In addition, this study was performed under the Declaration of Helsinki. Informed consent was obtained from all patients, whereas a waiver was granted for patients who died in other hospitals.

### 2.2. Demographic Data

We evaluated whether age, sex, race (defined by self-identification), body mass index (BMI), type of donor, time of transplant, as well as the presence of smoking and comorbidities including hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), heart disease, liver disease, and autoimmune disease, were associated with COVID-19-related outcomes. DM was defined by the use of insulin and/or oral antidiabetics, hypertension was defined by whether individuals were taking anti-hypertensive drugs, liver disease by whether hepatitis B or C were diagnosed, and heart disease by whether heart failure and/or coronary artery disease were present. We used the International Classification of Diseases-10.

### 2.3. Laboratory Parameters

At admission, we evaluated lymphocytes, creatinine, blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, lactate dehydrogenase (LDH), and C-reactive protein (CRP). We also evaluated the laboratory parameters before admission, including baseline creatinine (mean of the last three measurements), fasting blood glucose (FBG) (last measurement within six months), and glycated hemoglobin (HbA1c) (last measurement within a one year period). The estimated glomerular filtration rate (eGFR) was calculated using the formula defined in the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study:  $175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212$  (if black)  $\times 0.742$  (if woman) and was expressed in mL/min/1.73 m<sup>2</sup> of the body surface.

## 2.4. Statistical Analysis

We verified the impact of HTN in kidney transplant recipients with COVID-19 on the outcomes of mortality, transfer to intensive care unit (ICU), acute kidney injury (AKI) classified in accordance with Kidney Disease Improving Global Outcomes (KDIGO) guidelines, need for hemodialysis (HD) and supplemental oxygen (O<sub>2</sub>), and invasive mechanical ventilation (IMV). We then evaluated the impact of hypertension (HTN) in KTRs by dividing them into two groups: HTN (+) and non-HTN or HTN (−).

Independent samples *t*-test and Chi-square test were used to identify the association between HTN and demographic and laboratory parameters, and the outcomes previously mentioned. Data were described as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR). Frequencies and percentages were reported for qualitative data. Variables that were univariably associated with a value of  $p \leq 0.1$  were simultaneously included in a multivariable binary logistic regression model to estimate the odds ratios (OR) and 95% confidence interval (CI) between HTN and outcomes. Receiver Operating Characteristic (ROC) curves were used to identify the laboratory parameters associated with COVID-19-related outcomes. To calculate the CRP and LDH cut-off values with better sensitivity and specificity for outcomes, we used the Youden index. We analyzed the data using IBM® SPSS (Statistical Product and Services Solutions, version 18.0, SPSS Inc, Chicago, IL, USA). A  $p$  value  $< 0.05$  was considered significant for all data analyses.

## 3. Results

HTN was an independent risk factor for mortality (OR = 1.96, 95% CI 1.044–3.682,  $p = 0.036$ ; Table S1), ICU (OR = 1.94, 95% CI 1.125–3.330,  $p = 0.017$ ; Table S2), and HD (OR = 2.15, 95% CI 1.188–3.891,  $p = 0.011$ ; Table S3), but not for oxygen requirement (OR = 0.98, 95% CI 0.581–1.660,  $p = 0.947$ ; Table S4) and IMV (OR = 1.72, 95% CI 0.958–3.097,  $p = 0.069$ ; Table S5). Composite analyses including the outcomes of mortality, ICU, and HD also documented HTN as an independent risk factor (OR = 2.18, 95% CI 1.103–4.305,  $p = 0.025$ ; Table S6). In addition, composite analyses including at least one of these outcomes (mortality or ICU or HD) confirmed HTN as an independent risk factor (OR = 1.99, 95% CI 1.163–3.399,  $p = 0.012$ ; Table S7).

When KTRs with HTN were compared to non-HTN, DM (44.4%) and heart disease (13.3%) were found more often (Table 1). To note, only 45 (20%) and 36 (16%) KTR individuals with HTN were taking angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), respectively.

**Table 1.** Demographic data, laboratory data, and outcomes in kidney transplant recipients according to the presence of hypertension (HTN).

|                               | HTN (+)<br>( <i>n</i> = 225, 75%) | HTN (−)<br>( <i>n</i> = 75, 25%) | Total<br>( <i>N</i> = 300, 100%) | Univariable Analysis              | Multivariable Analysis            |
|-------------------------------|-----------------------------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|
| <b>Demographic data</b>       |                                   |                                  |                                  |                                   |                                   |
| Age (years)                   | 53.2 $\pm$ 11.4                   | 50.4 $\pm$ 14.1                  | 52.5 $\pm$ 12.2                  | 1.02 (0.997–1.042, $p = 0.085$ )  | 1.00 (0.979–1.026, $p = 0.862$ )  |
| Male ( <i>n</i> , %)          | 136 (60.4)                        | 36 (48.0)                        | 172 (57.3)                       | 1.66 (0.978–2.801, $p = 0.060$ )  | 1.76 (1.018–3.041, $p = 0.043$ )  |
| Race ( <i>n</i> , %)          |                                   |                                  |                                  |                                   |                                   |
| White                         | 134 (59.6)                        | 50 (66.7)                        | 184 (61.3)                       | 0.74 (0.425–1.275, $p = 0.274$ )  |                                   |
| Black/brown                   | 85 (37.8)                         | 25 (33.3)                        | 110 (36.7)                       |                                   |                                   |
| Transplant time (months)      | 68 (33.0;142.0)                   | 101 (39.5;142.5)                 | 81.5 (33.8;142.3)                | 1.00 (0.995–1.002, $p = 0.436$ )  |                                   |
| Donor type ( <i>n</i> , %)    |                                   |                                  |                                  |                                   |                                   |
| Living                        | 58 (25.8)                         | 27 (36.0)                        | 85 (28.3)                        | 1.62 (0.927–2.830, $p = 0.090$ )  | 1.47 (0.820–2.635, $p = 0.196$ )  |
| Deceased                      | 167 (74.2)                        | 48 (64.0)                        | 215 (71.7)                       |                                   |                                   |
| BMI (kg/m <sup>2</sup> )      | 27.2 $\pm$ 4.7                    | 26.1 $\pm$ 5.3                   | 26.9 $\pm$ 4.9                   | 1.05 (0.991–1.113, $p = 0.100$ )  |                                   |
| BMI $\geq 25$ ( <i>n</i> , %) | 93 (41.3)                         | 27 (36.0)                        | 120 (40.0)                       | 1.19 (0.682–2.063, $p = 0.546$ )  |                                   |
| BMI $\geq 30$ ( <i>n</i> , %) | 52 (23.1)                         | 13 (17.3)                        | 65 (21.7)                        | 1.40 (0.710–2.757, $p = 0.332$ )  |                                   |
| DM ( <i>n</i> , %)            | 100 (44.4)                        | 17 (22.7)                        | 117 (39.0)                       | 2.73 (1.496–4.979, $p = 0.001$ )  | 2.38 (1.250–4.510, $p = 0.008$ )  |
| COPD ( <i>n</i> , %)          | 7 (3.1)                           | 2 (2.7)                          | 9 (3.0)                          | 1.17 (0.238–5.768, $p = 0.845$ )  |                                   |
| Heart disease ( <i>n</i> , %) | 30 (13.3)                         | 2 (2.7)                          | 32 (10.7)                        | 5.62 (1.309–24.903, $p = 0.020$ ) | 4.24 (0.952–18.897; $p = 0.058$ ) |

Table 1. Cont.

|                                | HTN (+)<br>(n = 225, 75%) | HTN (−)<br>(n = 75, 25%) | Total<br>(N = 300, 100%) | Univariable Analysis                 | Multivariable Analysis               |
|--------------------------------|---------------------------|--------------------------|--------------------------|--------------------------------------|--------------------------------------|
| Neoplasia (n, %)               | 15 (6.7)                  | 6 (8.0)                  | 21 (7.0)                 | 0.82 (0.307–2.200, <i>p</i> = 0.696) |                                      |
| Liver disease (n, %)           | 9 (4.0)                   | 0 (0)                    | 9 (3.0)                  | - (-, <i>p</i> = 0.999)              |                                      |
| Autoimmune disease (n, %)      | 4 (1.8)                   | 2 (2.7)                  | 6 (2.0)                  | 0.66 (0.119–3.681, <i>p</i> = 0.636) |                                      |
| Smoking (n, %)                 | 48 (21.3)                 | 14 (18.7)                | 62 (20.7)                | 1.24 (0.626–2.444, <i>p</i> = 0.540) |                                      |
| <b>Laboratory data</b>         |                           |                          |                          |                                      |                                      |
| Basal eGFR                     | 47 (30;64)                | 48 (32;65)               | 46.8 (30.8;64.2)         | 1.00 (0.990–1.011, <i>p</i> = 0.936) |                                      |
| Admission eGFR                 | 34 (19;49)                | 35 (22;52)               | 34 (20;50)               | 1.00 (0.985–1.009, <i>p</i> = 0.633) |                                      |
| Previous glycemia (mg/dL)      | 97 (86.3;136)             | 94 (82;108)              | 96 (84;121)              | 1.00 (0.999–1.009, <i>p</i> = 0.158) |                                      |
| CRP (mg/dL)                    | 6.3 (2.1;13.2)            | 5.2 (1.2;10.6)           | 5.7 (2.0;12.6)           | 1.03 (0.988–1.063, <i>p</i> = 0.187) |                                      |
| LDH (U/L)                      | 288.5 (227;405.5)         | 273 (191;354)            | 287 (220;395)            | 1.00 (1.000–1.003, <i>p</i> = 0.103) |                                      |
| Lymphocytes (mm <sup>3</sup> ) | 695(461.8;1195.3)         | 852 (520;1122)           | 738 (468;1174.5)         | 1.00 (1.000–1.000, <i>p</i> = 0.795) |                                      |
| D-dimer (μg/L)                 | 1.2 (0.6;2.3)             | 1.2 (0.5;1.8)            | 1.2 (0.6;2.3)            | 1.11 (0.987–1.258, <i>p</i> = 0.080) |                                      |
| AST (U/L)                      | 28 (20;40)                | 32 (24;43)               | 28 (21;41)               | 1.00 (0.991–1.006, <i>p</i> = 0.663) |                                      |
| ALT (U/L)                      | 21 (14;32.5)              | 20 (16;28)               | 21 (15;32)               | 1.00 (0.990–1.014, <i>p</i> = 0.768) |                                      |
| <b>Outcomes</b>                |                           |                          |                          |                                      |                                      |
| Mortality (n, %)               | 74 (32.9)                 | 15 (20.0)                | 89 (29.7)                | 1.96 (1.044–3.682, <i>p</i> = 0.036) | 1.67 (0.572–4.850, <i>p</i> = 0.349) |
| ICU (n, %)                     | 114 (50.7)                | 26 (34.7)                | 140 (46.7)               | 1.94 (1.125–3.330, <i>p</i> = 0.017) | 1.83 (0.724–4.646, <i>p</i> = 0.201) |
| O <sub>2</sub> (n, %)          | 122 (54.2)                | 41 (54.7)                | 163 (54.3)               | 0.98 (0.581–1.660, <i>p</i> = 0.947) |                                      |
| IMV (n, %)                     | 83 (36.9)                 | 19 (25.3)                | 102 (34.0)               | 1.72 (0.958–3.097, <i>p</i> = 0.069) | 0.47 (0.124–1.781, <i>p</i> = 0.267) |
| AKI (n, %)                     | 134 (59.6)                | 40 (53.3)                | 174 (58.0)               | 1.29 (0.761–2.180, <i>p</i> = 0.345) |                                      |
| Stage 1                        | 25 (11.1)                 | 13 (17.3)                | 38 (12.7)                | 0.60 (0.288–1.235, <i>p</i> = 0.164) |                                      |
| Stage 2                        | 9 (4.0)                   | 7 (9.3)                  | 16 (5.3)                 | 0.41 (0.145–1.128, <i>p</i> = 0.084) | 0.44 (0.146–1.340, <i>p</i> = 0.149) |
| Stage 3                        | 100 (44.4)                | 20 (26.7)                | 120 (40.0)               | 2.20 (1.237–3.911, <i>p</i> = 0.007) | 1.54 (0.383–6.211, <i>p</i> = 0.542) |
| HD (n, %)                      | 91 (40.4)                 | 18 (24.0)                | 109 (36.3)               | 2.15 (1.188–3.891, <i>p</i> = 0.011) | 1.12 (0.221–5.637, <i>p</i> = 0.895) |

HTN: hypertension; BMI: body mass index; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate (in mL/min/1.73 m<sup>2</sup>); CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICU: intensive care unit; O<sub>2</sub>: use of supplemental oxygen; IMV: invasive mechanical ventilation; AKI: acute kidney injury; HD: hemodialysis. All variables are median and IQR, except age and BMI, which are means ± SD. Univariable and multivariable analyses are represented by odds ratios, 95% confidence intervals, and *p*-values, respectively.

Despite the presence of HTN, we did not find a difference in laboratory parameters when compared to non-hypertensive KTRs (Table 1). However, clinical outcomes were worse in hypertensive recipients, including higher mortality (OR = 1.96), need for ICU admission (OR = 1.94), development of AKI, particularly stage 3 (OR = 2.20), and need for HD (OR = 2.15) (Table 1).

Next, we investigated the main risk factors, including demographic data and laboratory parameters that were associated with mortality, transferring to the ICU, and hemodialysis requirement in kidney transplant recipients with HTN, as these outcomes were statistically different when compared to non-HTN individuals.

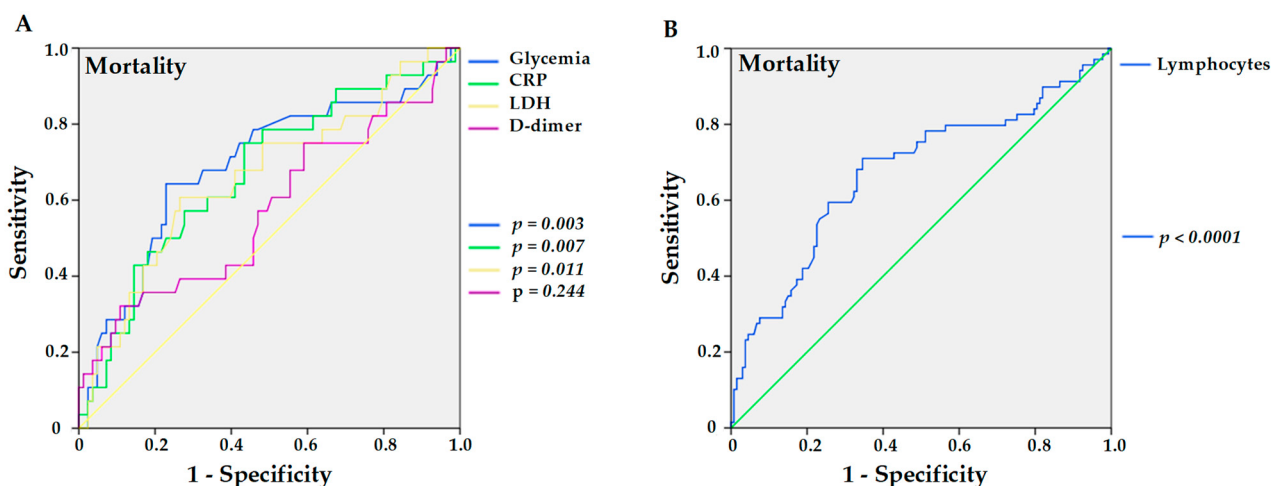
In the hypertensive group, age, DM, heart disease, smoking, glycemic control before admission, CRP, LDH, lymphocytes, and D-dimer were significantly associated with mortality (Table 2). In the multivariable analysis, age, heart disease, smoking, previous glycemic control, and lymphopenia remained risk factors for mortality in KTR hypertensive group (Table 2).

**Table 2.** Risk factors for mortality in kidney transplant recipients with hypertension (HTN).

|                                    | Not Alive<br>( <i>n</i> = 74, 32.9%) | Alive<br>( <i>n</i> = 151, 67.1%) | Univariable Analysis                  | Multivariable Analysis                |
|------------------------------------|--------------------------------------|-----------------------------------|---------------------------------------|---------------------------------------|
| <b>Demographic Data</b>            |                                      |                                   |                                       |                                       |
| Age (years)                        | 58.6 ± 10.5                          | 50.5 ± 11.0                       | 1.07 (1.041–1.104, <i>p</i> < 0.0001) | 1.06 (1.026–1.100, <i>p</i> = 0.001)  |
| Male ( <i>n</i> , %)               | 44 (59.5)                            | 92 (60.9)                         | 0.94 (0.533–1.659, <i>p</i> = 0.832)  |                                       |
| Race ( <i>n</i> , %)               |                                      |                                   |                                       |                                       |
| White                              | 46 (62.2)                            | 88 (58.3)                         | 1.18 (0.665–2.081, <i>p</i> = 0.577)  |                                       |
| Black/brown                        | 24 (32.4)                            | 61 (40.4)                         |                                       |                                       |
| Transplant time (months)           | 78 (41;125.8)                        | 65 (30;143.5)                     | 1.00 (0.997–1.005, <i>p</i> = 0.654)  |                                       |
| Donor type ( <i>n</i> , %)         |                                      |                                   |                                       |                                       |
| Living                             | 14 (18.9)                            | 44 (29.1)                         | 1.76 (0.893–3.477, <i>p</i> = 0.102)  |                                       |
| Deceased                           | 60 (81.1)                            | 107 (70.9)                        |                                       |                                       |
| BMI (kg/m <sup>2</sup> )           | 27.2 ± 4.4                           | 27.1 ± 4.9                        | 1.00 (0.945–1.067, <i>p</i> = 0.894)  |                                       |
| BMI ≥ 25 ( <i>n</i> , %)           | 32 (43.2)                            | 61 (40.4)                         | 1.21 (0.677–2.144, <i>p</i> = 0.526)  |                                       |
| BMI ≥ 30 ( <i>n</i> , %)           | 17 (23.0)                            | 35 (23.2)                         | 1.04 (0.532–2.019, <i>p</i> = 0.915)  |                                       |
| DM ( <i>n</i> , %)                 | 40 (54.1)                            | 60 (39.7)                         | 1.78 (1.018–3.128, <i>p</i> = 0.043)  | 0.96 (0.461–1.994, <i>p</i> = 0.911)  |
| COPD ( <i>n</i> , %)               | 2 (2.7)                              | 5 (3.3)                           | 0.81 (0.154–4.283, <i>p</i> = 0.805)  |                                       |
| Heart disease ( <i>n</i> , %)      | 17 (23.0)                            | 13 (8.6)                          | 3.17 (1.444–6.943, <i>p</i> = 0.004)  | 3.70 (1.302–10.526, <i>p</i> = 0.014) |
| Neoplasia ( <i>n</i> , %)          | 7 (9.5)                              | 8 (5.3)                           | 1.87 (0.650–5.364, <i>p</i> = 0.246)  |                                       |
| Liver disease ( <i>n</i> , %)      | 5 (6.8)                              | 4 (2.6)                           | 2.66 (0.693–10.227, <i>p</i> = 0.154) |                                       |
| Autoimmune disease ( <i>n</i> , %) | 1 (1.4)                              | 3 (2.0)                           | 0.68 (0.069–6.610, <i>p</i> = 0.736)  |                                       |
| Smoking ( <i>n</i> , %)            | 22 (29.7)                            | 26 (17.2)                         | 2.12 (1.071–4.180, <i>p</i> = 0.031)  | 2.20 (1.051–4.616, <i>p</i> = 0.036)  |
| <b>Laboratory Data</b>             |                                      |                                   |                                       |                                       |
| Basal eGFR                         | 49 (25;63)                           | 46 (32;63)                        | 1.00 (0.988–1.010, <i>p</i> = 0.870)  |                                       |
| Admission eGFR                     | 30 (17;46)                           | 35 (22;50)                        | 1.00 (0.982–1.008, <i>p</i> = 0.434)  |                                       |
| Previous glycemia (mg/dL)          | 115 (93;191)                         | 92 (83;114)                       | 1.01 (1.006–1.017, <i>p</i> < 0.0001) | 1.02 (1.007–1.029, <i>p</i> = 0.002)  |
| CRP (mg/dL)                        | 13.2 (5.5;19.0)                      | 4.4 (1.7;10.3)                    | 1.08 (1.038–1.119, <i>p</i> < 0.0001) | 1.03 (0.964–1.095, <i>p</i> = 0.410)  |
| LDH (U/L)                          | 360 (271.5;474.5)                    | 270 (224;356)                     | 1.00 (1.000–1.003, <i>p</i> = 0.049)  | 1.00 (0.999–1.004, <i>p</i> = 0.193)  |
| Lymphocytes (mm <sup>3</sup> )     | 524 (348;789)                        | 819 (570;1230)                    | 1.00 (0.999–1.000, <i>p</i> = 0.039)  | 1.00 (0.997–1.000, <i>p</i> = 0.043)  |
| D-dimer (µg/L)                     | 1.5 (0.7;2.8)                        | 1.1 (0.6;2.1)                     | 1.10 (1.020–1.194, <i>p</i> = 0.014)  | 1.19 (0.988–1.426, <i>p</i> = 0.067)  |
| AST (U/L)                          | 29 (20;41.5)                         | 27 (21;39)                        | 1.00 (0.992–1.009, <i>p</i> = 0.889)  |                                       |
| ALT (U/L)                          | 22.5 (13.8;32.3)                     | 21 (15;33)                        | 1.00 (0.990–1.013, <i>p</i> = 0.836)  |                                       |

HTN: hypertension; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate (in mL/min/1.73 m<sup>2</sup>); CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase. Age and BMI are means ± SD, while transplant time, basal eGFR, admission eGFR, previous glycemia, CRP, LDH, lymphocytes, D-dimer, AST, and ALT are medians and IQR. Univariable and multivariable analyses are indicated as odds ratios, 95% confidence intervals, and *p*-values.

On ROC curve analysis, pre-admission glucose values above 116.0 mg/dL resulted in a sensitivity of 64.3% and specificity of 77.1%, with an area under the curve (AUC) of 0.691 (*p* = 0.003) for mortality in hypertensive KTRs, as shown in Figure 1A. Likewise, values greater than 6.3 mg/dL for CRP had a sensitivity of 75.0%, specificity of 56.6%, and AUC of 0.671 (*p* = 0.007) (Figure 1A). LDH had a sensitivity of 60.7%, specificity of 73.5%, and AUC of 0.66 (*p* = 0.011) for values greater than 334 U/L, whereas D-dimer exhibited a sensitivity of 32.1%, specificity of 89.2%, and AUC of 0.574 (*p* = 0.244) for values greater than 2.51 µg/L (Figure 1A). In addition, lymphopenia showed a sensitivity of 71%, specificity of 65.4%, and AUC of 0.675 (*p* < 0.0001) for values less than 673 mm<sup>3</sup> for mortality in hypertensive patients, as shown in Figure 1B.



**Figure 1.** Sensitivities and specificities of higher levels of previous glycemia ( $p = 0.003$ ), C-reactive protein (CRP,  $p = 0.007$ ), lactate dehydrogenase (LDH;  $p = 0.011$ ), and D-dimer ( $p = 0.244$ ) (A), and lower levels of lymphocytes ( $p < 0.0001$ ) (B) in hypertensive kidney transplant recipients with COVID-19 for the outcome of mortality.

When the risk factors for transferring to ICU were analyzed in the hypertensive group, we observed similar risk factors to those found for mortality outcome, including age, heart disease, glycemic control before admission, CRP, LDH, and D-dimer, in addition to eGFR at admission, as shown in Table 3. To note, age, heart disease, glycemic control before admission, LDH, and D-dimer remained risk factors in multivariable analyses, as well as lymphopenia (Table 3). Moreover, the majority of patients transferred to ICU needed IMV ( $n = 83$ , 72.8%), had AKI ( $n = 100$ , 87.7%), needed HD ( $n = 85$ , 74.6%), and died ( $n = 72$ , 63.2%).

**Table 3.** Risk factors for intensive care unit (ICU) admission in kidney transplant recipients with hypertension (HTN).

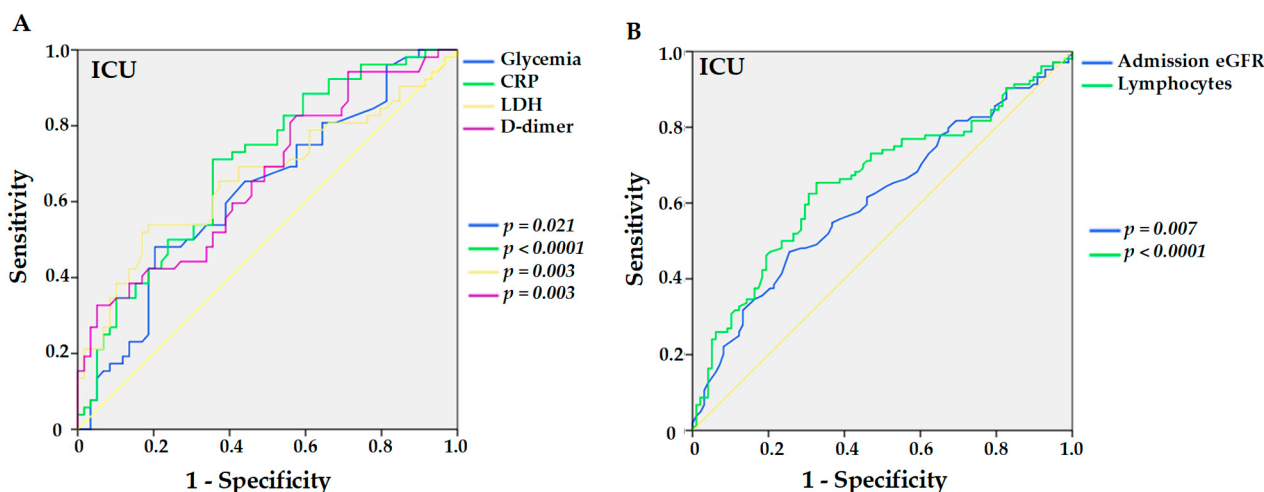
|                                | ICU<br>( $n = 114$ , 50.7%) | No ICU<br>( $n = 111$ , 49.3%) | Univariable Analysis              | Multivariable Analysis            |
|--------------------------------|-----------------------------|--------------------------------|-----------------------------------|-----------------------------------|
| <b>Demographic Data</b>        |                             |                                |                                   |                                   |
| Age (years)                    | 56.9 $\pm$ 11.1             | 49.3 $\pm$ 10.5                | 1.07 (1.039–1.096, $p < 0.0001$ ) | 1.05 (1.018–1.081, $p = 0.002$ )  |
| Male ( $n$ , %)                | 65 (57.0)                   | 71 (64.0)                      | 0.75 (0.437–1.278, $p = 0.287$ )  |                                   |
| Race ( $n$ , %)                |                             |                                |                                   |                                   |
| White                          | 70 (61.4)                   | 64 (57.7)                      | 1.17 (0.686–1.991, $p = 0.567$ )  |                                   |
| Black/brown                    | 39 (34.2)                   | 46 (41.4)                      |                                   |                                   |
| Transplant time (months)       | 84 (37.5;137)               | 61 (29;142.5)                  | 1.00 (0.997–1.005, $p = 0.549$ )  |                                   |
| Donor type ( $n$ , %)          |                             |                                |                                   |                                   |
| Living                         | 29 (25.4)                   | 29 (26.1)                      | 1.04 (0.570–1.884, $p = 0.906$ )  |                                   |
| Deceased                       | 85 (74.6)                   | 82 (73.9)                      |                                   |                                   |
| BMI ( $\text{kg}/\text{m}^2$ ) | 27.4 $\pm$ 4.6              | 26.9 $\pm$ 4.8                 | 1.02 (0.967–1.084, $p = 0.422$ )  |                                   |
| BMI $\geq 25$ ( $n$ , %)       | 48 (42.1)                   | 45 (40.5)                      | 1.07 (0.622–1.830, $p = 0.815$ )  |                                   |
| BMI $\geq 30$ ( $n$ , %)       | 29 (25.4)                   | 23 (20.7)                      | 1.31 (0.698–2.450, $p = 0.401$ )  |                                   |
| DM ( $n$ , %)                  | 53 (46.5)                   | 47 (42.3)                      | 1.18 (0.699–2.003, $p = 0.531$ )  |                                   |
| COPD ( $n$ , %)                | 5 (4.4)                     | 2 (1.8)                        | 2.50 (0.475–13.164, $p = 0.280$ ) |                                   |
| Heart disease ( $n$ , %)       | 23 (20.2)                   | 7 (6.3)                        | 3.76 (1.540–9.159, $p = 0.004$ )  | 4.84 (1.316–17.829, $p = 0.018$ ) |
| Neoplasia ( $n$ , %)           | 11 (9.6)                    | 4 (3.6)                        | 2.86 (0.881–9.259, $p = 0.080$ )  | 4.99 (0.547–45.405, $p = 0.154$ ) |
| Liver disease ( $n$ , %)       | 6 (5.3)                     | 3 (2.7)                        | 2.00 (0.488–8.203, $p = 0.336$ )  |                                   |
| Autoimmune disease ( $n$ , %)  | 3 (2.6)                     | 1 (0.9)                        | 2.97 (0.305–29.022, $p = 0.349$ ) |                                   |
| Smoking ( $n$ , %)             | 31 (27.2)                   | 17 (15.3)                      | 1.97 (0.994–3.890, $p = 0.052$ )  | 2.10 (1.010–4.360, $p = 0.047$ )  |

Table 3. Cont.

|                                | ICU<br>( <i>n</i> = 114, 50.7%) | No ICU<br>( <i>n</i> = 111, 49.3%) | Univariable Analysis                  | Multivariable Analysis               |
|--------------------------------|---------------------------------|------------------------------------|---------------------------------------|--------------------------------------|
| <b>Laboratory Data</b>         |                                 |                                    |                                       |                                      |
| Basal eGFR                     | 44 (27;60)                      | 48 (33;64.7)                       | 1.00 (0.985–1.005, <i>p</i> = 0.327)  |                                      |
| Admission eGFR                 | 29 (17;45)                      | 39 (26;52)                         | 0.99 (0.973–0.997, <i>p</i> = 0.018)  | 0.98 (0.956–1.004, <i>p</i> = 0.094) |
| Previous glycemia (mg/dL)      | 108.5 (89;163.8)                | 92 (83;107.5)                      | 1.01 (1.006–1.018, <i>p</i> < 0.0001) | 1.01 (1.001–1.022, <i>p</i> = 0.026) |
| CRP (mg/dL)                    | 10.1 (3.7;17.3)                 | 3.7 (1.4;9.6)                      | 1.08 (1.038–1.124, <i>p</i> < 0.0001) | 1.01 (0.947–1.079, <i>p</i> = 0.739) |
| LDH (U/L)                      | 351.5 (241;483.5)               | 250.5 (219.8;317.8)                | 1.00 (1.002–1.007, <i>p</i> = 0.001)  | 1.00 (1.001–1.008, <i>p</i> = 0.024) |
| Lymphocytes (mm <sup>3</sup> ) | 585 (373.8;903.8)               | 861 (578.5;1289.8)                 | 1.00 (0.999–1.000, <i>p</i> = 0.095)  | 1.00 (0.998–1.000, <i>p</i> = 0.025) |
| D-dimer (μg/L)                 | 1.6 (0.8;2.9)                   | 0.9 (0.5;1.7)                      | 1.17 (1.041–1.303, <i>p</i> = 0.008)  | 1.70 (1.102–2.626, <i>p</i> = 0.016) |
| AST (U/L)                      | 29 (20;42)                      | 27 (21;37)                         | 1.01 (0.997–1.020, <i>p</i> = 0.146)  |                                      |
| ALT (U/L)                      | 22 (14;31)                      | 21 (15;33.5)                       | 1.00 (0.990–1.013, <i>p</i> = 0.798)  |                                      |

HTN: hypertension; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate (in mL/min/1.73 m<sup>2</sup>); CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase. Age and BMI are means ± SD, while transplant time, basal eGFR, admission eGFR, previous glycemia, CRP, LDH, lymphocytes, D-dimer, AST, and ALT are medians and IQR. Univariable and multivariable analyses are indicated as odds ratios, 95% confidence intervals, and *p*-values.

In the analysis of the ROC curve for transferring to ICU, pre-admission glucose and CRP greater than 116.0 mg/dL and 6.1 mg/dL yielded, respectively, sensitivities of 48.1% and 71.2%, specificities of 79.7% and 64.4%, AUC of 0.627 and 0.696 (*p* = 0.021 and *p* < 0.0001), as shown in Figure 2A. LDH and D-dimer yielded, respectively, sensitivities of 53.8% and 32.7%, specificities of 81.4% and 94.9%, AUC of 0.662 and 0.663 (*p* = 0.003, both), for values greater than 334 U/L and 2.46 μg/L (Figure 2A). eGFR at admission and lymphocytes, including values less than 26.5 mL/min/1.73 m<sup>2</sup> and 686 mm<sup>3</sup> respectively, yielded sensitivities of 47.1% and 64.4%, specificities of 74.5% and 67.3, and AUC of 0.610 and 0.658 (*p* = 0.007 and *p* < 0.0001) (Figure 2B).



**Figure 2.** Sensitivities and specificities of higher levels of previous glycemia (*p* = 0.021), C-reactive protein (CRP, *p* < 0.0001), lactate dehydrogenase (LDH, *p* = 0.003), and D-dimer (*p* = 0.003) (A), and lower levels of estimated glomerular ratio (eGFR) at admission (*p* = 0.007) and lymphocytes (*p* < 0.0001) (B) in hypertensive kidney transplant recipients with COVID-19 for the outcome of transferring to the ICU.

Importantly, renal allograft graft function worsened in the hypertensive group, as 134 (59.6%) individuals had AKI, at different stages according to KDIGO, and 91 (40.4%) needed HD. Therefore, age, deceased donor, liver disease, eGFR at baseline and admission, glycemic control before admission, CRP, and LDH were associated with the need for HD (shown in Table 4). Nevertheless, only age was statistically significant in the multivariable

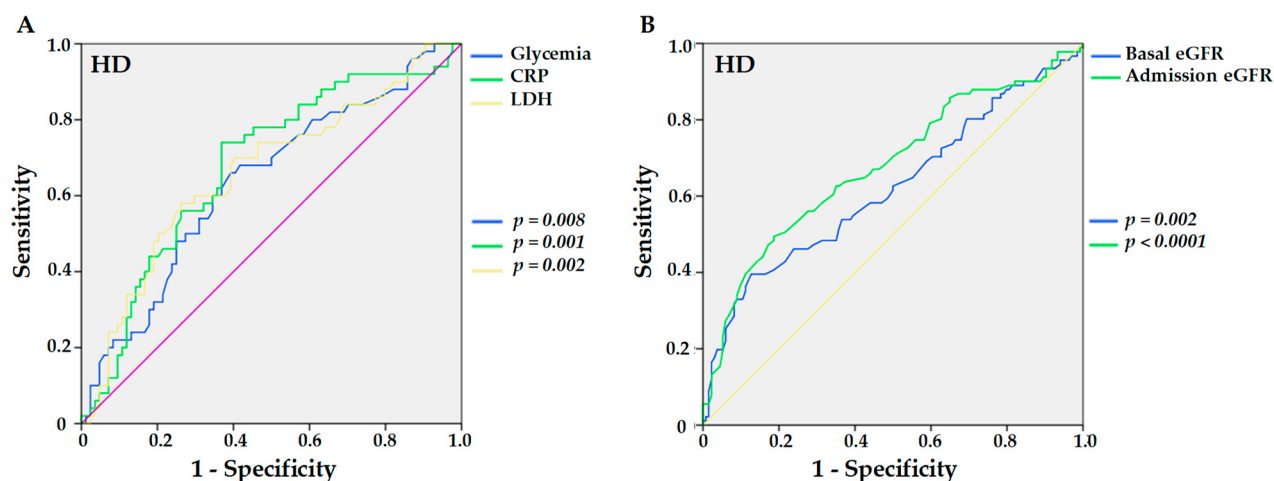
analysis, as shown in Table 4. Among the hypertensive patients who required HD, 85 (93.4%) were transferred to the ICU, 77 (84.6%) needed IMV, and 66 (72.5%) died.

**Table 4.** Risk factors for the need for hemodialysis (HD) in kidney transplant recipients with hypertension (HTN).

|                                    | HD<br>( <i>n</i> = 91, 40.4%) | No HD<br>( <i>n</i> = 134, 59.6%) | Univariable Analysis                  | Multivariable Analysis                |
|------------------------------------|-------------------------------|-----------------------------------|---------------------------------------|---------------------------------------|
| <b>Demographic Data</b>            |                               |                                   |                                       |                                       |
| Age (years)                        | 56.4 ± 11.0                   | 50.9 ± 11.3                       | 1.05 (1.019–1.072, <i>p</i> = 0.001)  | 1.05 (1.015–1.077, <i>p</i> = 0.003)  |
| Male ( <i>n</i> , %)               | 56 (61.5)                     | 80 (59.7)                         | 1.08 (0.626–1.863, <i>p</i> = 0.782)  |                                       |
| Race ( <i>n</i> , %)               |                               |                                   |                                       |                                       |
| White                              | 57 (62.6)                     | 77 (57.5)                         | 1.24 (0.719–2.142, <i>p</i> = 0.438)  |                                       |
| Black/brown                        | 30 (33.0)                     | 55 (41.0)                         |                                       |                                       |
| Transplant time (months)           | 85 (41;130)                   | 62 (29;143.8)                     | 1.00 (0.997–1.004, <i>p</i> = 0.683)  |                                       |
| Donor type ( <i>n</i> , %)         |                               |                                   |                                       |                                       |
| Living                             | 17 (18.7)                     | 41 (30.6)                         | 1.92 (1.009–3.649, <i>p</i> = 0.047)  | 1.15 (0.503–2.643, <i>p</i> = 0.737)  |
| Deceased                           | 74 (81.3)                     | 93 (69.4)                         |                                       |                                       |
| BMI (kg/m <sup>2</sup> )           | 27.3 ± 4.5                    | 27.1 ± 4.9                        | 1.01 (0.950–1.067, <i>p</i> = 0.815)  |                                       |
| BMI ≥ 25 ( <i>n</i> , %)           | 37 (40.7)                     | 56 (41.8)                         | 0.95 (0.549–1.649, <i>p</i> = 0.859)  |                                       |
| BMI ≥ 30 ( <i>n</i> , %)           | 23 (25.3)                     | 29 (21.6)                         | 1.23 (0.653–2.306, <i>p</i> = 0.526)  |                                       |
| DM ( <i>n</i> , %)                 | 45 (49.5)                     | 55 (41.0)                         | 1.41 (0.822–2.402, <i>p</i> = 0.214)  |                                       |
| COPD ( <i>n</i> , %)               | 4 (4.4)                       | 3 (2.2)                           | 2.01 (0.439–9.191, <i>p</i> = 0.369)  |                                       |
| Heart disease ( <i>n</i> , %)      | 17 (18.7)                     | 13 (9.7)                          | 2.14 (0.982–4.655, <i>p</i> = 0.056)  | 2.11 (0.772–5.756, <i>p</i> = 0.146)  |
| Neoplasia ( <i>n</i> , %)          | 8 (8.8)                       | 7 (5.2)                           | 1.75 (0.611–5.004, <i>p</i> = 0.298)  |                                       |
| Liver disease ( <i>n</i> , %)      | 7 (7.7)                       | 2 (1.5)                           | 5.50 (1.116–27.109, <i>p</i> = 0.036) | 2.41 (0.445–13.048, <i>p</i> = 0.307) |
| Autoimmune disease ( <i>n</i> , %) | 2 (2.2)                       | 3 (2.2)                           | 1.48 (0.205–10.724, <i>p</i> = 0.696) |                                       |
| Smoking ( <i>n</i> , %)            | 26 (28.6)                     | 22 (16.4)                         | 1.78 (0.917–3.470, <i>p</i> = 0.088)  | 1.69 (0.835–3.407, <i>p</i> = 0.145)  |
| <b>Laboratory Data</b>             |                               |                                   |                                       |                                       |
| Basal eGFR                         | 41 (21;58)                    | 50 (35;68)                        | 0.99 (0.974–0.996, <i>p</i> = 0.009)  | 1.00 (0.977–1.017, <i>p</i> = 0.753)  |
| Admission eGFR                     | 25 (13;43)                    | 40 (26;53)                        | 0.97 (0.960–0.988, <i>p</i> < 0.0001) | 0.98 (0.951–1.002, <i>p</i> = 0.075)  |
| Previous glycemia (mg/dL)          | 108.5 (90;164.5)              | 92.5 (83;112.8)                   | 1.01 (1.005–1.015, <i>p</i> < 0.0001) | 1.01 (0.999–1.017, <i>p</i> = 0.075)  |
| CRP (mg/dL)                        | 10.1 (4.5;17.1)               | 3.9 (1.7;10.5)                    | 1.05 (1.016–1.088, <i>p</i> = 0.004)  | 1.03 (0.975–1.084, <i>p</i> = 0.306)  |
| LDH (U/L)                          | 357.5 (247.3;488.3)           | 268 (221;347)                     | 1.00 (1.000–1.004, <i>p</i> = 0.041)  | 1.00 (0.999–1.003, <i>p</i> = 0.498)  |
| Lymphocytes (mm <sup>3</sup> )     | 534.5 (371;834)               | 847 (584.3;1260.8)                | 1.00 (0.999–1.000, <i>p</i> = 0.161)  |                                       |
| D-dimer (µg/L)                     | 1.5 (0.7;2.7)                 | 1.1 (0.6;2.1)                     | 1.07 (0.990–1.153, <i>p</i> = 0.087)  | 1.17 (0.986–1.385, <i>p</i> = 0.073)  |
| AST (U/L)                          | 29 (20;42)                    | 27 (21;38)                        | 1.00 (0.993–1.009, <i>p</i> = 0.880)  |                                       |
| ALT (U/L)                          | 23 (14;32)                    | 21 (15;32.8)                      | 1.00 (0.988–1.011, <i>p</i> = 0.941)  |                                       |

HTN: hypertension; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate (in mL/min/1.73 m<sup>2</sup>); CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase. Age and BMI are means ± SD, while transplant time, basal eGFR, admission eGFR, previous glycemia, CRP, LDH, lymphocytes, D-dimer, AST, and ALT are medians and IQR. Univariable and multivariable analyses are indicated as odds ratios, 95% confidence intervals, and *p*-values.

When HD was required, for glycemia control before admission and CRP, values greater than 98.5 and 4.56 mg/dL, the analyses of the ROC curve yielded sensitivities of 66.0% and 74.0%, specificities of 60.7% and 63.1%, and AUC of 0.638 and 0.678 (*p* = 0.008 and *p* = 0.001, respectively), while for LDH, sensitivity was 58.0% and specificity was 73.8% for values above 334 mg/dL (*p* = 0.002) and AUC was 0.662 as shown in Figure 3A. In addition, eGFR at baseline and admission showed, respectively, sensitivities of 39.6% and 49.5%, specificities of 87.3% and 81.3%, and AUC of 0.621 and 0.678 (*p* = 0.002 and *p* < 0.0001) for values less than 29.5 and 24 mL/min/1.73 m<sup>2</sup> for the need for HD (Figure 3B).



**Figure 3.** Sensitivities and specificities of higher levels of previous glycemia ( $p = 0.008$ ), C-reactive protein (CRP,  $p = 0.001$ ), and lactate dehydrogenase (LDH,  $p = 0.002$ ) (A), and lower levels of eGFR at baseline ( $p = 0.002$ ) and at admission ( $p < 0.0001$ ) (B) in hypertensive kidney transplant recipients with COVID-19 for the outcome of the need for hemodialysis (HD).

We next evaluated the outcomes in the non-hypertensive KTR group ( $n = 75$ ) by using univariable analyses. Thus, age ( $p = 0.006$ ), eGFR at admission ( $p = 0.023$ ), CRP ( $p = 0.021$ ), and LDH ( $p = 0.019$ ) were also associated with the mortality outcome, as shown in Table S8. In addition, DM (42.3% vs. 12.2%,  $p = 0.005$ ), LDH ( $p = 0.004$ ), and lymphopenia ( $p = 0.017$ ) were associated with admission to ICU of the non-hypertensive KTRs, as documented in Table S9. For HD requirement, eGFR at admission (23 vs. 43 mL/min/1.73 m<sup>2</sup>,  $p = 0.001$ ) and LDH ( $p = 0.009$ ) were risk factors, as shown in Table S8. Therefore, after performing multivariable analyses in the non-hypertensive KTR group, age was associated with mortality (Table S8), as verified in the hypertensive KTR group (Table 2). LDH, a marker of tissue damage, was a risk factor in both non-HTN and HTN patients for mortality (Tables 2 and S8), need for ICU transferring (Tables 3 and S9), and HD requirement (Tables 4 and S10). To note, in non-hypertensive KTRs, DM was an important risk factor for stratifying these patients for ICU requirement (Table S9). Low rates of eGFR at admission were a risk factor for HD requirement in both non-HTN (Table S10) and HTN patients (Table 4).

#### 4. Discussion

Our study showed that KTRs with HTN had higher rates of mortality, need for ICU admission, development of AKI, and need for HD when affected by COVID-19. Even though the need for IMV was not different between hypertensive and non-hypertensive recipients, the former required IMV more often. The risk factors that were associated with those worse outcomes in KTRs with HTN comprised demographic and laboratory data, including age, the presence of other comorbidities, particularly DM and heart disease, higher levels of previous glucose, CRP, LDH, and D-dimer, and lower levels of eGFR and lymphocytes on admission.

As previously documented in the literature throughout the first year of the pandemic, KTRs presented high rates of disease progression and mortality [11], even when compared to non-transplant patients [12]. However, the association between solid organ transplant (SOT) and increased mortality was debated in the literature, as the presence of comorbidities per se can explain the higher rates of mortality. Therefore, with the application of a propensity score, two distinct studies showed that mortality of KTRs and the general population were similar, suggesting that the worse outcomes of KTRs were mainly explained by the number of comorbidities and not entirely attributable to chronic immunosuppression [13,14]. A recent systematic review and meta-analysis supported these findings [15].

In line with these findings, the National COVID Cohort Collaborative documented that SOT recipients with comorbidities, in particular, HTN, DM, coronary artery disease, and CKD, were tested more often for COVID-19 when compared to patients without these comorbidities [16]. In addition, COVID-19 was associated with AKI, graft rejection, and graft failure, as well as with the occurrence of major adverse cardiac events (acute myocardial infarction, angina, stent occlusion/thrombosis, stroke, transient ischemic attack, congestive heart failure, or death) in SOT setting [16].

When we compared our data to an analysis of 2,054 Brazilian non-transplant individuals during the same period of the COVID-19 pandemic, we verified that our population was younger (53 years old vs. 58 years old) and presented more comorbidities (HTN: 74.7% vs. 52.9%; DM: 39% vs. 29.2%; obesity: 21.7% vs. 17.2%) [17]. Despite these demographic differences, we observed similar rates of ICU transferring (46.7% vs. 47.6%) and IMV (34% vs. 32.5%), yet we encountered higher in-hospital mortality rates (29.7% vs. 22%) and need for HD (36.3% vs. 12.2%) [17]. These findings may be explained by the greater number of comorbidities and lower kidney function in the renal transplant population. Likewise, a Brazilian longitudinal cohort study of 398,063 admissions in public hospitals of non-transplanted individuals with COVID-19 of all ages documented a case-fatality rate of 21.7%, decreasing from 31.8% to 18.2% following the same time of our study (March to October 2020) [18].

HTN is an independent risk factor for COVID-19 progression and mortality [19], as we have also demonstrated. Conversely, the British and Irish Hypertension Society documented, after examining over 17 million health records in England, that HTN or a recorded blood pressure  $\geq 140/90$  mmHg were not associated with higher mortality rates after full adjustment [20]. Therefore, the isolated diagnosis of HTN was associated with a slightly higher risk of mortality (HR = 1.07), which is explained by the strong age-related association.

Age is an independent risk factor for COVID-19 mortality [21,22], which may be explained by age-related immunosenescence [23]. Moreover, people over 60 years old have a significantly higher prevalence of cardio-metabolic risk factors, such as HTN, DM, obesity, and dyslipidemia, which also contribute to the worsening of COVID-19 [24]. In a multicenter study with 1,303 hospitalized patients, 39.9% had a cardio-metabolic disease and, when compared to patients without the cardio-metabolic disease, those patients had more COVID-19-related complications, including ARDS, AKI, secondary infection, hypoproteinemia, and coagulopathy [25]. In addition, the cardio-metabolic group had higher incidences of COVID-19 progression, including admission to ICU, IMV, and mortality. Similarly, in a larger cohort with 29,995 participants, cardio-metabolic risk factors, adjusted for age and gender, were still associated with COVID-19 hospitalization and mortality, comprising obesity (aOR = 4.09), pre-diabetes (aOR = 2.56), DM (aOR = 3.96), sedentary time (aOR per hour/day increase = 1.10) and grade 2 HTN (aOR = 2.44), and high-density lipoprotein cholesterol (aOR per mmol/L increase = 0.33) [26]. These findings highlight the paramount importance of adherence to pharmacological and non-pharmacological approaches to decrease the cardio-metabolic syndrome burden, and ultimately, the COVID-19 severity, in particular, in the kidney transplant population.

Likewise, the presence of comorbidities may also adversely impact the COVID-19 severity in the transplant setting. Thus, in our group of KTRs with HTN, 44.4% also had DM. A combined prevalence of HTN and DM appears to confer the greatest mortality (OR = 2.75) when HTN is analyzed separately (OR = 1.69) [27]. On top of these findings, hyperglycemia has emerged as an important risk factor for COVID-19 progression. In a study of 3,854 patients, glycemic levels greater than  $>170$  mg/dL were also associated with worse outcomes in COVID-19, including an increase in intubation rate (OR = 15.6) and mortality (OR = 3.6), longer hospitalization time, and increased risk for developing ARDS (OR = 9.3) [28]. Using propensity-score matching, our group also documented that higher previous fasting blood glucose was associated with worse outcomes on KTRs independently of DM status [29]. As SARS-CoV-2 induces adipose tissue dysfunction by binding to ACE2

receptor [8], the reduction of adiponectin and adiponectin/leptin ratio is associated with the increase in type I interferon signaling pathway and activation of the innate immune response, which leads to insulin resistance and, consequently, hyperglycemia [28]. These findings may also explain the association between previous glucose control and COVID-19 adverse outcomes in our KTRs with HTN, in particular, ICU transferring, need for HD, and mortality. To note, in KTRs without HTN, we did not verify this association.

From the pathophysiology perspective of COVID-19, SARS-CoV-2 induces direct cell toxicity, dysregulation of RAAS and kallikrein-kinin system, endothelial cell damage associated with thromboinflammation and thromboembolic events, dysregulation of the immune system characterized by hyperactivation of the innate immune system, hyperinflammation caused by inhibition of interferon signaling, T cell lymphodepletion by exhaustion, and the production of proinflammatory cytokines, particularly IL-6 and TNF $\alpha$ , which ultimately lead to cytokine storm [30,31].

Therefore, ACE2 triggers the entry of SARS-CoV-2 into host cells [8] and is highly expressed in the heart, kidneys, and lungs, which explains SARS-CoV-2 tropism and damage to these organs [32]. Strikingly, ACE2 is over-expressed within the lungs of individuals with comorbidities [33], contributing to COVID-19 progression and mortality, as observed in our population of KTRs with HTN, DM, CKD, and cardiac disease. Therefore, viral pathogen-associated molecular patterns (PAMPs) bind to Toll-like receptors-4 located in alveolar macrophage and activate adaptor protein MyD88-TNF receptor-associated factor (TRAF) 6 pathway and nuclear factor kappa B (NF- $\kappa$ B) translocation into the nucleus, as well as the inflammasome, and ultimately the proinflammatory cytokine release, as reviewed elsewhere [34]. Smoking can also augment the inflammatory microenvironment in the lungs and contributes to COVID-19 mortality [35], as we observed in our study.

In addition, the presence of those comorbidities is associated with chronic endothelial dysfunction, which is aggravated by SARS-CoV-2 infection and endotheliitis [8]. Endothelial dysfunction is related to vascular and cardiac complications in patients with COVID-19 as these patients exhibited substantially lower flow-mediated dilation of peripheral arteries during the post-infection stage [36]. Therefore, temporal changes in the endothelium-mediated dilation of peripheral arteries, found in acute COVID-19 to the post-infection stage, suggest that endothelial vascular dysfunction may be a chronic complication of this disease [37].

In clinical practice, the interaction of SARS-CoV-2 with the ACE2 receptor did not affect the decision of using RAAS blockers, primarily ACEi and ARBs. These drugs neither increase ACE2 expression within the motile cilia of upper and lower airway epithelial cells [38] nor increase the risk of COVID-19 and the likelihood of a positive test [39,40], even when adjusted for age, gender, and cardiovascular risk [41]. Moreover, poor blood-pressure control was associated with worse outcomes in HTN patients with COVID-19, indicating that these patients may have more advanced atherosclerosis and target organ damage [42]. Therefore, anti-hypertensive drugs should not be discontinued in hypertensive patients during the COVID-19 pandemic.

In addition, early identification of laboratory parameters associated with SARS-CoV-2-mediated thromboinflammation is a key aspect to manage KTRs during the pandemic. Longitudinal analyses of these markers indicate different degrees of inflammation (increased levels of IL-6 and CRP), infection (increased levels of ferritin and neutrophils and decreased levels of lymphocytes), thrombosis (increased D-dimer and thrombin associated with decreased fibrinolysis), and tissue damage (increased LDH, AST, and ALT, and decreased fibrinogen) [30].

Importantly, as we verified in our group of KTRs with HTN who died, increased levels of CRP [43], LDH [44], and D-dimer can be used as prognostic factors in COVID-19. These markers, as well as procalcitonin and high sensitivity-troponin I, are also useful tools for risk-stratifying KTRs with COVID-19 [11,22]. In addition, lymphopenia is a surrogate marker of poor prognosis in COVID-19 [11,45], which prompts the reduction or withdrawal of immunosuppressive drugs used in transplant settings, particularly antimetabolites [11].

AKI is paramount in determining the severity of COVID-19 and is independently associated with progression and mortality, including all stages and the need for HD [46]. Predictors of AKI include age, black race, male gender, HTN, DM, obesity, and lower eGFR [47]. In our population, 58% of our population developed AKI regardless of the presence of HTN, although in KTRs with HTN the degree of AKI was more severe. Similar rates of AKI were found in KTRs during the COVID-19 pandemic [11,48,49]. Systemic inflammation and kidney function, which is usually lower in deceased donors, and hepatic diseases, pose these patients at higher risk of AKI [22,49], as we also verified in our population.

Our study has some limitations, as we performed a retrospective analysis in a single center, the number of patients that were excluded due to lack of data, other laboratory parameters were not available (such as immune profiling, cardiac and hematologic markers), the low number of patients using ACE inhibitors or ARBs, and the lack of use of drugs that were later demonstrated to have efficacy during the pandemic, such as dexamethasone and tocilizumab.

## 5. Conclusions

In conclusion, demographic and laboratory parameters may be used to improve risk stratification at hospital admission in KTRs with HTN. Therefore, the early identification of factors that predict COVID-19 progression and mortality in KTRs affected by COVID-19 contributes to therapeutic decisions, patient flow management, and allocation of resources.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/v14112409/s1>, Figure S1: Flowchart of patients included for selection of study patients. DGF = Delayed graft function; Table S1: Risk factors for mortality in kidney transplant recipients; Table S2: Risk factors for intensive care unit (ICU) admission in kidney transplant recipients; Table S3: Risk factors for the need for hemodialysis (HD) admission in kidney transplant recipients; Table S4: Risk factors for the use of supplemental oxygen (O<sub>2</sub>) admission in kidney transplant recipients; Table S5: Risk factors for the need for invasive mechanical ventilation (IMV) admission in kidney transplant recipients; Table S6: Risk factors for composite outcomes of mortality, and ICU and HD in kidney transplant recipients; Table S7: Risk factors for composite outcomes of mortality, or ICU or HD in kidney transplant recipients; Table S8: Risk factors for mortality in kidney transplant recipients without hypertension (HTN); Table S9: Risk factors for intensive care unit (ICU) admission in kidney transplant recipients without hypertension (HTN); Table S10: Risk factors for the need for hemodialysis (HD) in kidney transplant recipients without hypertension (HTN).

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**Informed Consent Statement:** Informed consent was obtained from all patients, whereas a waiver was granted for patients who died in other hospitals.

**Data Availability Statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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## References

- Romero, S.K.; Reissig, D.; Petereit-Haack, G.; Schmauder, S.; Nienhaus, A.; Seidler, A. The isolated effect of age on the risk of COVID-19 severe outcomes: A systematic review with meta-analysis. *BMJ Glob. Health* **2021**, *6*, e006434. [\[CrossRef\]](#) [\[PubMed\]](#)
- Ejaz, H.; Alsrhani, A.; Zafar, A.; Javed, H.; Junaid, K.; Abdalla, A.E.; Abosalif, K.O.A.; Ahmed, Z.; Younas, S. COVID-19 and comorbidities: Deleterious impact on infected patients. *J. Infect. Public Health* **2020**, *13*, 1833–1839. [\[CrossRef\]](#)
- Ng, W.H.; Tipih, T.; Makoah, N.A.; Vermeulen, J.G.; Goedhals, D.; Sempa, J.B.; Burt, F.J.; Taylor, A.; Mahalingam, S. Comorbidities in SARS-CoV-2 Patients: A Systematic Review and Meta-Analysis. *mBio* **2021**, *12*, e03647-20. [\[CrossRef\]](#) [\[PubMed\]](#)
- Udomkarnjananun, S.; Kerr, S.J.; Townamchai, N.; Susantitaphong, P.; Tulvatana, W.; Praditpornsilpa, K.; Eiam-Ong, S.; Avihingsanon, Y. Mortality risk factors of COVID-19 infection in kidney transplantation recipients: A systematic review and meta-analysis of cohorts and clinical registries. *Sci. Rep.* **2021**, *11*, 20073. [\[CrossRef\]](#) [\[PubMed\]](#)
- Nishiga, M.; Wang, D.W.; Han, Y.; Lewis, D.B.; Wu, J.C. COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. *Nat. Rev. Cardiol.* **2020**, *17*, 543–558. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zhong, L.; Wu, Y.; Gao, J.; Zhang, J.; Xie, Q.; He, H.; Ji, J.; Liu, Z.; Wang, C.; Liu, Z. Effects of hypertension on the outcomes of COVID-19: A multicentre retrospective cohort study. *Ann. Med.* **2021**, *53*, 770–776. [\[CrossRef\]](#) [\[PubMed\]](#)
- Cunningham, J.W.; Vaduganathan, M.; Claggett, B.L.; Jering, K.S.; Bhatt, A.S.; Rosenthal, N.; Solomon, S.D. Clinical Outcomes in Young US Adults Hospitalized with COVID-19. *JAMA Intern. Med.* **2020**, *81*, 379–381. [\[CrossRef\]](#) [\[PubMed\]](#)
- Beyerstedt, S.; Casaro, E.B.; Rangel, E.B. COVID-19: Angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur. J. Clin. Microbiol. Infect. Dis.* **2021**, *40*, 905–919. [\[CrossRef\]](#) [\[PubMed\]](#)
- De Freitas, V.M.; Chiloff, D.M.; Bosso, G.G.; Teixeira, J.O.P.; Hernandez, I.C.G.; Padilha, M.D.P.; Moura, G.C.; de Andrade, L.G.M.; Mancuso, F.; Finamor, F.E.; et al. A Machine Learning Model for Predicting Hospitalization in Patients with Respiratory Symptoms during the COVID-19 Pandemic. *J. Clin. Med.* **2022**, *11*, 4574. [\[CrossRef\]](#)
- Moses, J.C.; Adibi, S.; Wickramasinghe, N.; Nguyen, L.; Angelova, M.; Islam, S.M.S. Smartphone as a Disease Screening Tool: A Systematic Review. *Sensors* **2022**, *22*, 3787. [\[CrossRef\]](#) [\[PubMed\]](#)
- Cravedi, P.; Mothi, S.S.; Azzi, Y.; Haverly, M.; Farouk, S.S.; Perez-Saez, M.J.; Redondo-Pachon, M.D.; Murphy, B.; Florman, S.; Cyrino, L.G.; et al. COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium. *Am. J. Transplant.* **2020**, *20*, 3140–3148. [\[CrossRef\]](#) [\[PubMed\]](#)
- Caillard, S.; Chavarot, N.; Francois, H.; Matignon, M.; Greze, C.; Kamar, N.; Gatault, P.; Thaumat, O.; Legris, T.; Frimat, L.; et al. Is COVID-19 infection more severe in kidney transplant recipients? *Am. J. Transplant.* **2021**, *21*, 1295–1303. [\[CrossRef\]](#) [\[PubMed\]](#)
- Molnar, M.Z.; Bhalla, A.; Azhar, A.; Tsujita, M.; Talwar, M.; Balaraman, V.; Sodhi, A.; Kadaria, D.; Eason, J.D.; Hayek, S.S.; et al. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. *Am. J. Transplant.* **2020**, *20*, 3061–3071. [\[CrossRef\]](#)
- Chavarot, N.; Gueguen, J.; Bonnet, G.; Jdidou, M.; Trimaille, A.; Burger, C.; Amrouche, L.; Weizman, O.; Pommier, T.; Aubert, O.; et al. COVID-19 severity in kidney transplant recipients is similar to nontransplant patients with similar comorbidities. *Am. J. Transplant.* **2021**, *21*, 1285–1294. [\[CrossRef\]](#)
- Gatti, M.; Rinaldi, M.; Bussini, L.; Bonazzetti, C.; Pascale, R.; Pasquini, Z.; Fani, F.; Pinho Guedes, M.N.; Azzini, A.M.; Carrara, E.; et al. Clinical outcome in solid organ transplant recipients affected by COVID-19 compared to general population: A systematic review and meta-analysis. *Clin. Microbiol. Infect.* **2022**, *28*, 1057–1065. [\[CrossRef\]](#) [\[PubMed\]](#)
- Vinson, A.J.; Agarwal, G.; Dai, R.; Anzalone, A.J.; Lee, S.B.; French, E.; Olex, A.; Madhira, V.; Mannon, R.B. COVID-19 in Solid Organ Transplantation: Results of the National COVID Cohort Collaborative. *Transplant. Direct.* **2021**, *7*, e775. [\[CrossRef\]](#) [\[PubMed\]](#)
- Marcolino, M.S.; Ziegelmann, P.K.; Souza-Silva, M.V.R.; Nascimento, I.J.B.; Oliveira, L.M.; Monteiro, L.S.; Sales, T.L.S.; Ruschel, K.B.; Martins, K.P.M.P.; Etges, A.P.B.S.; et al. Clinical characteristics and outcomes of patients hospitalized with COVID-19 in Brazil: Results from the Brazilian COVID-19 registry. *Int. J. Infect. Dis.* **2021**, *107*, 300–310. [\[CrossRef\]](#)
- Zimmermann, I.R.; Sanchez, M.N.; Frio, G.S.; Alves, L.C.; Pereira, C.C.A.; Lima, R.T.S.; Machado, C.; Santos, L.M.P.; Silva, E.N.D. Trends in COVID-19 case-fatality rates in Brazilian public hospitals: A longitudinal cohort of 398,063 hospital admissions from 1st March to 3rd October 2020. *PLoS ONE* **2021**, *16*, e0254633. [\[CrossRef\]](#) [\[PubMed\]](#)
- Pranata, R.; Lim, M.A.; Huang, I.; Raharjo, S.B.; Lukito, A.A. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. *J. Renin. Angiotensin. Aldosterone Syst.* **2020**, *21*, 1470320320926899. [\[CrossRef\]](#) [\[PubMed\]](#)
- Clark, C.E.; McDonagh, S.T.J.; McManus, R.J.; Martin, U. COVID-19 and hypertension: Risks and management. A scientific statement on behalf of the British and Irish Hypertension Society. *J. Hum. Hypertens.* **2021**, *35*, 304–307. [\[CrossRef\]](#) [\[PubMed\]](#)
- Jager, K.J.; Kramer, A.; Chesnaye, N.C.; Couchoud, C.; Sanchez-Alvarez, J.E.; Garneata, L.; Collart, F.; Hemmelder, M.H.; Ambuhl, P.; Kerschbaum, J.; et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int.* **2020**, *98*, 1540–1548. [\[CrossRef\]](#) [\[PubMed\]](#)
- Caillard, S.; Chavarot, N.; Francois, H.; Matignon, M.; Snanoudj, R.; Turret, J.; Greze, C.; Thaumat, O.; Frimat, L.; Westeel, P.F.; et al. Clinical Utility of Biochemical Markers for the Prediction of COVID-19-Related Mortality in Kidney Transplant Recipients. *Kidney Int. Rep.* **2021**, *6*, 2689–2693. [\[CrossRef\]](#) [\[PubMed\]](#)
- Cunha, L.L.; Perazzio, S.F.; Azzi, J.; Cravedi, P.; Riella, L.V. Remodeling of the Immune Response with Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. *Front. Immunol.* **2020**, *11*, 1748. [\[CrossRef\]](#) [\[PubMed\]](#)

24. Sharifi, Y.; Payab, M.; Mohammadi-Vajari, E.; Aghili, S.M.M.; Sharifi, F.; Mehrdad, N.; Kashani, E.; Shadman, Z.; Larijani, B.; Ebrahimpur, M. Association between cardiometabolic risk factors and COVID-19 susceptibility, severity and mortality: A review. *J. Diabetes Metab. Disord.* **2021**, *20*, 1743–1765. [[CrossRef](#)] [[PubMed](#)]
25. Chen, Q.; Wang, L.; Li, C.; Hu, W.; Fan, Y.; Chen, Z.; Wu, L.; Lu, Z.; Ye, J.; Chen, S.; et al. Chronic Cardio-Metabolic Disease Increases the Risk of Worse Outcomes Among Hospitalized Patients with COVID-19: A Multicenter, Retrospective, and Real-World Study. *J. Am. Heart Assoc.* **2021**, *10*, e018451. [[CrossRef](#)]
26. Tornhammar, P.; Jernberg, T.; Bergstrom, G.; Blomberg, A.; Engstrom, G.; Engvall, J.; Fall, T.; Gisslen, M.; Janson, C.; Lind, L.; et al. Association of cardiometabolic risk factors with hospitalisation or death due to COVID-19: Population-based cohort study in Sweden (SCAPIS). *BMJ Open* **2021**, *11*, e051359. [[CrossRef](#)] [[PubMed](#)]
27. Basu, A.; Agwu, J.C.; Barlow, N.; Lee, B. Hypertension is the major predictor of poor outcomes among inpatients with COVID-19 infection in the UK: A retrospective cohort study. *BMJ Open* **2021**, *11*, e047561. [[CrossRef](#)] [[PubMed](#)]
28. Reiterer, M.; Rajan, M.; Gomez-Banoy, N.; Lau, J.D.; Gomez-Escobar, L.G.; Ma, L.; Gilani, A.; Alvarez-Mulett, S.; Sholle, E.T.; Chandar, V.; et al. Hyperglycemia in acute COVID-19 is characterized by insulin resistance and adipose tissue infectivity by SARS-CoV-2. *Cell Metab.* **2021**, *33*, 2174–2188. [[CrossRef](#)]
29. Rangel, E.B.; de Lucena, D.D.; Aguiar-Brito, I.; de Andrade, L.G.M.; Veronese-Araujo, A.; Cristelli, M.P.; Tedesco-Silva, H.; Medina-Pestana, J.O. COVID-19 in Kidney Transplant Recipients with Diabetes Mellitus: A Propensity Score Matching Analysis. *Transpl. Int.* **2022**, *35*, 10375. [[CrossRef](#)] [[PubMed](#)]
30. Gupta, A.; Madhavan, M.V.; Sehgal, K.; Nair, N.; Mahajan, S.; Sehrawat, T.S.; Bikdeli, B.; Ahluwalia, N.; Ausiello, J.C.; Wan, E.Y.; et al. Extrapulmonary manifestations of COVID-19. *Nat. Med.* **2020**, *26*, 1017–1032. [[CrossRef](#)]
31. Van de Veerdonk, F.L.; Giamarellos-Bourboulis, E.; Pickkers, P.; Derde, L.; Leavis, H.; van Crevel, R.; Engel, J.J.; Wiersinga, W.J.; Vlaar, A.P.J.; Shankar-Hari, M.; et al. A guide to immunotherapy for COVID-19. *Nat. Med.* **2022**, *28*, 39–50. [[CrossRef](#)] [[PubMed](#)]
32. Puelles, V.G.; Lutgehetmann, M.; Lindenmeyer, M.T.; Sperhake, J.P.; Wong, M.N.; Allweiss, L.; Chilla, S.; Heinemann, A.; Wanner, N.; Liu, S.; et al. Multiorgan and Renal Tropism of SARS-CoV-2. *N. Engl. J. Med.* **2020**, *383*, 590–592. [[CrossRef](#)] [[PubMed](#)]
33. Pinto, B.G.G.; Oliveira, A.E.R.; Singh, Y.; Jimenez, L.; Goncalves, A.N.A.; Ogawa, R.L.T.; Creighton, R.; Schatzmann Peron, J.P.; Nakaya, H.I. ACE2 Expression Is Increased in the Lungs of Patients with Comorbidities Associated with Severe COVID-19. *J. Infect. Dis.* **2020**, *222*, 556–563. [[CrossRef](#)] [[PubMed](#)]
34. Bartoloni, E.; Perricone, C.; Cafaro, G.; Gerli, R. Hypertension and SARS-CoV-2 infection: Is inflammation the missing link? *Cardiovasc. Res.* **2020**, *116*, e193–e194. [[CrossRef](#)]
35. Xie, J.; Zhong, R.; Wang, W.; Chen, O.; Zou, Y. COVID-19 and Smoking: What Evidence Needs Our Attention? *Front. Physiol.* **2021**, *12*, 603850. [[CrossRef](#)]
36. Mejia-Renteria, H.; Travieso, A.; Sagir, A.; Martinez-Gomez, E.; Carrascosa-Granada, A.; Toya, T.; Nunez-Gil, I.J.; Estrada, V.; Lerman, A.; Escaned, J. In-vivo evidence of systemic endothelial vascular dysfunction in COVID-19. *Int. J. Cardiol.* **2021**, *345*, 153–155. [[CrossRef](#)]
37. Haffke, M.; Freitag, H.; Rudolf, G.; Seifert, M.; Doehner, W.; Scherbakov, N.; Hanitsch, L.; Wittke, K.; Bauer, S.; Konietzschke, F.; et al. Endothelial dysfunction and altered endothelial biomarkers in patients with post-COVID-19 syndrome and chronic fatigue syndrome (ME/CFS). *J. Transl. Med.* **2022**, *20*, 138. [[CrossRef](#)]
38. Lee, I.T.; Nakayama, T.; Wu, C.T.; Goltsev, Y.; Jiang, S.; Gall, P.A.; Liao, C.K.; Shih, L.C.; Schurch, C.M.; McIlwain, D.R.; et al. ACE2 localizes to the respiratory cilia and is not increased by ACE inhibitors or ARBs. *Nat. Commun.* **2020**, *11*, 5453. [[CrossRef](#)]
39. Mancía, G.; Rea, F.; Ludergrani, M.; Apolone, G.; Corrao, G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of COVID-19. *N. Engl. J. Med.* **2020**, *382*, 2431–2440. [[CrossRef](#)]
40. Reynolds, H.R.; Adhikari, S.; Pulgarin, C.; Troxel, A.B.; Iturrate, E.; Johnson, S.B.; Hausvater, A.; Newman, J.D.; Berger, J.S.; Bangalore, S.; et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of COVID-19. *N. Engl. J. Med.* **2020**, *382*, 2441–2448. [[CrossRef](#)]
41. De Abajo, F.J.; Rodriguez-Martin, S.; Lerma, V.; Mejia-Abril, G.; Aguilar, M.; Garcia-Luque, A.; Laredo, L.; Laosa, O.; Centeno-Soto, G.A.; Angeles, G.M.; et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: A case-population study. *Lancet* **2020**, *395*, 1705–1714. [[CrossRef](#)]
42. Sheppard, J.P.; Nicholson, B.D.; Lee, J.; McGagh, D.; Sherlock, J.; Koshiaris, C.; Oke, J.; Jones, N.R.; Hinton, W.; Armitage, L.; et al. Association Between Blood Pressure Control and Coronavirus Disease 2019 Outcomes in 45,418 Symptomatic Patients with Hypertension: An Observational Cohort Study. *Hypertension* **2021**, *77*, 846–855. [[CrossRef](#)] [[PubMed](#)]
43. Lentner, J.; Adams, T.; Knutson, V.; Zeien, S.; Abbas, H.; Moosavi, R.; Manuel, C.; Wallace, T.; Harmon, A.; Waters, R.; et al. C-reactive protein levels associated with COVID-19 outcomes in the United States. *J. Osteopath. Med.* **2021**, *121*, 869–873. [[CrossRef](#)] [[PubMed](#)]
44. Henry, B.M.; Aggarwal, G.; Wong, J.; Benoit, S.; Vikse, J.; Plebani, M.; Lippi, G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. *Am. J. Emerg. Med.* **2020**, *38*, 1722–1726. [[CrossRef](#)] [[PubMed](#)]
45. Huang, I.; Pranata, R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): Systematic review and meta-analysis. *J. Intensive Care* **2020**, *8*, 36. [[CrossRef](#)]
46. Ng, J.H.; Hirsch, J.S.; Hazzan, A.; Wanchoo, R.; Shah, H.H.; Malieckal, D.A.; Ross, D.W.; Sharma, P.; Sakhiya, V.; Fishbane, S.; et al. Outcomes among Patients Hospitalized with COVID-19 and Acute Kidney Injury. *Am. J. Kidney Dis.* **2021**, *77*, 204–215. [[CrossRef](#)]

- 
47. Bowe, B.; Cai, M.; Xie, Y.; Gibson, A.K.; Maddukuri, G.; Al-Aly, Z. Acute Kidney Injury in a National Cohort of Hospitalized US Veterans with COVID-19. *Clin. J. Am. Soc. Nephrol.* **2020**, *16*, 14–25. [[CrossRef](#)]
  48. Azzi, Y.; Parides, M.; Alani, O.; Loarte-Campos, P.; Bartash, R.; Forest, S.; Colovai, A.; Ajaimy, M.; Liriano-Ward, L.; Pynadath, C.; et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. *Kidney Int.* **2020**, *98*, 1559–1567. [[CrossRef](#)]
  49. Mansour, S.G.; Malhotra, D.; Simonov, M.; Yamamoto, Y.; Arora, T.; Subair, L.; Alausa, J.; Moledina, D.G.; Greenberg, J.H.; Wilson, F.P.; et al. A Comparison Study of Coronavirus Disease 2019 Outcomes in Hospitalized Kidney Transplant Recipients. *Kidney360* **2021**, *2*, 494–506. [[CrossRef](#)]