Review Article

Coronavirus disease 2019 in kidney transplant recipients: a systematic review and meta-analysis

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Abstract

Introduction: The clinical presentation and outcomes of coronavirus disease 2019 (COVID-19) in kidney transplant recipients (KTRs) have not been well studied.

Methods: We performed a meta-analysis to examine the presenting features, outcomes and the effect of treatment on outcomes of KTRs with COVID-19. Database search was performed up to 5 September 2020 through PubMed, Embase, Web of Science, Scopus and CENTRAL.

Results: Overall, 23 studies (1,373 patients) were included in the review and meta-analysis. The most common presenting symptoms included fever (74.0%, 95% confidence interval [CI] 65.3–81.1), cough (63.3%, 95% CI 56.5–69.6) and dyspnoea (47.5%, 95% CI 39.6–55.6). Pooled rates of mortality and critical illness were 21.1% (95% CI 15.3–28.4) and 27.7% (95% CI 21.5–34.8), respectively. Acute kidney injury occurred in 38.9% (95% CI 30.6–48.1) and dialysis was required in 12.4% (95% CI 8.3–18.0) of the cases.

Conclusion: Kidney transplant recipients with COVID-19 have a similar clinical presentation as the general population, but they have higher morbidity and mortality. It is uncertain whether high-dose corticosteroid or hydroxychloroquine reduces the risks of mortality in KTRs with COVID-19.

Keywords: Coronavirus disease 2019, COVID-19, kidney transplantation, meta-analysis, systematic review

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first detected in China at the end of 2019 and had evolved into a global pandemic[1] with profound impact on transplantation services around the world.[2,3] Older patients and patients with multiple comorbidities are at increased risk of severe complications, including acute respiratory distress syndrome requiring intensive care support, and death.[4] While kidney transplant recipients (KTRs) are likely to be more vulnerable to severe complications given their immunocompromised status and multiple comorbidities,[5] some have argued that immunosuppression may have protective effects against the severe systemic inflammatory response responsible for severe disease in COVID-19.[6] Also, KTRs have been known to present atypically for other viral illnesses due to factors such as immunosuppression and uraemia.[7] Risk factors for severe COVID-19 in this population and the impact of treatment, such as modification of immunosuppression, remain unclear. Similar studies of COVID-19 have been performed in the general population.[8-12] In the KTR population, systematic reviews[13-17] have been performed; however, meta-analysis has rarely been conducted.[18] The present systematic review and meta-analysis examines the clinical, laboratory and radiological features of KTRs diagnosed with COVID-19, and their outcomes.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews

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and Meta-Analyses guidelines. The protocol of this systematic review is registered at Prospero (Registration ID: CRD42020183896).

A search for studies that examined COVID-19 in KTRs, limited to studies in the English language, was performed on 5 September 2020 on the databases, PubMed, Embase, Web of Science, Scopus and CENTRAL, according to the registered search strategy [see Supplemental Digital Appendix] with the keywords 'COVID-19', 'kidney' and 'transplant' and their related terms. References of retrieved articles were manually screened for additional eligible publications. Publications were screened for duplication using the Mendeley Reference Management Software.

Two investigators (QYH and TLL) independently screened all titles and abstracts and subsequently reviewed all potentially relevant full-text articles for eligibility for inclusion. Only studies with five or more subjects were included. Disagreement about study inclusion was resolved by consensus. If consensus could not be reached, additional reviewers (HH and TK) arbitrated the disagreement.

The quality of studies included in the meta-analysis was assessed using the Joanna Briggs Institute critical appraisal tools for prevalence studies.[19] The methodological quality was categorised into low (score ≤3), moderate (4–6) and high (≥7). The level of evidence for primary outcomes was assessed using the Grades of Recommendation, Assessment, Development and Evaluation approach.[20]

Data on study and patient characteristics, clinical, laboratory and radiological findings, management strategies and outcomes were extracted independently by two reviewers (QYH and TLL) using a standardised data extraction form. Critical illness was defined as the need for intensive care unit admission and/or mechanical ventilation, as per previous similar studies.[9,10] Missing data were requested from corresponding authors.

The primary outcomes (mortality, critical illness and need for dialysis) and secondary outcomes (need for oxygen, acute kidney injury) were treated as dichotomous variables. All continuous and categorical demographic, clinical and treatment variables were summarised as mean with 95% confidence interval (95% CI) and event rate/proportion with corresponding 95% CI using the random-effects model. Subgroup analysis was also conducted based on continents. I^2 index and Q statistic were applied to assess heterogeneity among the studies, and I^2 ≥75.0% was considered as considerable heterogeneity.[21] The robustness of pooled conclusion was evaluated using a sensitivity analysis including studies with low and moderate risk of bias (ROB). Meta-regression analyses were also performed to examine the effect of high-dose corticosteroids or hydroxychloroquine use on mortality after adjusting for mechanical ventilation. Bubble plot with a fitted meta-regression line of proportion of outcomes was also plotted. Bubbles were sized according to the precision of each estimate, with larger bubbles denoting more precise estimates. Publication bias was assessed using the funnel plot, Egger's test and Begg's test.[22,23] Studies that reported individual-level data were first converted to aggregate level data and then all included studies were pooled using random-effects model. All reported P values were two sided, P <0.05 was considered statistically significant. Statistical analyses were performed using Comprehensive Meta–Analysis Version 3.3.07 (Biostat Inc, Englewood, NJ, USA) software. Meta-regression analysis was performed in SAS version 9.2.2 (SAS Institute, Cary, NC, USA).

RESULTS

Our search identified 1,575 records. After removal of duplicates, 945 unique records were identified, of which 636 records were excluded after screening of titles and abstracts. Of the 309 remaining studies, 23 studies (1,373 patients)[24-46] were included for systematic review and meta-analysis after full-text review [Figure 1]. Details of the included studies are reported in Table 1. The methodological quality for studies included for meta-analysis was assessed to be high for five studies, moderate for 14 studies and low for four studies [Table S1, Supplemental Digital Appendix].

A total of 1,373 KTRs diagnosed with COVID-19 from 23 studies were included in the meta-analysis. The characteristics, outcomes and management strategies for cases included for meta-analysis are summarised in Table 2. The pooled mean age (23 studies, 1,337 participants) was 55.3 (95% CI 53.0–57.6) years and the proportion of males (23 studies, 1,369 participants) was 63.6%

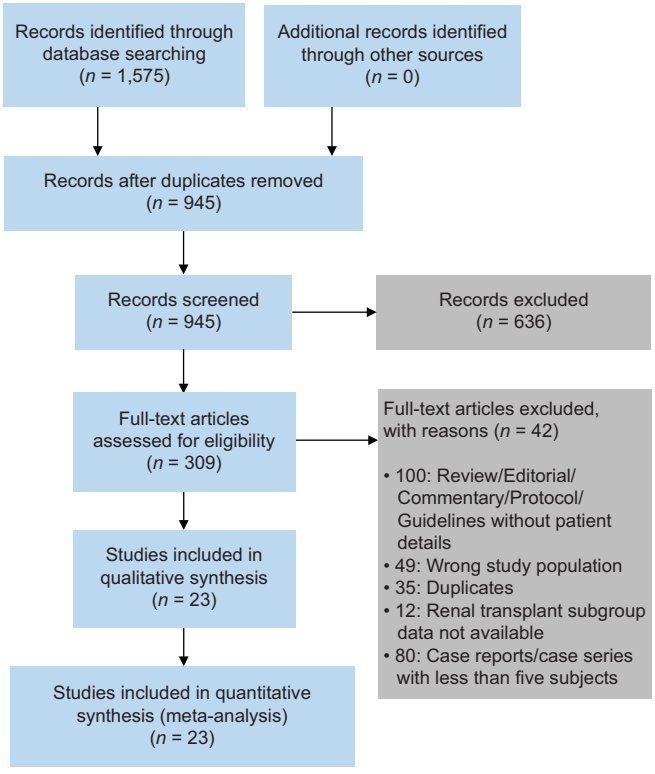

Figure 1: Study selection flow diagram.

Table 1. Characteristics of included studies.

Cohort study	Country	Sample size, *n*	Time frame (in 2020)	Median follow-up duration[a] (day)	Mean age[b] (yr)	Male, *n* (%)
Asia						
Zhang *et al*.[24]	China	5	1 Jan–28 Feb	29 (range 22–32)	44.8±11.5	4 (80.0)
Zhu *et al*.[25]	China	10	17 Jan–5 Feb	35.5 (range 6–49)	45.0±14.0	8 (80.0)
Molaei *et al*.[36]	Iran	10	8 Feb–28 Mar	20.4±12.9	59.6±7.72	8 (80.0)
Monfared *et al*.[40]	Iran	22	20 Feb–19 Apr	8.5 (IQR 5.25–13.5)	52 (IQR 40.75–62.75)	15 (68.2)
Abolghasemi *et al*.[41]	Iran	24	20 Mar–20 May	6.6 (range 5–9)	49 (range 29–64)	15 (62.5)
Europe						
Silva *et al*.[42]	Portugal	5	28 Feb–27 Apr	30 (range 10–37)	50.8±13.8	5 (100)
Banerjee *et al*.[43]	UK	7	2 Mar–17 Mar	25 (range 5–27)	57.4±9.6	4 (57.1)
Tschopp *et al*.[44]	Switzerland	13	9 Mar–6 Apr	33 (range 8–44)	59.2±13.6	9 (69.2)
Meziyerh *et al*.[45]	Netherlands	15	1 Mar–4 May	30	56 (IQR 49–72)	9 (60.0)
Devresse *et al*.[46]	Belgium	22	14 Mar–15 Apr	18 (range 5–30)	57 (range 41–73)	8 (44.4)
Felldin *et al*.[26]	Sweden	35	21 Feb–22 Jun	NR	53.1±12.3	23 (65.7)
Maritati *et al*.[27]	Italy	5	17 Mar–6 May	34.8	66±9.27	3 (60.0)
Cavagna *et al*.[28]	Italy	6	1 Feb–28 Apr	NR	57.5 (IQR 51–64)	5 (83.3)
Mella *et al*.[29]	Italy	6	4 Mar–26 Apr	NR	55.5±9.3	6 (100)
Bossini *et al*.[30]	Italy	53	1 Mar–16 Apr	NR	60 (IQR 50–67)	42 (79.2)
Demir *et al*.[31]	Turkey	40	1 Feb–4 May	32 (IQR 14–51)	44.9±14.8	20 (50.0)
Caillard *et al*.[32]	France	279	4 Mar–21 Apr	22	61.6 (range 50.8–69.0)	182 (65.2)
Crespo *et al*.[33]	Spain	414	18 Mar–16 May	44	62 (IQR 52–71)	265 (64.0)
North America						
Columbia University Kidney Transplant Program[34]	USA	15	Until 27 Mar	7 (range 3–11)	50.6±21.4	10 (66.6)
Nair *et al*.[35]	USA	10	1 Mar–27 Mar	25 (IQR 11–26)	56.3±15.8	6 (60.0)
Lubetzky *et al*.[37]	USA	54	13 Mar–20 Apr	37	57 (IQR 29–83)	38 (70.4)
Others						
De Sandes-Freitas *et al*.[38]	Brazil	5	10–30 Apr	14	39.2±24.0	4 (80.0)
Kates *et al*.[39]	International	318	1 Mar–15 Apr	>28	56 (IQR 46–66)	186 (58.5)

[a]Data presented as median unless otherwise specified. [b]Data presented as mean ± standard deviation, unless otherwise specified. IQR: interquartile range, NR: not reported

(95% CI 60.7–66.4). The common comorbidities reported included hypertension (18 studies, 916 participants: 76.1%; 95% CI 68.3–82.5) and diabetes mellitus (18 studies, 916 participants: 31.5%; 95% CI 23.9–40.3). Baseline immunosuppression used consisted mainly of calcineurin inhibitors (CNIs) (18 studies, 927 participants: 84.8%; 95% CI 82.2–87.1), mycophenolate (18 studies, 1,016 participants: 75.7%; 95% CI 69.8–80.8) and corticosteroids (19 studies, 1,330 participants: 74.8%; 95% CI 67.7–80.8).

The most common presenting symptoms on meta-analysis were fever (20 studies, 1,314 participants: 74.0%; 95% CI 65.3–81.1), cough (19 studies, 900 participants: 63.3%; 95% CI 56.5–69.6) and dyspnoea (20 studies, 1,314 participants: 47.5%; 95% CI 39.6–55.6) [Table 2]. Diarrhoea was reported in 13 studies (487 participants: 29.7%; 95% CI 23.6–36.5), while gastrointestinal symptoms were reported in 13 studies (885 participants: 33.2%; 95% CI 25.3–42.2).

The pooled mean white blood cell count, lymphocyte count and C-reactive protein level on presentation were 6.02×10^9/L (95% CI 5.63–6.42), 0.69×10^9/L (95% CI 0.62–0.76) and 72.4 mg/dL (95% CI 57.3–87.4), respectively [Table 2].

Chest X-rays on admission were commonly reported to be normal (six studies, 381 participants: 81.2%; 95% CI 70.4–88.7), had bilateral or multifocal infiltrates (five studies, 111 participants: 65.2%; 95% CI 52.0–76.5) or unilateral infiltrates (four studies, 106 participants: 20.5%; 95% CI 12.2–32.2).

Common strategies for modification of immunosuppressants included discontinuation of antimetabolite (16 studies, 465 participants: 84.6%; 95% CI 73.7–91.5) and reduction or discontinuation of CNI (14 studies, 253 participants: 76.62%; 95% CI 57.4–88.9). The CNI was completely discontinued in 16 studies (491 participants: 29.0%; 95% CI 16.6–45.7). On the other hand, corticosteroid dose was increased in 16 studies (1,001 participants: 41.4%; 95% CI 24.6–60.5).

Hydroxychloroquine use was reported in 20 studies (1,266 participants: 65.3%; 95% CI 48.1–79.2), while protease

Table 2. Characteristics, treatments and outcomes of patients in included studies.

Characteristic	No. of studies	No. of patients	Pooled mean/event rate (95% CI)	I^2 (%)
Demographic/comorbidity				
Age (yr)	23	1,337	55.28 (53.00, 57.56)	83.52
Male	23	1,369	63.59 (60.67, 66.41)	4.51
Diabetes mellitus	18	916	31.52 (23.87, 40.33)	74.81
Hypertension	18	916	76.10 (68.28, 82.49)	67.96
Cardiac disease	11	495	19.64 (14.20, 26.52)	25.50
Malignancy	11	711	8.26 (4.13, 15.85)	63.35
Time after transplant (mth)	20	1,304	82.88 (70.66, 95.09)	82.14
Baseline Immunosuppression				
Calcineurin inhibitors (CNI)	18	927	84.81 (82.23, 87.07)	0.0
Mycophenolate	18	1,016	75.72 (69.79, 80.81)	49.08
Corticosteroids	19	1,330	74.83 (67.74, 80.81)	69.50
mTOR inhibitors	17	1,270	10.22 (6.57, 15.55)	0.0
Symptoms				
Fever	20	1,314	73.98 (65.25, 81.14)	81.91
Cough	19	900	63.28 (56.49, 69.58)	53.81
Dyspnoea	20	1,314	47.52 (39.58, 55.59)	75.41
Sputum	8	79	12.10 (4.98, 26.55)	27.79
Rhinorrhoea	8	336	9.23 (6.55, 12.87)	0.00
Sore throat	9	132	11.69 (7.10, 18.68)	0.00
Myalgia	11	474	33.15 (24.71, 42.83)	39.04
Fatigue	10	407	36.75 (21.86, 54.70)	66.64
Vomiting	10	162	12.07 (7.76, 18.30)	0.00
Diarrhoea	13	487	29.65 (23.63, 36.47)	23.59
Gastrointestinal symptoms	13	885	33.21 (25.30, 42.21)	66.07
Laboratory features				
White blood cell ($\times 10^9$/L)	14	504	6.02 (5.63, 6.42)	38.16
Lymphocyte ($\times 10^9$/L)	17	702	0.69 (0.62, 0.76)	69.72
C-reactive protein (mg/dL)	15	398	72.37 (57.32, 87.42)	78.66
Chest X-ray findings				
Normal	6	381	81.18 (70.41, 88.66)	46.76
Bilateral/multifocal	5	111	65.21 (51.98, 76.46)	34.97
Unilateral	4	106	20.45 (12.22, 32.19)	28.86
Treatment				
Increased corticosteroids	16	1,001	41.44 (24.61, 60.53)	92.13
Discontinued antimetabolite	16	465	84.61 (73.69, 91.52)	74.67
Reduced or discontinued CNI	14	253	76.62 (57.36 88.87)	79.34
Discontinued CNI	16	491	29.02 (16.55, 45.74)	81.49
Hydroxychloroquine	20	1,266	65.25 (48.05, 79.22)	93.26
Protease inhibitor	15	1,163	20.22 (9.39, 38.27)	92.54
Anti-influenza agents	11	371	28.17 (8.53, 62.27)	90.26
Tocilizumab	12	1,178	13.03 (7.97, 20.59)	77.72
Intravenous immunoglobulin	10	426	15.98 (5.68, 37.56)	82.20
Remdesivir	3	615	2.27 (1.07, 4.76)	32.74
Convalescent plasma	5	987	2.68 (1.80, 3.96)	0.00
Outcomes				
Acute kidney injury	17	859	38.94 (30.54, 48.06)	9.26
Need for dialysis	16	857	12.37 (8.3, 18.04)	19.65
Required oxygen	13	463	61.71 (27.79, 87.09)	83.38
Required mechanical ventilation	22	1,331	24.50 (20.35, 29.20)	45.94
Required ICU/mechanical ventilation	22	1,331	27.65 (21.49, 34.8)	64.08
Death	23	1,373	21.08 (15.27, 28.37)	49.58

I^2 represents heterogeneity statistics. Age and all laboratory results are expressed as mean with 95% confidence interval (CI). All other variables are expressed as event rate with 95% CI. ICU: intensive care unit, mTOR: mammalian target of rapamycin

inhibitors were used in 15 studies (1,163 participants: 20.2%; 95% CI 9.4–38.3). Interleukin-6 receptor antagonists, such as tocilizumab, were used in 12 studies (1,178 participants: 13.0%; 95% CI 8.0–20.6).

Other drugs reported included remdesivir (three studies, 13 participants), convalescent plasma (two studies, 11 participants), anti-influenza agents (e.g. oseltamivir, umifenovir or favipiravir) (11 studies, 68 participants), intravenous immunoglobulin (10 studies, 28 participants), ribavirin (three studies, nine participants) and anakinra (one study, three participants). Concomitant antibiotic use was reported in 577 out of 1,106 cases with available data, including azithromycin (393 of 1,056 cases with available data).

The pooled mortality rate from meta-analysis of 23 studies (1,373 participants) was 21.1% (95% CI 15.3–28.4) [Figure 2]. Similar findings were observed after excluding studies with high ROB [Figure S1, Supplemental Digital Appendix]. Meta-analysis of 13 studies (412 participants) showed a pooled rate of critical illness of 27.7% (95% CI 21.5–34.8) [Figure 3]. There was substantial heterogeneity observed in both outcomes of death (I^2 = 49.6%) and critical illness (I^2 = 64.1%). In the subgroup analysis based on the geographic distribution of studies, heterogeneity was found in studies from Asia and Europe [Table S2, Supplemental Digital Appendix]. In sensitivity analysis, after excluding studies with high ROB, similar findings were observed [Figure S2, Supplemental Digital Appendix]. The need for oxygen was reported in 13 studies (463 participants: 61.7; 95% CI 27.8–87.1) with substantial heterogeneity. In subgroup analysis, according to the geographic distribution of studies, moderate heterogeneity was observed in Europe and North America [Table S2, Supplemental Digital Appendix]. The rate of acute kidney injury was reported in 17 studies (859 participants: 38.9%; 95% CI 30.5–48.1), while the need for dialysis was reported in 16 studies (857 participants:

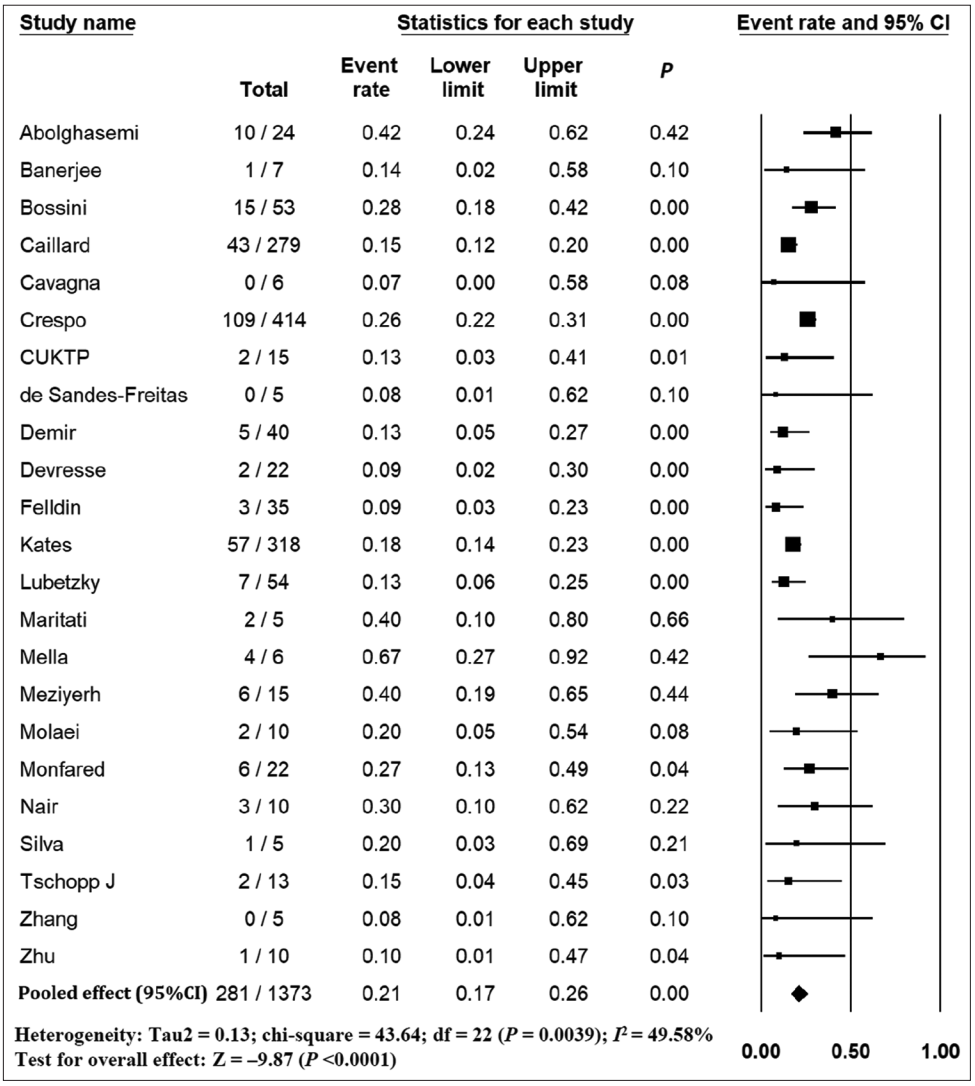

Figure 2: Forest plot shows the incidence of mortality in kidney transplant recipients with COVID-19. CI: confidence interval

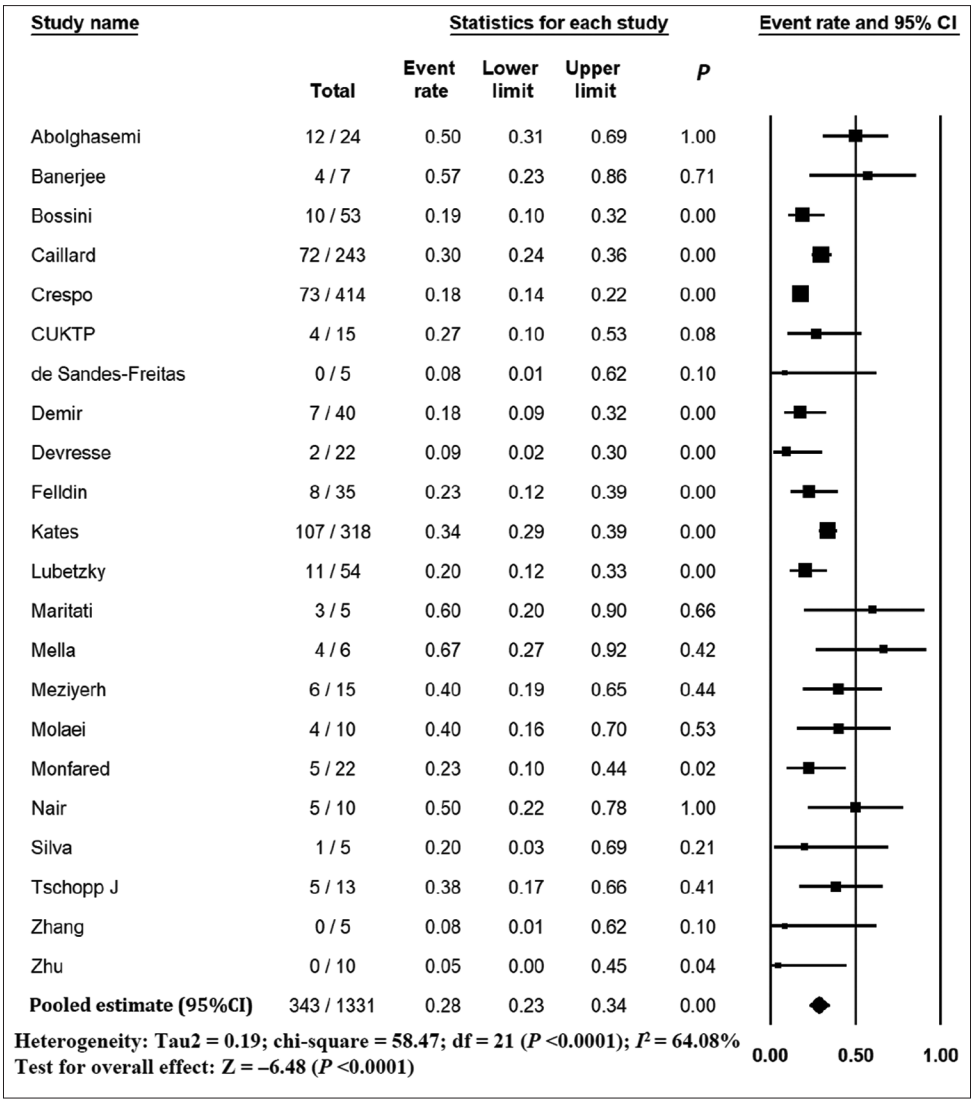

Figure 3: Forest plot shows the incidence of critical illness in kidney transplant recipients with COVID-19. CI: confidence interval

12.4%; 95% CI 8.3–18.0) [Figure 4]. Similar findings were observed after excluding studies with high ROB [Figure S3, Supplemental Digital Appendix]. Publication bias for the primary outcomes based on funnel plots and Egger's regression test did not demonstrate evidence of publication bias [Figures S4–S6, Supplemental Digital Appendix]. In very low-certainty evidence, the use of high-dose corticosteroids or hydroxychloroquine was not associated with mortality outcomes in meta-regression after adjusting for the need for mechanical ventilation [Table S3 and Figure S7, Supplemental Digital Appendix].

DISCUSSION

This review demonstrated that fever, cough and dyspnoea were the common presenting symptoms in KTRs with COVID-19. In addition, approximately one-third of patients presented with diarrhoea or gastrointestinal symptoms. Furthermore, KTRs with COVID-19 may have higher risk of developing acute kidney injury, higher requirement of dialysis and increased acceptable mortality as compared to the general population It is uncertain whether different treatments (high-dose corticosteroids or hydroxychloroquine) reduce the risks of mortality in KTRs with COVID-19, given the suboptimal quality of included studies in the review.

This review also demonstrated that KTRs with COVID-19 had similar presenting symptoms as the general population with COVID-19,[8,9,11,12] including fever (74.0% vs. 72.4%–87.3%), cough (63.3% vs. 53.9%–60.3%) and dyspnoea (44.4% vs. 18.8%–38.3%). However, diarrhoea was more common in KTRs than in the general population (29.7% vs. 6.8%–9.5%). A previous systematic review of COVID-19 in KTRs including 12 case reports with 204 patients reported similar findings.[13] The presence of gastrointestinal symptoms may reflect more

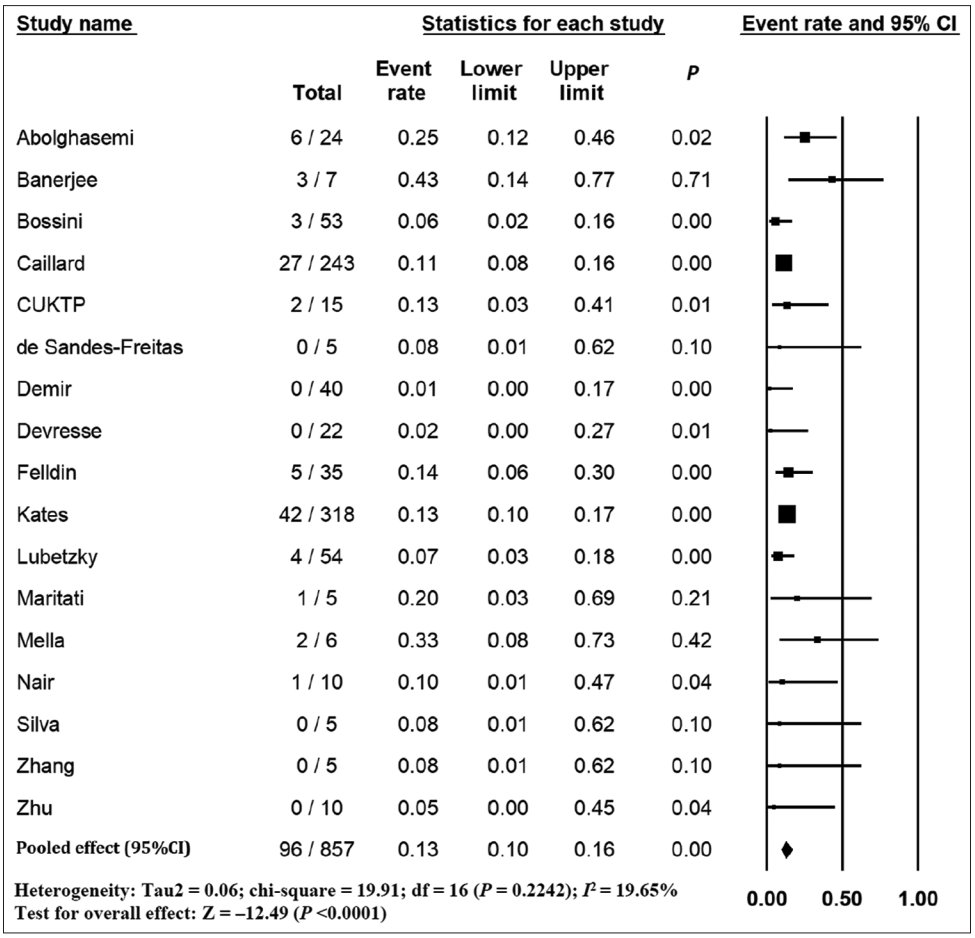

Figure 4: Forest plot shows the incidence of need for dialysis in kidney transplant recipients with COVID-19. CI: confidence interval

severe COVID-19 in the KTR cohorts[12,47,48] or alterations in the gut immune response and microbiota from uraemia or immunosuppression.[49,50]

In terms of outcomes, the need for oxygen (61.7% vs. 62.6%–71.5%) and intensive care unit admission (27.7% vs. 10.6%–25.6%) for KTRs may be similar to the general population.[8-12] However, KTRs with COVID-19 may have higher risk of acute kidney injury (38.9% vs. 5.7%–7.1%) and higher need for dialysis (12.4% vs. 4.7%–8.3%)[12,51,52] than the general population.

The mortality rate for the general population with COVID-19 was reported to be 3.6%–6.8% in previous meta-analyses.[8,9] However, the present review demonstrated that the mortality rate for KTRs with COVID-19 (21.1%) was higher than for general population with COVID-19. Previous systematic reviews also reported similarly high mortality rates (21.2%–23%)[13,14,16,17,37] in KTRs with COVID-19, which was even higher (46%) for hospitalised patients.[16] The mortality rate reported in the large dialysis cohort studies[53-55] ranged between 14% and 24.9%, which was higher than that of the general population and was slightly lower than or similar to that of KTRs.

Worse outcomes in KTR patients have been shown in studies comparing KTR and non-transplant cohorts.[24,55] Outcomes in the KTR cohort may be worse due to a higher prevalence of risk factors such as advanced age, comorbidities and chronic kidney disease.[56,57] The impact of immunosuppression on the outcomes of KTRs with COVID-19 is uncertain.[58] While immunosuppression may exacerbate COVID-19 by inhibiting appropriate antiviral immune responses, it may also attenuate detrimental hyperinflammatory responses and inhibit viral replication directly.[58-60] Studies on immunosuppression in the non-transplant populations have also not reported worse outcomes.[61,62]

Previous studies in the general population with COVID-19 reported that advanced age, presence of comorbidities,[9,57] laboratory findings such as leucocytosis, lymphopenia and transaminitis, raised lactate dehydrogenase, C-reactive protein and procalcitonin,[10,63] and presence of ground-glass opacities on computed tomography[64] may predict worse outcomes. Analysis of available KTR individual patient-level data from case reports and case series suggested that longer transplant vintage, hypoxaemia and higher lactate dehydrogenase levels are associated with mortality.[17]

Studies on corticosteroids[65,66] and tocilizumab[67,68] showed that they may be useful for the treatment of severe COVID-19, while studies on hydroxychloroquine,[69] protease inhibitors[70,71] and azithromycin[72] did not demonstrate benefit. While remdesivir may shorten the time to recovery in patients with COVID-19[73,74] and vaccines are being developed,[75,76] their efficacy in the KTR subgroup is unclear. Moreover, participants with kidney disease are frequently excluded from COVID-19 clinical trials.[77] In our study, it is uncertain whether different treatments, including increased dose of corticosteroids or use of hydroxychloroquine, reduced the risk of mortality in KTRs with COVID-19 because the quality of evidence was graded as very low, given that all included studies were observational studies and had small sample size with imprecision.

To the best of our knowledge, this is one of the largest systematic reviews and meta-analyses performed on the outcomes of KTRs with COVID-19. However, there are several limitations in this review. Given that new COVID-19 studies are published at a high rate, unindexed or recently published studies that were excluded may have altered the outcomes of our analysis. Excluding non-English studies may also have introduced selection bias. All studies included were observational studies and had relatively small sample sizes. There were some missing data for which we attempted, but were unable, to obtain responses from the primary authors. Moreover, the follow-up duration in many studies was inadequate, with multiple patients still admitted at the time of publication. There was also significant heterogeneity in the reporting and definition of parameters and outcomes. Of note, the largest study, which contributed more than half the cases, was a national registry study that relied on reporting of cases and data by individual centres and collected only limited data. Individual patient data, which may have been able to provide clearer information regarding prognostic factors and response to therapy, were not available.

In conclusion, KTRs with COVID-19 may have similar clinical presentation to the general population, except in the case of diarrhoea. In addition, KTRs with COVID-19 may have higher risk of developing acute kidney injury, higher requirement of dialysis and increased mortality compared to the general population. More high-quality studies and international collaboration are required to investigate the impact of various clinical factors and management strategies on the outcomes of COVID-19 in KTR.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Supplemental digital content

Appendix at https://links.lww.com/SMJ/XXX

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APPENDIX

Table S1. Methodological Quality Assessment for Cohort Studies

Author (Country)	Q1. Was the sample frame appropriate to address the target population?	Q2. Were study participants sampled in an appropriate way?	Q3. Was the sample size adequate?	Q4. Were the study subjects and the setting described in detail?	Q5. Was the data analysis conducted with sufficient coverage of the identified sample?	Q6. Were valid methods used for the identification of the condition?	Q7. Was the condition measured in a standard, reliable way for all participant?	Q8. Was there appropriate statistical analysis?	Q9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall Quality Score
Asia										
Zhang et al [24]	Yes	Yes	No	No	Yes	Yes	No	No	Yes	5
Zhu et al [25]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	6
Monfared et al [40]	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	6
Abolghase et al [41]	No	No	No	Yes	Yes	No	No	No	Yes	3
Molaei et al [36]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	6
Europe										
Banerjee et al [43]	Yes	Yes	No	No	Yes	Yes	No	No	Yes	5
Tschopp et al [44]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	6
Devresse et al [46]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	5
Maritati et al [27]	No	No	No	Yes	Yes	Yes	No	No	Yes	4
Cavagna et al [28]	Yes	No	No	No	No	No	No	No	Yes	2
Mella et al [29]	No	No	No	No	Yes	Yes	No	No	Yes	3
Silva et al [42]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	7

Bossini et al [30]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Demir et al [31]	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Caillard et al [32]	No	No	Yes	No	Yes	Yes	No	Yes	Yes	5
Crespo et al [33]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
Felldin et al [26]	Yes	Yes	No	No	Yes	Yes	No	No	Yes	5
Meziyerh et al [45]	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	6
North America										
Nair et al [35]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	7
Columbia University Kidney Transplant Program [34]	No	No	No	No	Yes	Yes	No	No	Yes	3
Lubetzky et al [37]	No	No	No	Yes	Yes	Yes	Yes	No	Yes	5
Others										
De Sandes-Freitas et al [38]	Yes	Yes	No	No	Yes	Yes	No	No	Yes	5
Kates et al [39]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	6

Figure S1. Forest Plot Showing Incidence of Mortality in Kidney Transplant Recipients With COVID-19 (excluding studies with high risk of bias)

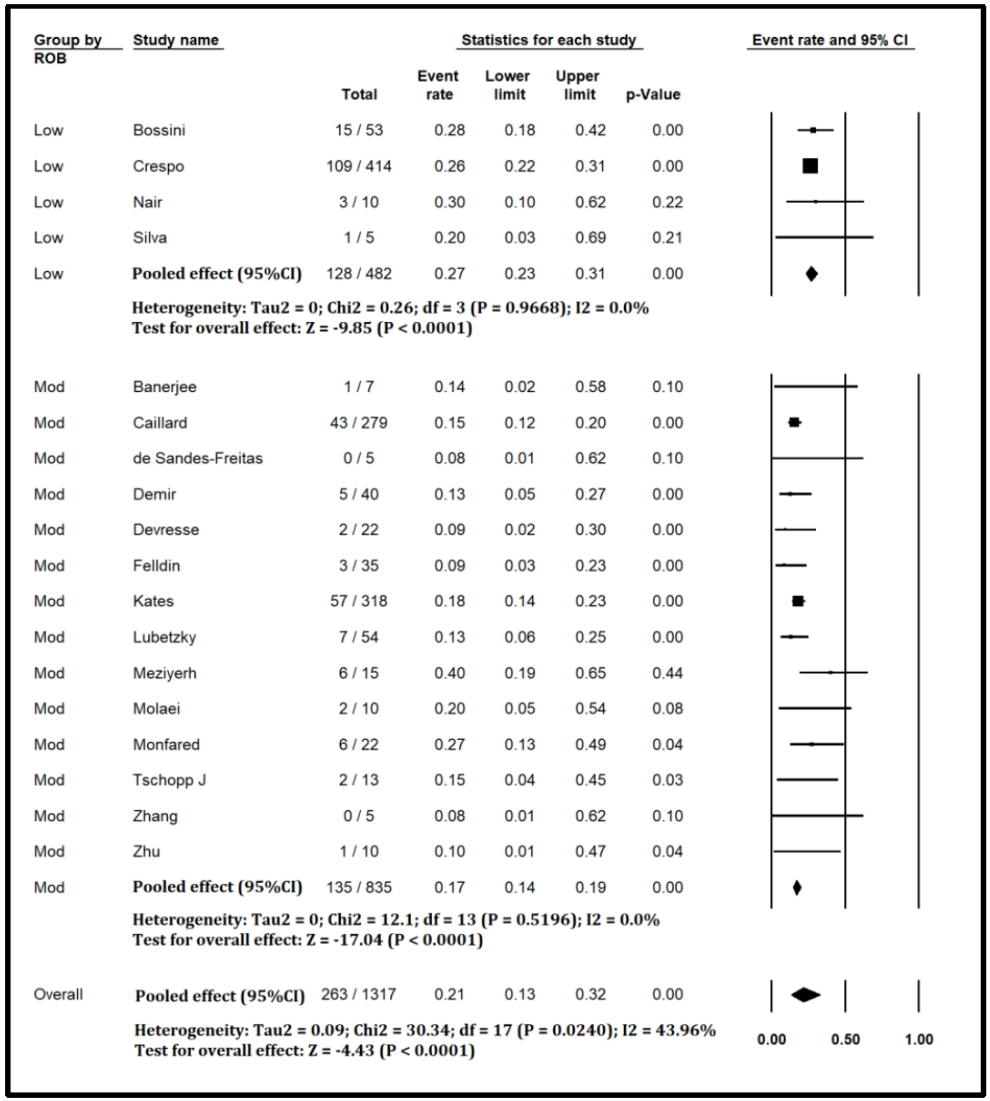

Table S2. Subgroup Analysis of Outcomes Based on the Geographical Distribution of Studies

Outcomes	Event rates (95% Confidence Interval), I^2 (%)			
	Asia	Europe	North America	Overall
Mortality	26.79 (15.37, 42.44), 16.58	21.05 (15.48, 27.96), 59.89	16.55 (8.09, 30.88), 0.00	21.08 (15.27, 28.37), 48.46
Critical illness	31.45 (17.96, 49.03), 50.49	26.83 (19.87, 35.16), 65.34	28.51 (15.45, 46.54), 44.76	27.65 (21.49, 34.8), 58.38
Dialysis	17.79 (6.77, 39.19), 7.13	12.45 (7.56, 19.81), 44.10	9.41 (3.83, 21.33), 0.00	12.37 (8.3, 18.04), 23.89
AKI	46.3 (32.99, 60.16), 0.00	37.99 (31.27, 45.2), 20.40	36.33 (24.7, 49.81), 24.11	38.94 (30.54, 48.06), 14.38
O2	89.63 (65.73, 97.49), 46.06	68.76 (49.34, 83.26), 81.85	42.09 (14.17, 76.19), 68.68	61.71 (27.79, 87.09), 83.39

Figure S2. Forest Plot Showing Incidence of Critical Illness in Kidney Transplant Recipients With COVID-19 (excluding studies with high risk of bias)

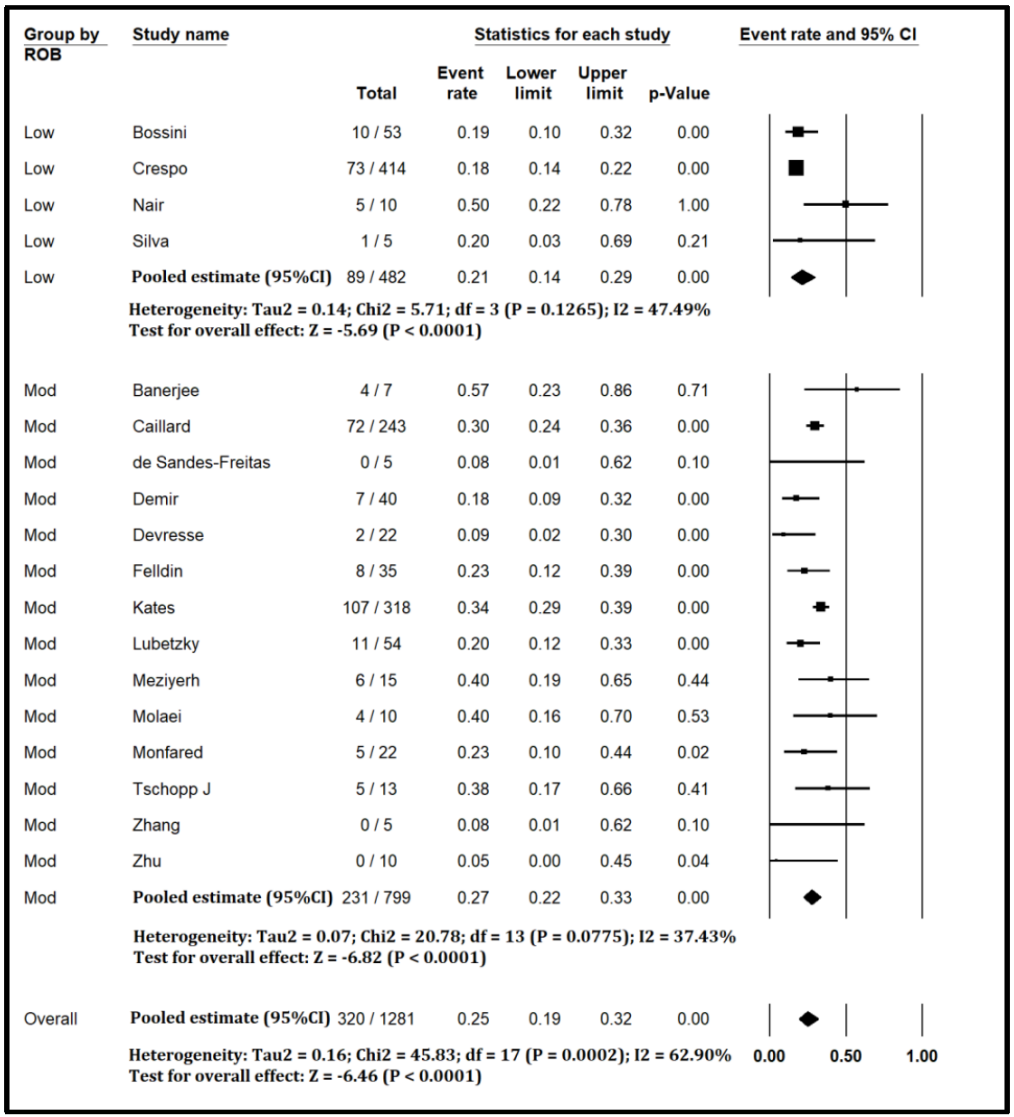

Figure S3. Forest Plot Showing Incidence of Need for Dialysis in Kidney Transplant Recipients With COVID-19 (excluding studies with high risk of bias)

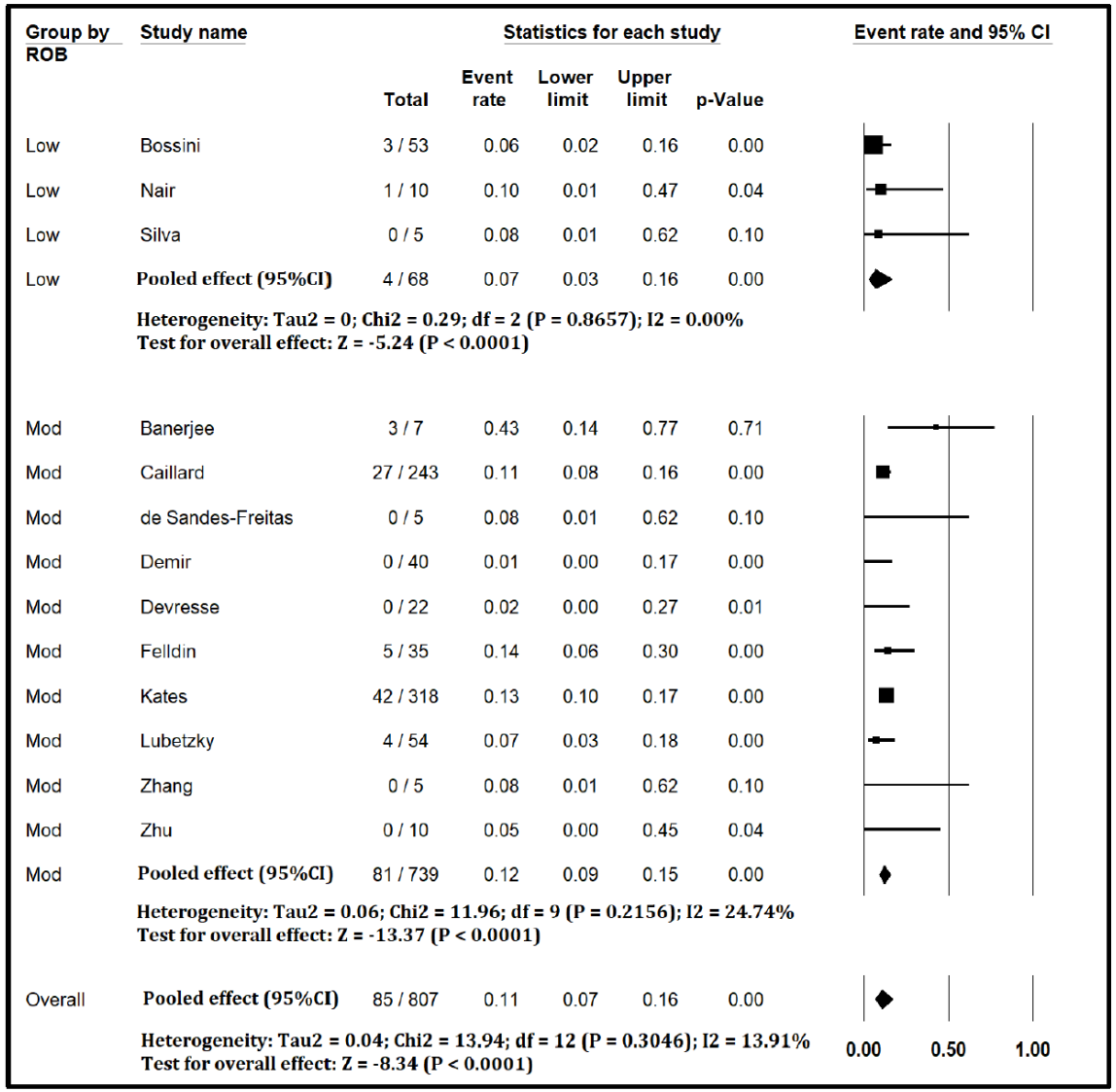

Figure S4. Funnel Plot for Mortality

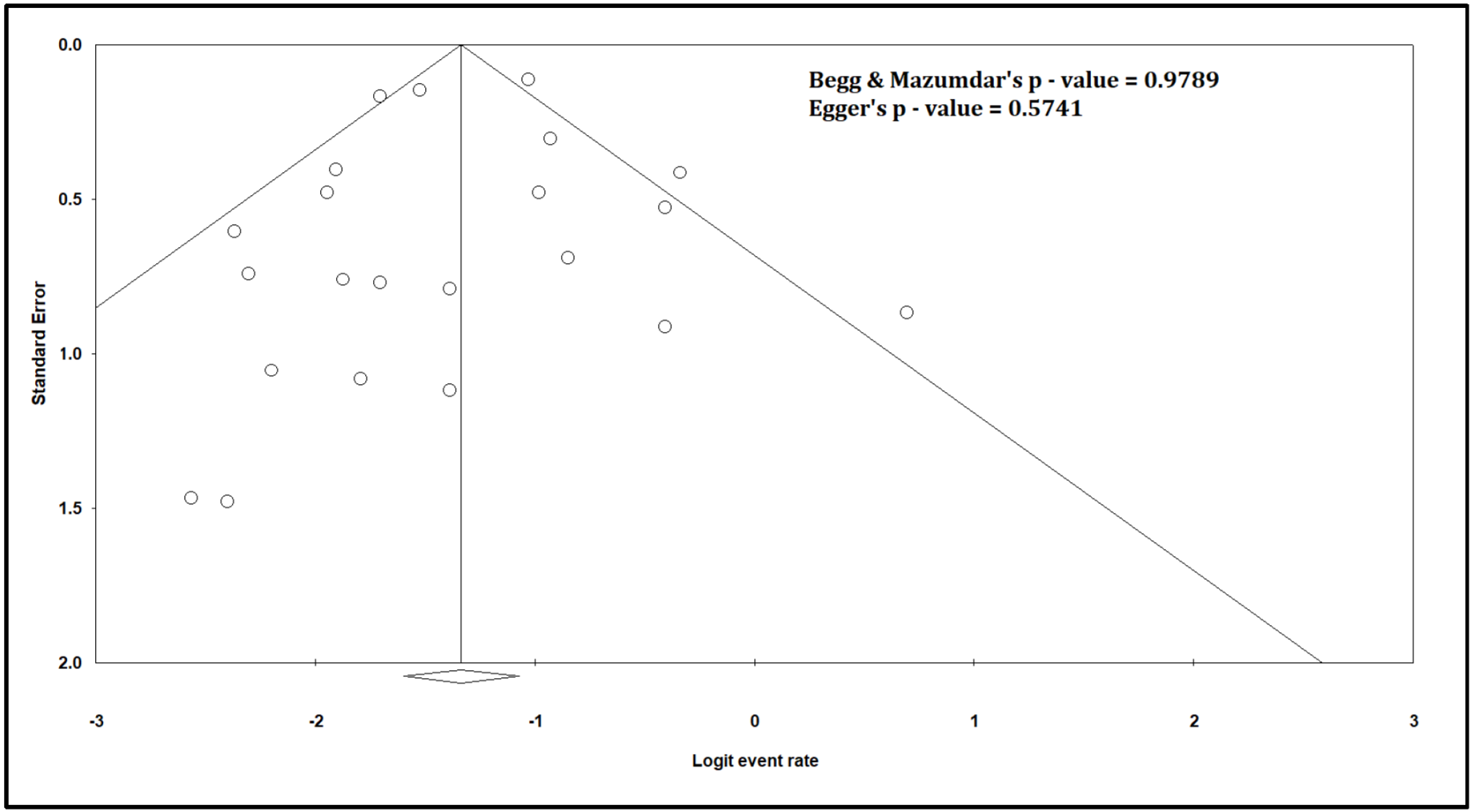

Figure S5. Funnel Plot for Critical illness

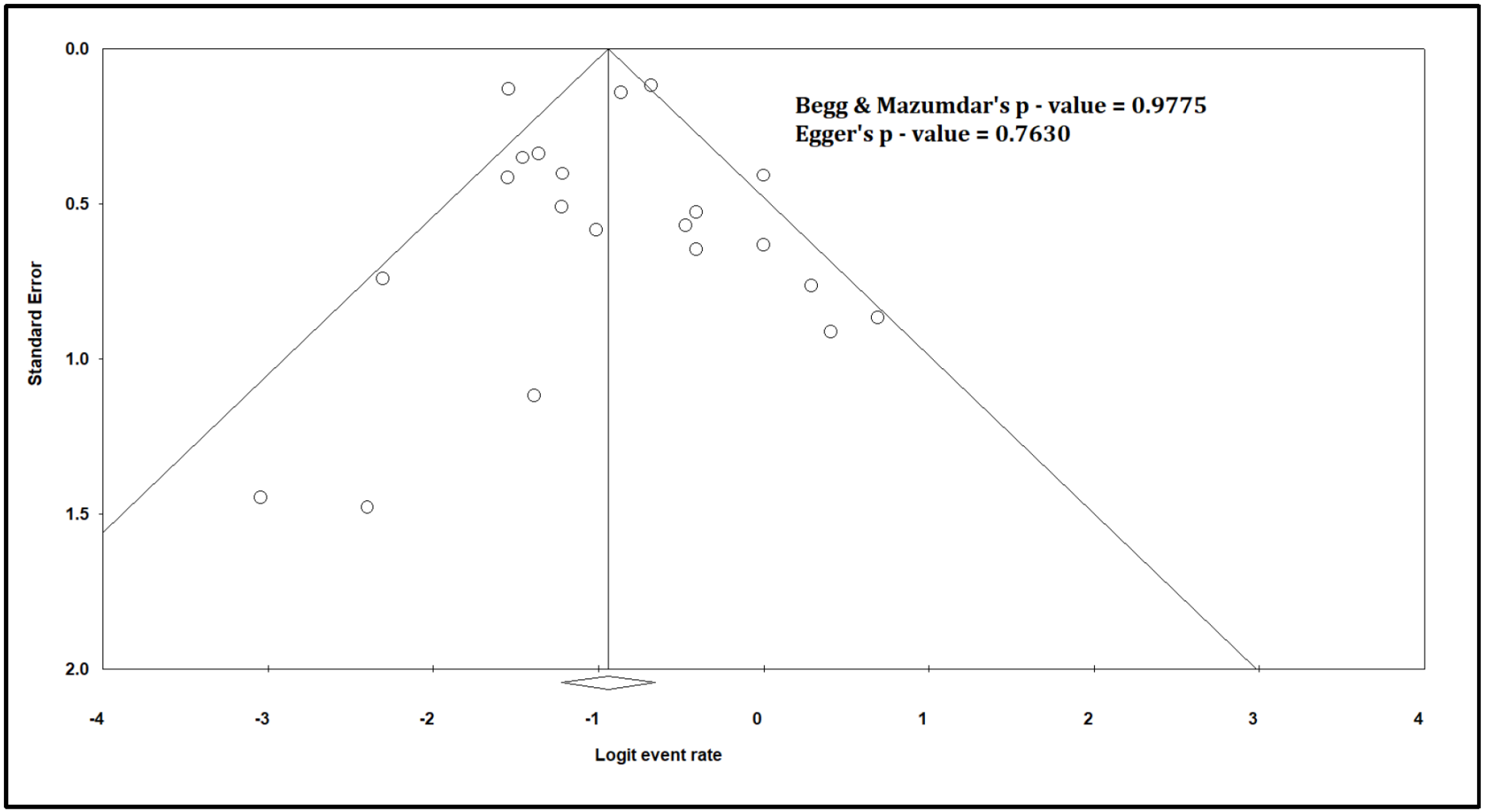

Figure S6. Funnel Plot for Need for Dialysis

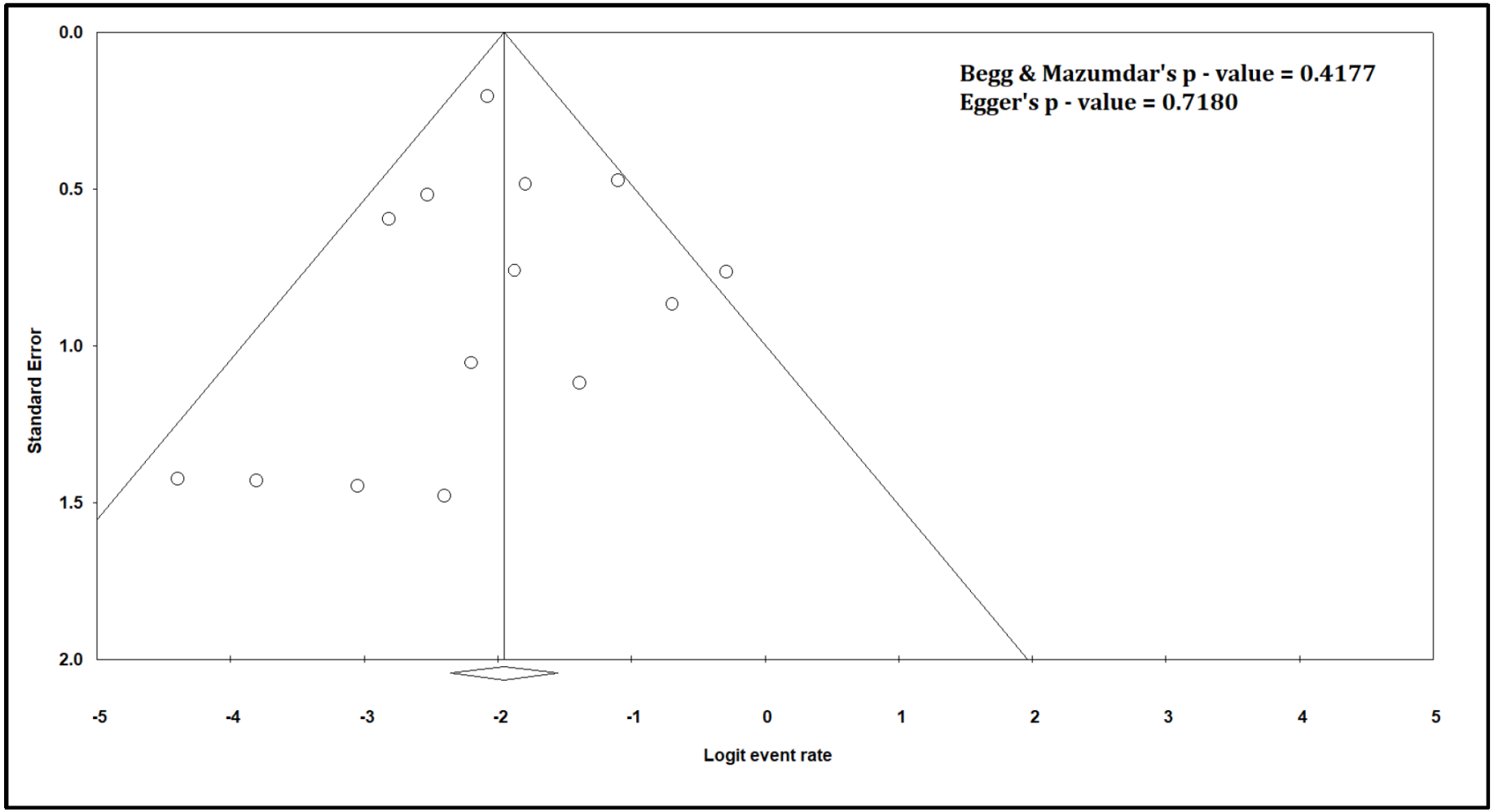

Table S3. Meta-regression of Factors Predicting Mortality

Variables	**Adjusted β estimate**	**95% Confidence Interval**	**p-value**
Increased corticosteroids	0.61	-0.07 – 1.30	0.07
Hydroxychloroquine	0.94	-0.04 – 1.93	0.06
Mechanical ventilation	3.15	0.98 – 5.31	0.009

Figure S7. Bubble plots for meta-regression of mortality rate against hydroxychloroquine use and increased corticosteroids