





# Survival and clinical outcomes of kidney transplant recipients with coronavirus disease infection: An updated systematic review and meta-analysis

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## ABSTRACT

The recent outbreak of the 2019 novel coronavirus disease (COVID-19) has raised a tremendous global concern among people, especially those with pre-existing comorbidities. Kidney transplant (KT) recipients represent a susceptible category of patients due to the long-term administration of immunosuppressive therapy. However, data on how COVID-19 is affecting these patients are scarce. We aim to systematically review the current findings regarding survival and clinical outcomes of KT recipients with COVID-19 infection. A comprehensive literature search was conducted from PubMed and Embase published up to May 2021. Studies reporting data on the incidence of COVID-19 infection among KT recipients were included. The primary outcomes analyzed in this study, including mortality rate, mechanical ventilation requirement, intensive care unit (ICU) admission, and acute kidney injury (AKI) occurrence, were measured as a pooled prevalence rate (PR) with 95% confidence intervals (CIs). All analyses were performed using STATA<sup>®</sup> 16. A total of 30 studies comprising 3,146 KT recipients with COVID-19 infections were included. The pooled PR of mortality among KT recipients with COVID-19 infection was 21% (95% CI, 18% to 25%), ICU admission, 24% (95% CI, 20% to 28%), mechanical ventilation, 18% (95% CI, 15% to 21%), and AKI, 48% (95% CI, 42% to 53%). Meta-regression analysis showed that age was significantly associated with a higher mortality rate ( $P < .01$ ). Mortality rate associated with age and relatively poor clinical outcomes were high among KT recipients with COVID-19 infection. Further studies addressing preventive measures for this at-risk population should be encouraged.

**Keywords:** COVID-19; kidney transplantation; SARS-CoV-2 infection; organ transplants.

## Introduction

In December 2019, in Wuhan, China, a peculiar infection began spreading among people causing signs of pneumonia of unknown origin. Biological testing indicated that this pneumonia-like infection was caused by a novel coronavirus, which was officially referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup>

As this pandemic continues to unfold, the data show wide variations in clinical characteristics down to outcomings. This COVID-19 occurred and spread throughout China. It con-

tinues to spread widely to various countries around the world.<sup>2</sup> To date, there have been several recommendations for community-based health interventions from multiple organizations, and there is still much debate about the optimal COVID-19 treatment strategy.

The incidence of each individual causes various symptoms. Among them, patients with immunosuppressive conditions, especially the kidney transplant (KT) recipients focused on in this study, theoretically have a higher risk for developing critical COVID-19. This occurs because KT recipients are in a chronic

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**Table 1. Research Question**

PICO Component	Description
Population	Kidney transplant recipients aged more than 18 years
Intervention/exposure	Coronavirus disease 2019 (COVID-19)
Comparison	None
Outcome	Mortality, mechanical ventilation, AKI, ICU admission

state of immunosuppression and comorbidity. The impact of chronic immunosuppression on clinical and survival outcomes of COVID-19 is currently unclear as there are only limited data on COVID-19 in transplant recipients.<sup>1,3</sup> However, it is relevant since host inflammatory responses appear to constitute an important cause of poorly associated organ injury.<sup>3</sup>

Even though there is a great concern on the severity of clinical manifestations and the survival outcomes of COVID-19 in the KT recipient population, published reviews evaluating the results of studies regarding this phenomenon are still limited.<sup>4,5</sup> Therefore, this study was made with the aim of assessing the survival and clinical outcome of transplant recipient patients with COVID-19 infection.

## Material and Methods

This research followed the recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>6</sup> Ethical approval was not required in this present study as its exclusive use of secondary data.

### Eligibility Criteria

This review used population, intervention/exposure, comparison, and outcome (PICO) framework as summarized in Table 1. We considered eligible for the inclusion of cross-sectional, cohort, case series, and case-control studies evaluat-

ing in KTs with positive swab test using real-time reverse transcription-polymerase chain reaction assay for SARS-CoV-2 reporting survival and clinical outcomes of the hospitalized patients. The exclusion criteria were (1) non-English articles, (2) study reported irrelevant outcomes to our interest, or the data could not be extracted; (3) animal studies and in vitro studies; and (4) conference papers, case-report, theses, and patents.

### Literature Search and Study Selection

We conducted a comprehensive literature search using PubMed, Scopus, and Embase with the search period up to May 2021, using the following keywords: COVID-19 OR Coronavirus OR SARS-CoV-2 AND Kidney Transplant recipient OR Renal Transplant recipient OR Kidney Transplantation OR Renal Transplantation. Titles and abstracts taken from database searches were screened independently by three authors (M.D.V.I.D., N.Y., and Y.P.K.) to assess their potential eligibility to be included. Relevant articles were examined in full-text for eligibility criteria. Any disagreements were resolved by evaluating the full-text articles and discussion with senior authors (Y.K.). We demonstrated the process of study search and selection in a search flow diagram.

### Data Collection and Quality Assessment

To ensure standardization of data extraction from the included articles, we used piloted data extraction forms. The data collected included (1) author, (2) location of the study, (3) design of the study, (4) number of participants, (5) average age of participant, (6) time on KT, and (7) percentage of men. The primary endpoints were the prevalence of mortality, mechanical ventilation, ICU admission, and AKI. The quality assessment was performed utilizing the Newcastle-Ottawa Scale, which evaluated the selection, comparability, and outcome of the included studies.<sup>7</sup> We further reported the pooled prevalence with 95% confidence intervals (CIs) for studies. All data were recorded into a database manager, Microsoft Excel 2019.

### Data Analysis

The data were pooled as weighted prevalence with 95% CI for the majority of a clinical outcome. We used the random-effect model if there was high heterogeneity found using the Chi-squared test and  $I^2$  statistic. High heterogeneity was described by  $P$ -value  $\leq .1$  in the Chi-squared test and  $I^2$  statistic  $> 50\%$ .<sup>8</sup> Otherwise, we used the fixed-effects Mantel-Haenszel model if there was low heterogeneity ( $P$ -value  $> .1$  or  $I^2$  statistic  $\leq 50\%$ ). To determine the influence of study-level covariates on the effect estimate and heterogeneity, we performed univariate random-effects meta-regression with restricted maximum likelihood method using age, male gender, and time on kidney

### Main Points

- The pooled prevalence rate of mortality among kidney transplant recipients with COVID-19 infection was 21% (18% to 25%).
- Meta-regression analysis results showed that age was significantly associated with the rate of mortality.
- The pooled prevalence rate of acute kidney injury among kidney transplant recipients with COVID-19 infection was 48% (42% to 53%).

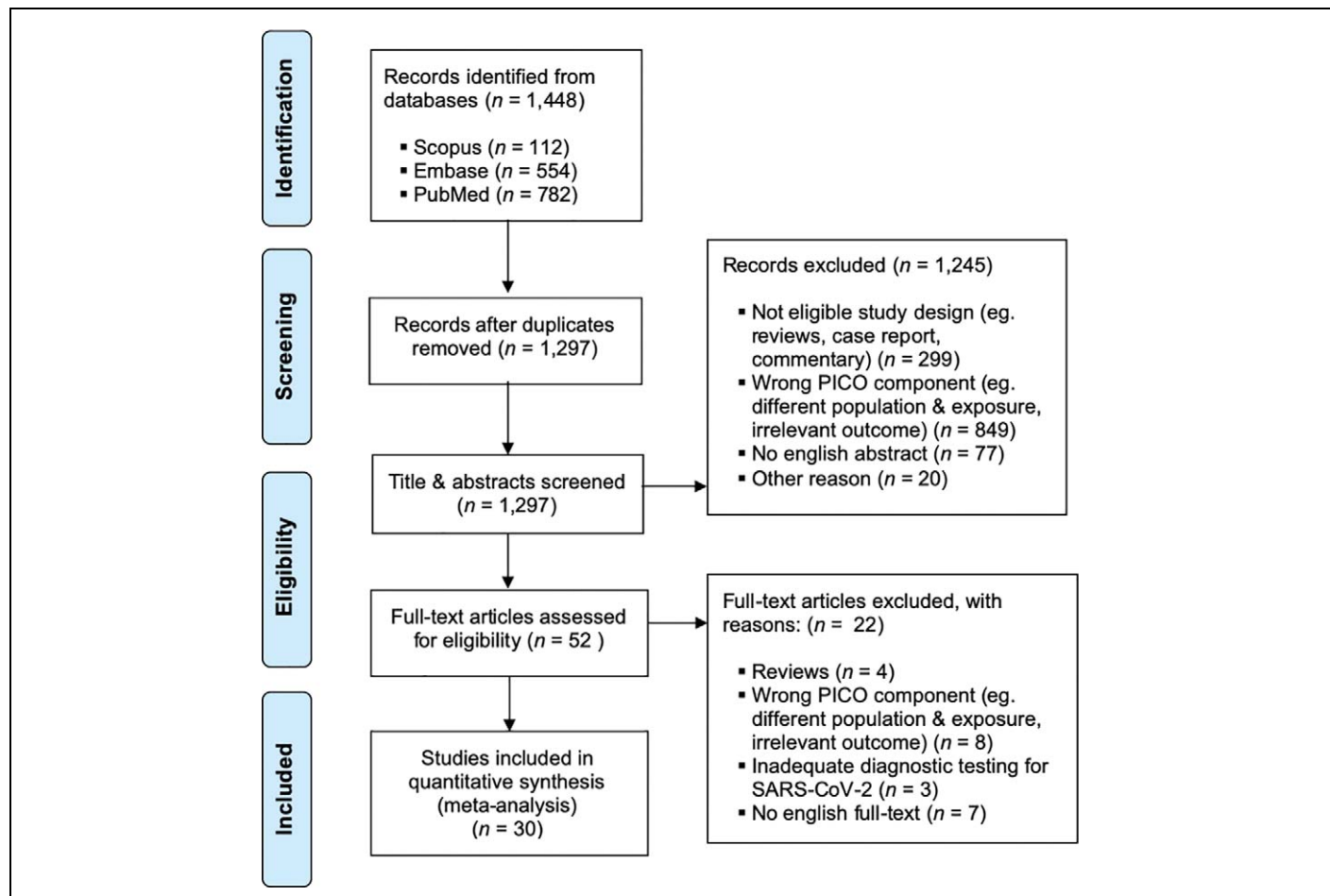


Figure 1. PRISMA flow diagram.

transplantation as the covariate. If  $P$ -value  $< .05$ , we consider the difference to have statistical significance. To assess the small-study effects, we used the Egger's regression test with a graphical funnel plot. Stata version 16.0 (StataCorp LLC, Texas, United States) was used for data analysis.<sup>9</sup>

## Results

### Study Search and Characteristics

The study selection process was summarized in Figure 1. From the multiple database searching, we identified a total of 1,448 records. After removing the duplication, we screened 1,297 abstracts and included 30 eligible studies for the meta-analysis.<sup>10–39</sup> The majority of the study design was cohort with less than 100 patients. Studies were reported from multiple regions of the world, but most of them reported from Spain. The baseline characteristics and the quality assessment of the

included studies were summarized in Tables 2 and 3, respectively. Studies reported similar characteristics regardless of their study location, the average age of the patients was 57 years old, and most patients were male (64.5%). Overall, the quality of the included studies was moderate, as displayed in Table 3.

### Survival and Clinical Outcome

Prevalence rates for mortality were reported in 30 studies that included 3,146 patients. The pooled prevalence rate of mortality was 21% (95% CI, 18% to 25%). The forest plot displayed in Figure 2 revealed that the  $I^2$  index was high among the studies (76.9%). Pooled analysis in Figure 3 showed that the ICU admission rate was 24% (95% CI, 20% to 28%) with substantial heterogeneity ( $I^2 = 73.4\%$ ). The need for mechanical ventilation rate was 18% (95% CI, 15% to 21%) with observed high heterogeneity ( $I^2 = 70.94\%$ ) as presented in Figure 4. The rate of AKI was 48% (95% CI, 42% to 53%,  $I^2 = 67.6\%$ ), summarized in Figure 5.

**Table 2. Baseline Characteristic of the Included Studies**

Author	Country	Study Design	Hospitalized Patient, n	Age (year)	Time on KT (Months)	Men (%)	COVID-19 Therapeutic Management	Primary endpoints Analyzed
Arenas et al. <sup>10</sup>	Spain	Prospective cohort	26	70.3	73	71.4	Hydroxychloroquine, ceftriaxone, azithromycin, lopinavir/ritonavir, tocilizumab, steroids, enoxaparin	Mortality rate, ventilation rate, ICU admission rate
Columbia University <sup>11</sup>	United States	Case series	15	51	49	77	Hydroxychloroquine, azithromycin	Mortality rate, ventilation rate, AKI rate
Crespo et al. <sup>22</sup>	Spain	Prospective cohort	16	73.6	49	75	Hydroxychloroquine, darunavir/ritonavir, tocilizumab, steroids	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Devresse et al. <sup>33</sup>	Belgium	Case series	18	57	89	44	Hydroxychloroquine, steroids	Mortality rate, ventilation rate, ICU admission rate
Elias et al. <sup>34</sup>	France	Prospective cohort	66	56.4	57.8	56	Hydroxychloroquine, tocilizumab, eculizumab	Mortality rate, ventilation rate, AKI rate
Rahbar et al. <sup>35</sup>	Iran	Prospective cohort	19	47.6	NR	68.4	Hydroxychloroquine, ribavirin, lopinavir/ritonavir, IVIG, oseltamivir	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Alberici et al. <sup>36</sup>	Italy	Case series	20	59	156	75	Hydroxychloroquine, lopinavir/ritonavir, dexamethasone, tocilizumab, darunavir/ritonavir	Mortality rate, AKI rate, ICU admission rate
Chen et al. <sup>37</sup>	United States	Retrospective cohort	30	56	84	53	Hydroxychloroquine + azithromycin	Mortality rate, ventilation rate
Fava et al. <sup>38</sup>	Spain	Retrospective cohort	104	59.7	59	55.7	Hydroxychloroquine, remdesivir, tocilizumab, lopinavir/ritonavir, ifn- $\beta$ , darunavir/cobicistat, darunavir/ritonavir	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Lubetsky et al. <sup>39</sup>	United States	Case series	39	57	NR	70	Hydroxychloroquine, remdesivir, azithromycin, convalescent plasma, doxycycline, il-6 receptor inhibitor	Mortality rate, ventilation rate, AKI rate
Pascual et al. <sup>13</sup>	Spain	Case series	24	66.5	1	46	Hydroxychloroquine, glucocorticoids, tocilizumab, lopinavir/ritonavir	Mortality rate, ventilation rate
Al Oltaibi et al. <sup>12</sup>	Kuwait	Retrospective cohort	82	49.3	72	76	Low molecular weight heparin, antibiotics	Mortality rate, ventilation rate, ICU admission rate

Table 2. (Continued)

Author	Country	Study Design	Hospitalized Patient, n	Age (year)	Time on KT (Months)	Men (%)	COVID-19 Therapeutic Management	Primary endpoints Analyzed
Benotmane et al. <sup>14</sup>	France	Retrospective cohort	41	63.9	86.4	78	Hydroxychloroquine, lopinavir/ritonavir, tocilizumab, azithromycin, corticosteroids	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Bodro et al. <sup>15</sup>	Spain	Retrospective cohort	33	55	66	61	Hydroxychloroquine, lopinavir/ritonavir, azithromycin, steroids	Mortality rate, ventilation rate, ICU admission rate
Bruno et al. <sup>16</sup>	Italy	Retrospective cohort	11	59.2	113.5	72.7	Hydroxychloroquine, darunavir/ritonavir, lopinavir/ritonavir, azithromycin, tocilizumab	Mortality rate, ventilation rate
Caillard et al. <sup>17</sup>	France	Retrospective cohort	273	62	74.6	66.3	Hydroxychloroquine, azithromycin, remdesivir, lopinavir/ritonavir, oseltamivir, tocilizumab	Mortality rate, ventilation rate, ICU admission rate
Chavarot et al. <sup>18</sup>	France	Retrospective cohort	100	64.7	61.2	64	Hydroxychloroquine, azithromycin, tocilizumab	Mortality rate, ventilation rate, ICU admission rate
Coll et al. <sup>19</sup>	Spain	Case series	375	62	66	65	Hydroxychloroquine, azithromycin, protease inhibitor, IFN- $\beta$	Mortality rate, ventilation rate, ICU admission rate
Craig-Schapiro et al. <sup>20</sup>	United States	Retrospective cohort	52	57	56.4	70	Hydroxychloroquine, remdesivir, tocilizumab, convalescent plasma	Mortality rate, ventilation rate, AKI rate
Dheir et al. <sup>21</sup>	Turkey	Cross-sectional	20	48	71.9	70	Favipiravir, hydroxychloroquine, dexamethasone, oseltamivir, convalescent plasma, antibiotics	Mortality rate, ventilation rate, AKI rate
Georgery et al. <sup>23</sup>	Belgium	Cohort	45	60	93	53	Hydroxychloroquine, dexamethasone	Mortality rate, ICU rate
Hillbrands et al. <sup>24</sup>	Multicentre	Prospective cohort	271	60	NR	62	Hydroxychloroquine, lopinavir/ritonavir, remdesivir, IFN, tocilizumab, steroids	Mortality rate, ventilation rate, ICU admission rate
Kute et al. <sup>25</sup>	India	Retrospective cohort	250	43	42	86	Hydroxychloroquine, azithromycin, tocilizumab, favipiravir, remdesivir, convalescent plasma, IVIG	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Mamode et al. <sup>26</sup>	United Kingdom	Retrospective cohort	121	56.2	79	63	Hydrocortisone, tocilizumab	Mortality rate, ventilation rate, ICU admission rate

Table 2. (Continued)

Author	Country	Study Design	Hospitalized Patient, n	Age (year)	Time on KT (Months)	Men (%)	COVID-19 Therapeutic Management	Primary endpoints Analyzed
Oto et al. <sup>27</sup>	Turkey	Retrospective cohort	109	48.4	60	62.2	Hydrocortisone, tocilizumab, lopinavir/ritonavir, macrolids, favipiravir, glucocorticoids, anakinra	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Ozturk et al. <sup>28</sup>	Turkey	Retrospective cohort	81	48	60	59.3	Hydroxychloroquine, oseltamivir, macrolides, lopinavir—ritonavir, favipiravir, glucocorticoids, tocilizumab, convalescent plasma, canakinumab/anakinra	Mortality rate, ventilation rate, ICU admission rate
Pierotti et al. <sup>29</sup>	Brazil	Retrospective cohort	51	51.9	74	49	Macrolide, narrow-spectrum for GNB, broad-spectrum for GNB, glycopeptide, enoxaparin	Mortality rate, ventilation rate, ICU admission rate
Santeusano et al. <sup>30</sup>	United States	Retrospective cohort	38	53.8	69.6	65.8	Hydroxychloroquine, convalescent plasma, anticoagulation, steroids	Mortality rate, ventilation rate, AKI rate
Tejada et al. <sup>31</sup>	United States	Retrospective cohort	25	56	78	56	Hydroxychloroquine + high dose corticosteroids, hydroxychloroquine	Mortality rate, ventilation rate, AKI rate, ICU admission rate
Villanego et al. <sup>32</sup>	Spain	Prospective cohort	791	60	72	62.8	Hydroxychloroquine, azithromycin, glucocorticoids, lopinavir/ritonavir, tocilizumab, remdesivir	Mortality rate, ventilation rate, ICU admission rate

### Publication Bias

Visual inspection of the funnel plot appears to be qualitatively symmetrical, as shown in Figure 6, which demonstrates no evidence of publication bias. Further results for Egger's test showed no evidence of small-study effects ( $P = .186$ ).

### Meta-Regression

Meta-regression analysis results showed that age was significantly associated with the rate of mortality ( $P < .01$ ) (Figure 7). However, no significant association was observed for male gender ( $P = .825$ ) and time on kidney transplantation ( $P = .655$ ).

### Discussion

This study provided the updated systematic review and meta-analysis of the survival and clinical outcomes of kidney trans-

plants with COVID-19 infection compared to the previously published systematic review, which evaluated 15 studies.<sup>5</sup> Preliminary reports suggested good clinical outcomes in renal patients with COVID-19 infection.<sup>40,41</sup> However, recent studies have reported that this susceptible category population had a higher mortality rate than observed in the general population.<sup>10,34,36</sup> Many studies hypothesized that immunosuppression may represent additional risk factors, although specific studies are still limited.<sup>42</sup> Even though the patients had immunosuppression, the symptoms of kidney transplant recipients with COVID-19 infection were reported similar to the general population, including fever, dry cough, and dyspnea.<sup>38</sup>

The global mortality rate from COVID-19 on the general population ranged from 0.7% to 10.8%, varied widely based on the location of the study.<sup>43</sup> In Spain, 18 solid organ transplant



**Table 3. Risk of Bias Assessment Using Newcastle-Ottawa Scale**

Study	Selection				Comparability		Outcome			Score
	1	2	3	4	1	2	1	2	3	
Arenas et al. <sup>10</sup>	+	+	+	+	–	–	+	+	–	★★★★★★
Columbia University 11	–	+	+	+	–	–	+	–	+	★★★★★
Crespo et al. <sup>22</sup>	–	+	+	+	–	–	+	+	+	★★★★★★
Devresse et al. <sup>33</sup>	+	+	+	+	–	–	+	–	–	★★★★★
Elias et al. <sup>34</sup>	+	+	+	+	–	–	+	+	+	★★★★★★★
Rahbar et al. <sup>35</sup>	–	+	+	+	–	–	+	+	+	★★★★★★
Alberici et al. <sup>36</sup>	+	–	+	+	–	–	+	+	+	★★★★★★
Chen et al. <sup>37</sup>	+	–	+	+	–	–	+	+	+	★★★★★★
Fava et al. <sup>38</sup>	+	+	+	+	–	–	+	–	+	★★★★★★
Lubetsky et al. <sup>39</sup>	+	–	+	+	–	–	+	+	+	★★★★★★
Pascual et al. <sup>13</sup>	+	–	+	+	–	–	+	–	–	★★★★
Al Oltaibi et al. <sup>12</sup>	+	+	+	+	–	–	+	+	+	★★★★★★★
Benotmane et al. <sup>14</sup>	+	+	+	+	–	–	+	+	+	★★★★★★★
Bodro et al. <sup>15</sup>	+	+	+	+	–	–	+	–	+	★★★★★★
Bruno et al. <sup>16</sup>	–	+	+	+	–	–	+	+	+	★★★★★★
Caillard et al. <sup>17</sup>	+	+	+	+	+	+	+	+	+	★★★★★★★★★
Chavarot et al. <sup>18</sup>	+	+	+	+	+	–	+	–	+	★★★★★★
Coll et al. <sup>19</sup>	+	+	+	+	–	–	+	+	+	★★★★★★★
Craig-Schapiro et al. <sup>20</sup>	+	+	+	+	+	+	+	+	+	★★★★★★★★★
Dheir et al. <sup>21</sup>	+	+	+	+	–	–	+	–	+	★★★★★★
Georgery et al. <sup>23</sup>	+	+	+	+	–	–	+	+	+	★★★★★★★
Hillbrands et al. <sup>24</sup>	+	+	+	+	+	+	+	+	+	★★★★★★★★★
Kute et al. <sup>25</sup>	+	+	+	+	–	+	+	+	+	★★★★★★★★
Mamode et al. <sup>26</sup>	+	+	+	+	–	–	+	–	–	★★★★★
Oto et al. <sup>27</sup>	+	+	+	+	–	+	+	+	+	★★★★★★★★★
Ozturk et al. <sup>28</sup>	+	+	+	+	–	+	+	+	+	★★★★★★★★★
Pierotti et al. <sup>29</sup>	+	+	+	+	–	+	+	+	–	★★★★★★★
Santeusano et al. <sup>30</sup>	+	+	+	+	–	+	+	+	+	★★★★★★★★★
Tejada et al. <sup>31</sup>	+	+	+	+	–	–	+	–	–	★★★★★
Villanego et al. <sup>32</sup>	+	+	+	+	–	+	+	+	–	★★★★★★★

(SOT) recipients diagnosed with COVID-19 had a mortality rate of 28%.<sup>44</sup> In this review, we observed a lower mortality rate from 30 studies comprising 3,146 kidney transplants with COVID-19, with a rate of 21% (18% to 25%). This result was similar to the study focused on SOT recipients diagnosed with COVID-19.<sup>44</sup> Pascual et al.<sup>42</sup> reported in their study that the fatality rate during the first 60 days after kidney transplantation was considerably higher than the mortality found outside the pandemic of COVID-19. Our meta-regression analysis reported a significant association of age with mortality, but not male

gender and time on KT. This result is consistent with previous studies demonstrating mortality from COVID-19 is highly associated with age, and the age of admitted patients is likely to have a consequential impact on mortality.<sup>45</sup>

Even though our analysis did not show a significant association between mortality and time of KT, this variable might affect disease severity. In the first months after transplantation, the full impact of immunosuppression is exerted, which leads the recipients to be at maximum risk of viral infection and severity

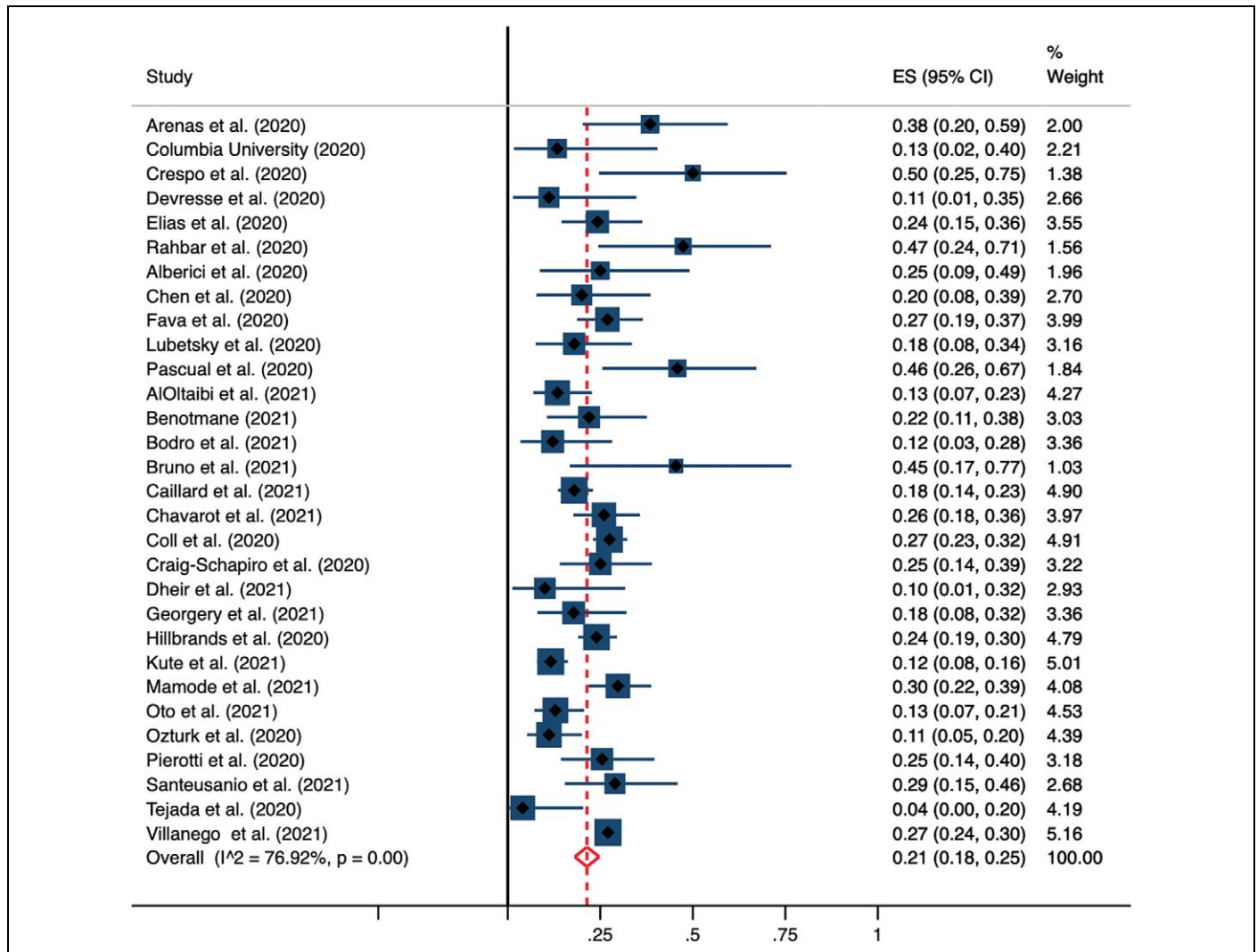


Figure 2. Pooled estimate on mortality rate of kidney transplant recipients with COVID-19 infection.

during this period.<sup>42</sup> The ICU admission rate from six studies was 21% (10-31%), comparable to the results of a meta-analysis of 37 studies focusing on ICU admission rate in the general population (26%).<sup>46</sup> However, this result could be biased because a study by Pascual et al<sup>42</sup> reported some patients with the indication for ICU refuse to be admitted. The rate of mechanical ventilation requirement among kidney transplant recipients with COVID-19 was also higher than the general population (19% vs 3.5%, respectively).

Kidney injury in COVID-19 infection was suggested to be caused indirectly by the cytokine storm.<sup>37</sup> However, Lubetzky et al<sup>39</sup> hypothesized that COVID-19 might directly affect the kidney as the SARS-CoV-2 found in the kidney and urine. A meta-analysis of 20 studies focusing on AKI incidence in the general population infected with COVID-19 showed an inci-

dence rate of 8.9% (4.6% to 14.5%).<sup>47</sup> Our findings demonstrated a considerably higher incidence of AKI than the general population, with a rate of 44% (35% to 53%). Lubetzky et al<sup>39</sup> proposed the potential explanation for the higher incidence of AKI in kidney transplant recipients with COVID-19. First, the recipients already have baseline stage 2 or 3 Chronic Kidney Disease (CKD) before the infection. Second, elevated tacrolimus trough level has been observed at admission in some patients, which may have further aggravated AKI.<sup>39</sup>

This research has a few limitations. First, most studies were conducted with relatively small sample size and a short follow-up period, which resulted in limited insight. Second, studies reported limited data on baseline characteristics that were not enough observation to be further analyzed. Third, studies reported varied therapeutic management, which resulted in



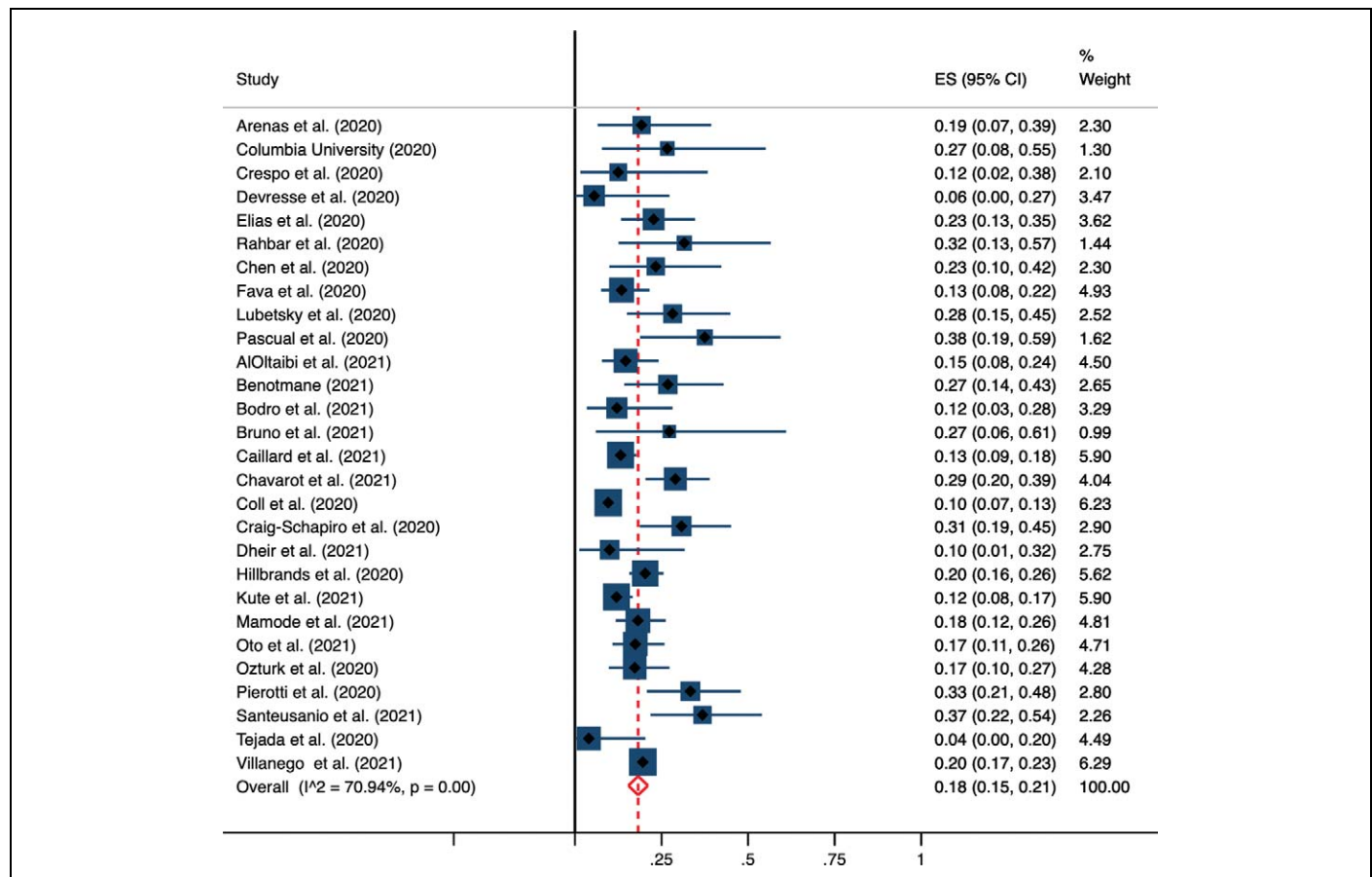


Figure 3. Pooled estimate on mechanical ventilation rate of kidney transplant recipients with COVID-19 infection.

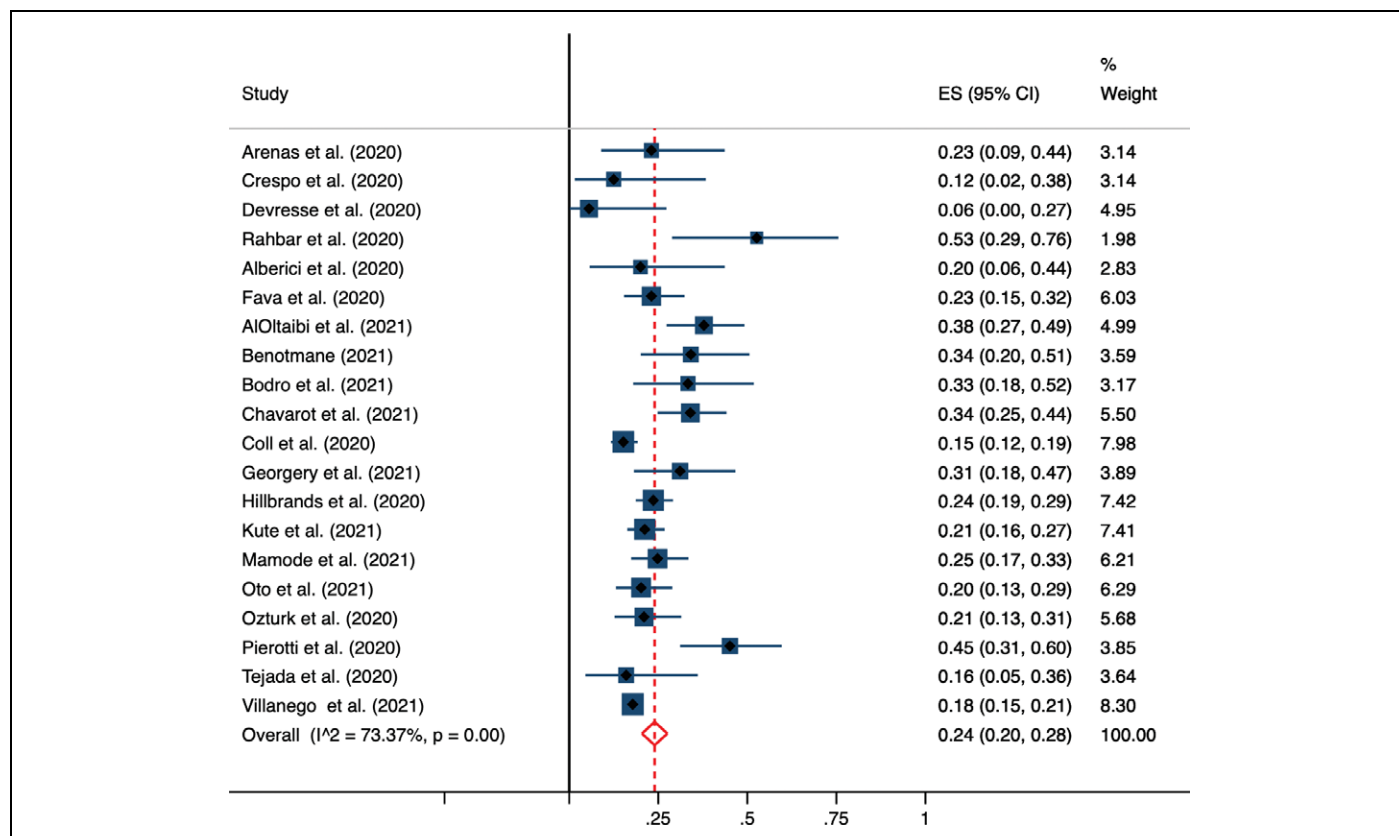


Figure 4. Pooled estimate on ICU admission rate of kidney transplant recipients with COVID-19 infection.

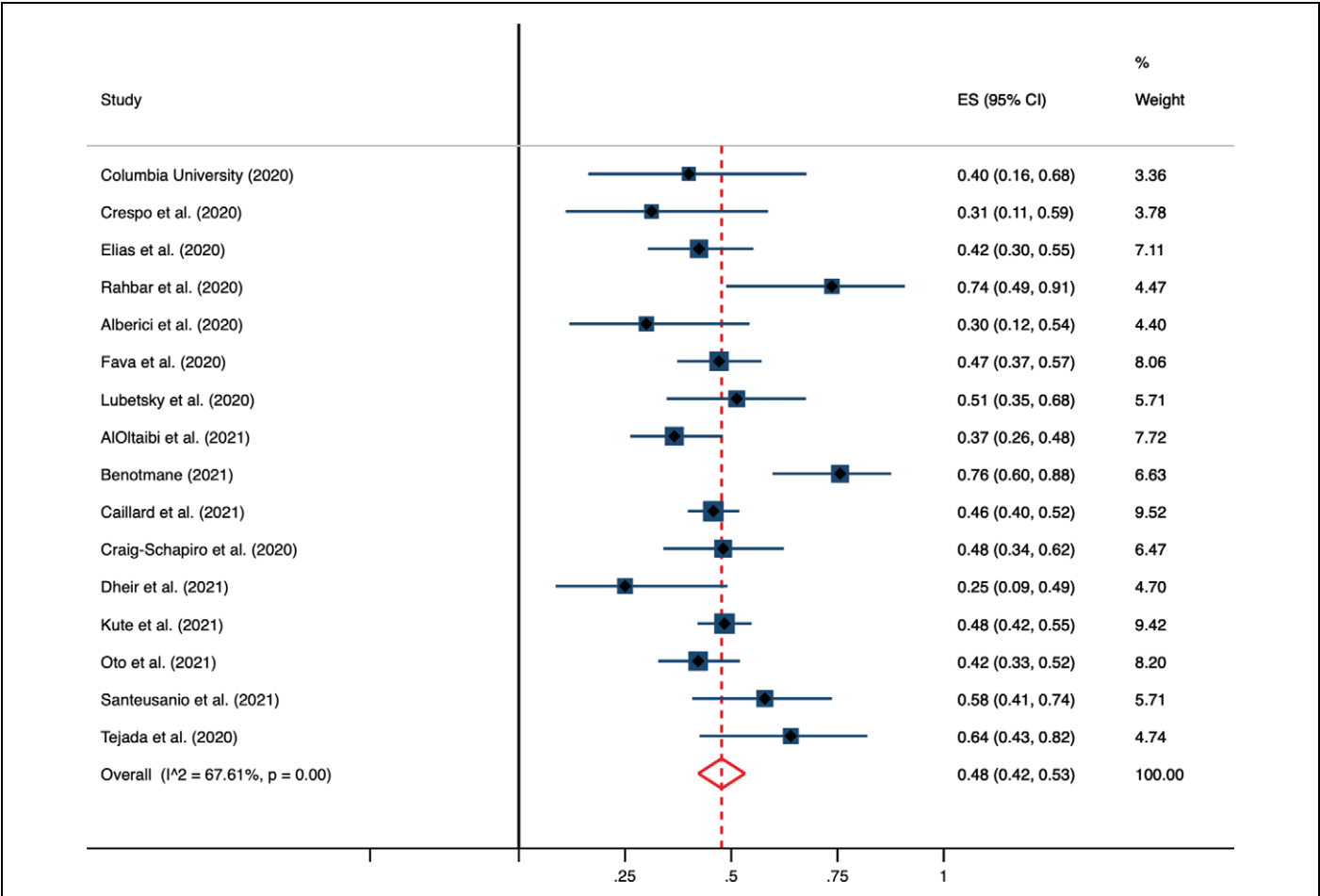


Figure 5. Pooled estimate on AKI rate of kidney transplant recipients with COVID-19 infection.

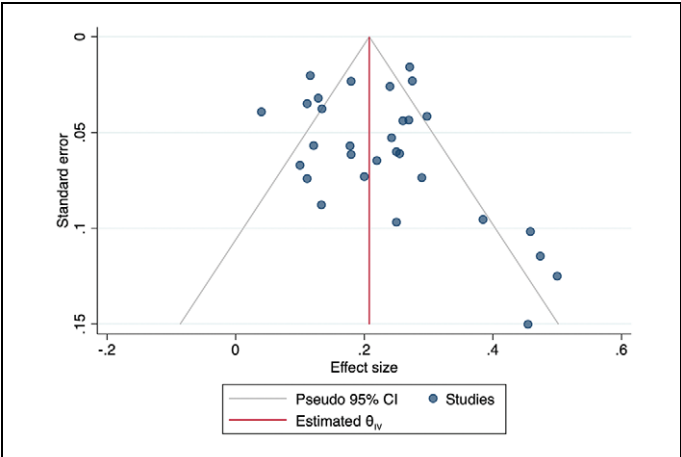


Figure 6. Funnel plot for mortality of kidney transplant recipients with COVID-19 infection.

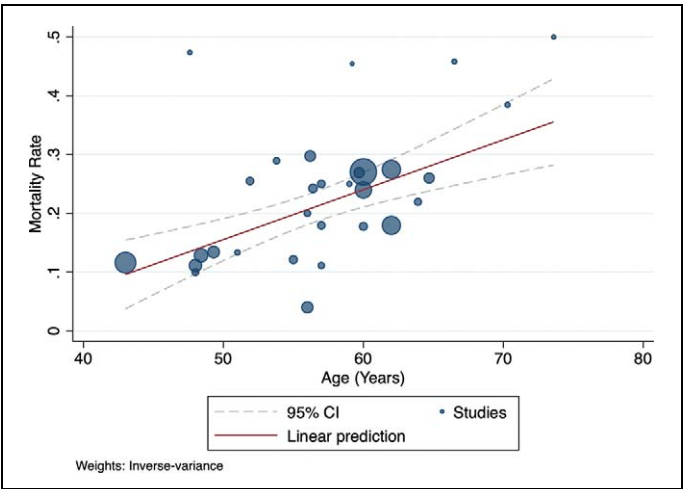


Figure 7. Meta-regression analysis on mortality rate of kidney transplant recipients with COVID-19 infection using age as moderator.

different clinical outcomes and produced considerable heterogeneity. The results of the studies, in general, show relatively higher mortality and poor clinical outcomes among kidney transplant recipients with COVID-19 infection. Therefore, preventive measures and adaptive treatment trials are urgently needed for this population.

## Conclusion

The mortality rate associated with age and relatively poor clinical outcomes were high among kidney transplant recipients compared to general population with COVID-19 infection. Further studies addressing preventive measures for this at-risk population should be encouraged.

**Peer-review:** Externally peer-reviewed.

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