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

Quan Yao Ho[1,2], MBBS, MRCP, Rehena Sultana[3], BSc, MSc, Tung Lin Lee[1], MBChB, MRCP, Sobhana Thangaraju[1,2], MBBS, MRCP, Terence Kee[1,2], BMBS, FRCP, Htay Htay[1,3], MBBS, FRCP

[1]Department of Renal Medicine, Singapore General Hospital, [2]SingHealth Duke-NUS Transplant Centre, [3]Duke-NUS Medical School, Singapore

Correspondence: Dr Ho Quan Yao, Consultant, Department of Renal Medicine, Singapore General Hospital, Outram Road, Singapore 169608. ho.quan.yao@singhealth.com.sg

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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 (1373 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.

Discussion: KTRs with COVID-19 have a similar clinical presentation as the general population but 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 has 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 co-morbidities,[5] some have argued that immunosuppression may have protective effects against the severe systemic inflammatory response responsible for severe disease in COVID-19.[6] KTRs have also 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, remains unclear. Similar studies of COVID-19 in the general population[8-12] have been performed. 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 examined the clinical, laboratory, radiological features, and clinical outcomes of KTRs with COVID-19.

METHODS

Our systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta‐Analyses (PRISMA) 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 following databases – PubMed, EMBASE, Web of Science, SCOPUS, and CENTRAL according to the registered search strategy (Appendix 1 of Supplementary Materials) 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 LTL) independently screened all titles and abstracts then subsequently reviewed all potentially relevant full-text articles for eligibility for inclusion. Only studies with 5 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 meta-analysis were assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for prevalence studies.[19] The methodological quality was categorised to low (score $\leqslant$ 3), moderate (4-6) and high ($\geqslant$ 7). The level of evidence for primary outcomes was assessed using GRADE (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 LTL) 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 was 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 summarized 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 $I^2 \geqslant 75.0\%$ 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. 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 were also plotted. Bubbles are sized according to the precision of each estimate with larger bubbles for more precise estimates. Publication bias was assessed using the funnel plot, Egger's and Begg's tests.[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 and P values < 0.05 were considered as statistical significance. Statistical analyses were performed using Comprehensive Meta–Analysis Version 3.3.07 (Biostat Inc, Englewood, New Jersey, USA) software. Meta–regression analysis was performed in SAS version 9.2.2 (Cary, NC).

RESULTS

Our search identified 1575 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 (n=1373)[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 5 studies, moderate for 14 studies and low for 4 studies (Supplemental Table S1).

A total of 1373 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 summarized in Table 2. The pooled mean age was (23 studies, 1337 participants: 55.3 years; 95% Confidence Interval (CI) 53.0-57.6) and male gender was (23 studies, 1369 participants: 63.6%; 95% CI 60.7-66.4). The common co-morbidities 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, 1016 participant: 75.7%; 95% CI 69.8-80.8) and corticosteroids (19 studies, 1330 participants: 74.8%; 95% CI 67.7-80.8).

The most common presenting symptoms on meta-analysis were fever (20 studies, 1314 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, 1314 participants: 47.5%; 95% CI 39.6-55.6; Table 2). Diarrheal 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 was $6.02x10^9$/L (95% CI 5.63-6.42), $0.69x10^9$/L (95% CI 0.62-0.76) and 72.4mg/dL (95% CI 57.3-87.4; Table 2) respectively.

Chest X-rays on admission were commonly reported to be normal (6 studies, 381 participants: 81.2%; 95% CI 70.4-88.7), had bilateral or multifocal infiltrates (5 studies, 111 participants: 65.2%; 95% CI 52.0-76.5), or unilateral infiltrates (4 studies, 106 participants: 20.5%; 95% CI 12.2-32.2).

Common strategies for modification of immunosuppressants included discontinuation of anti-metabolite (16 studies, 465 participants: 84.6%; 73.7-91.5) and reduction or discontinuation of CNI (14 studies, 253 participants: 76.62%; 95% CI 57.4-88.9). CNI was completely discontinued in 16 studies (491 participants: 29.0%; 95% CI 16.6-45.7). On the other hand, corticosteroids dose was increased in 16 studies (1001 participants: 41.4%; 95% CI 24.6-60.5).

Hydroxychloroquine use was reported in 20 studies (1266 participants: 65.3%; 95% CI 48.1-79.2), while protease inhibitors were used in 15 studies (1163 participants: 20.2%; 95% CI 9.4-38.3). Interleukin-6 receptor antagonists, such as tocilizumab, were used in 12 studies (1178 participants: 13.0%; 95% CI 8.0-20.6).

Other drugs reported included remdesivir (3 studies, 13 participants), convalescent plasma (2 studies, 11 participants), anti-influenza agents (e.g. oseltamivir, umifenovir or favipiravir) (11 studies, 68 participants), intravenous immunoglobulin (10 studies, 28 participants), ribavirin (3 studies, 9 participants) and anakinra (1 study, 3 participants). Concomitant antibiotic use was reported in 577 out of 1106 cases with available data including azithromycin (393 of 1056 cases with available data).

The pooled mortality rate from meta-analysis of 23 studies (1373 participants) was 21.1% (95% CI 15.3-28.4; Figure 2). Similar findings observed after excluding studies with high risk of bias (ROB) (Supplemental Figure S1). 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 geographical distribution of studies, heterogeneity persisted for studies in Asia and Europe (Supplemental Table S2). In sensitivity analysis, after excluding studies with high ROB, similar findings were observed (Supplemental Figure S2). 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 geographical distribution of studies, moderate heterogeneity was observed in Europe and North America (Supplemental Table S2). Rate of acute kidney injury was (17 studies, 859 participants: 38.9%; 95% CI 30.5-48.1) while need for dialysis was reported in 16 studies (857 participants: 12.4%; 95% CI 8.3-18.0; Table 2). Publication bias for the primary outcomes based on funnel plots and Egger's regression test did not demonstrate evidence of publication bias (Supplemental Figure S4-6).

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 need for mechanical ventilation (Supplemental Table S3 and Figure S7).

DISCUSSION

The present review demonstrated that fever, cough, and dyspnoea were common presenting symptoms in KTRs with COVID-19. In addition, approximately one-third of patients presented with diarrhoea or gastrointestinal symptoms. The incidence of developing acute kidney injury, requiring dialysis, and mortality were high in KTRs with COVID-19. It is uncertain whether different treatment (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.

The present review demonstrated that KTRs with COVID-19 had similar presenting symptoms to COVID-19 in the general population[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 the KTRs than general population (29.7% vs 6.8%-9.5%). A previous systematic review of COVID-19 in KTRs including 12 case reports, 204 patients, reported similar findings.[13] The presence of gastrointestinal symptoms may reflect more severe COVID-19 in the KTR cohorts[12,47,48] or alterations in 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 need for dialysis (12.4% vs 4.7%-8.3%)[12,51,52] than the general population.

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

The 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, co-morbidities 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 anti-viral immune responses, it may also attenuate detrimental hyperinflammatory responses and inhibit viral replication directly.[58-60] Studies in the non-transplant populations on immunosuppression have also not reported worse outcomes.[61,62]

Previous studies in the general population with COVID-19 reported that advanced age, presence of co-morbidities,[9,57] laboratory findings such as leukocytosis, lymphopenia, transaminitis, raised lactate dehydrogenase, C-reactive protein and procalcitonin[10,63] and presence of ground glass opacities on computed tomography scans[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 LDH levels were associated with mortality.[17]

The use of corticosteroids[65,66] and tocilizumab[67,68] for the treatment of severe COVID-19 may be useful, 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 under development,[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 treatment 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, 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 was unable to obtain responses from primary authors. Moreover, the follow-up duration in multiple studies was also inadequate, with multiple patients still admitted at the time of publication. There was 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, was not available.

In conclusion, KTRs with COVID-19 may have similar clinical presentation except diarrhoea compared to the general population. KTRs with COVID-19 may have higher risks of developing acute kidney injury, requiring dialysis, and 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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Table 1. Characteristics of Included Studies

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

IQR – interquartile range; SD – standard deviation; NR – not reported

Table 2. Characteristics, Treatments & Outcomes of Patients in Included Studies

Characteristics	Studies reported	Patients included	Pooled mean/ event rate (95% CI)	I^2 (%)
Demographics / Co-morbidities				
Age (years)	23	1337	55.28 (53.00, 57.56)	83.52
Male	23	1369	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, months	20	1304	82.88 (70.66, 95.09)	82.14
Baseline Immunosuppression				
Calcineurin inhibitors (CNI)	18	927	84.81 (82.23, 87.07) 75.72	0.0
Mycophenolate	18	1016	(69.79, 80.81)	49.08
Corticosteroids	19	1330	74.83 (67.74, 80.81) 10.22	69.50
mTOR inhibitors	17	1270	(6.57, 15.55)	0.0
Symptoms				
Fever	20	1314	73.98 (65.25, 81.14)	81.91
Cough	19	900	63.28 (56.49, 69.58)	53.81
Dyspnea	20	1314	47.52 (39.58, 55.59)	75.41
Sputum	8	79	12.10 (4.98, 26.55)	27.79
Rhinorrhea	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
GastrointestinaI symptoms	13	885	33.21 (25.30, 42.21)	66.07
Laboratory Features				
White blood cell, x109/L	14	504	6.02 (5.63, 6.42)	38.16
Lymphocyte, x109/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	1001	41.44 (24.61, 60.53)	92.13
Discontinue anti-metabolite	16	465	84.61 (73.69, 91.52)	74.67
Reduced or discontinued CNI	14	253	76.62 (57.36 88.87)	79.34
Discontinue CNI	16	491	29.02 (16.55, 45.74)	81.49
Hydroxychloroquine	20	1266	65.25 (48.05, 79.22)	93.26
Protease inhibitor	15	1163	20.22 (9.39, 38.27)	92.54
Anti-influenza agents	11	371	28.17 (8.53, 62.27)	90.26
Tocilizumab	12	1178	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
Require oxygen	13	463	61.71 (27.79, 87.09)	83.38
Require mechanical ventilation	22	1331	24.50 (20.35, 29.20)	45.94
Require ICU / mechanical ventilation	22	1331	27.65 (21.49, 34.8)	64.08
Death	23	1373	21.08 (15.27, 28.37)	49.58

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

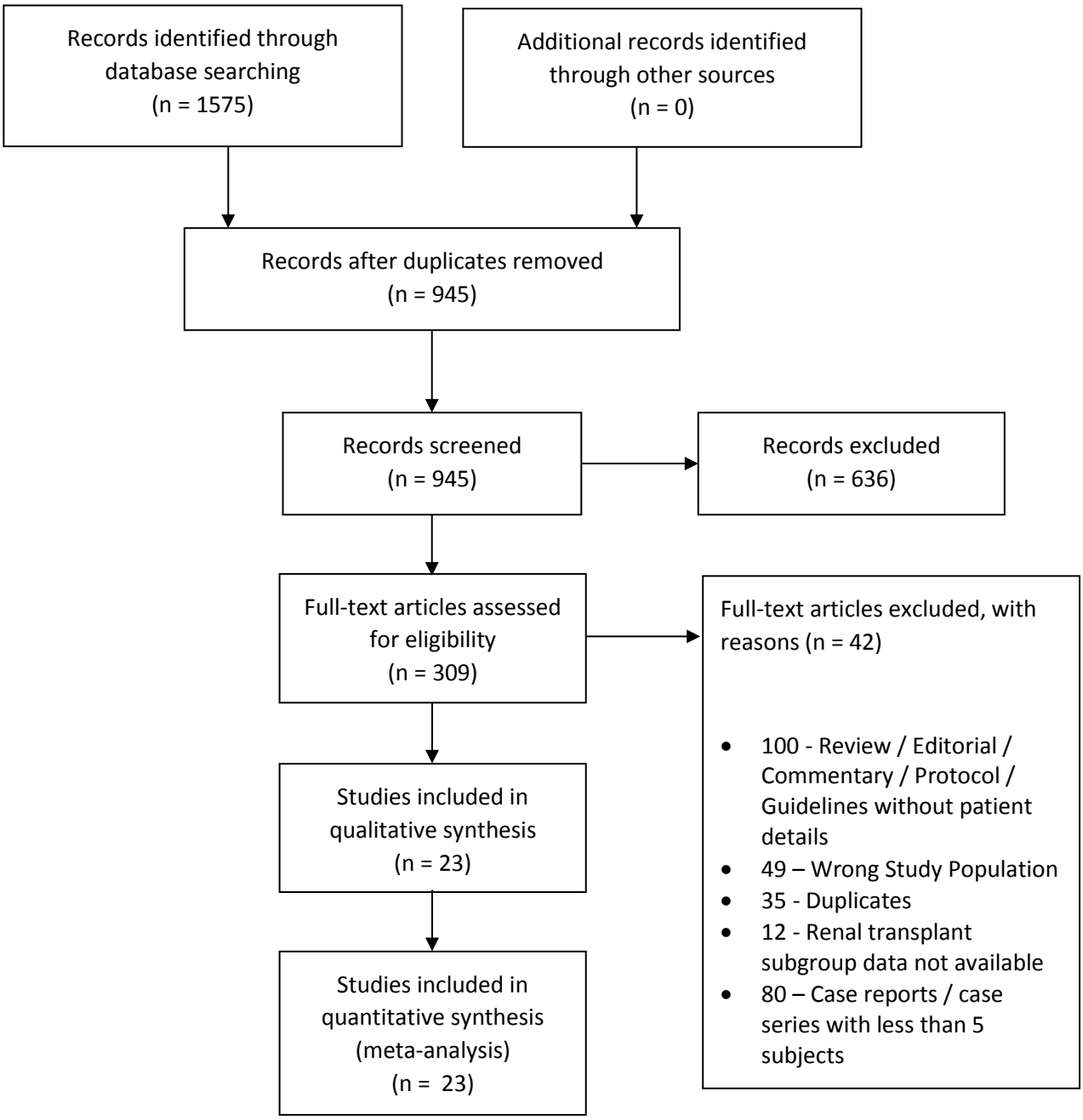

Figure 1. Study Selection Flow Diagram

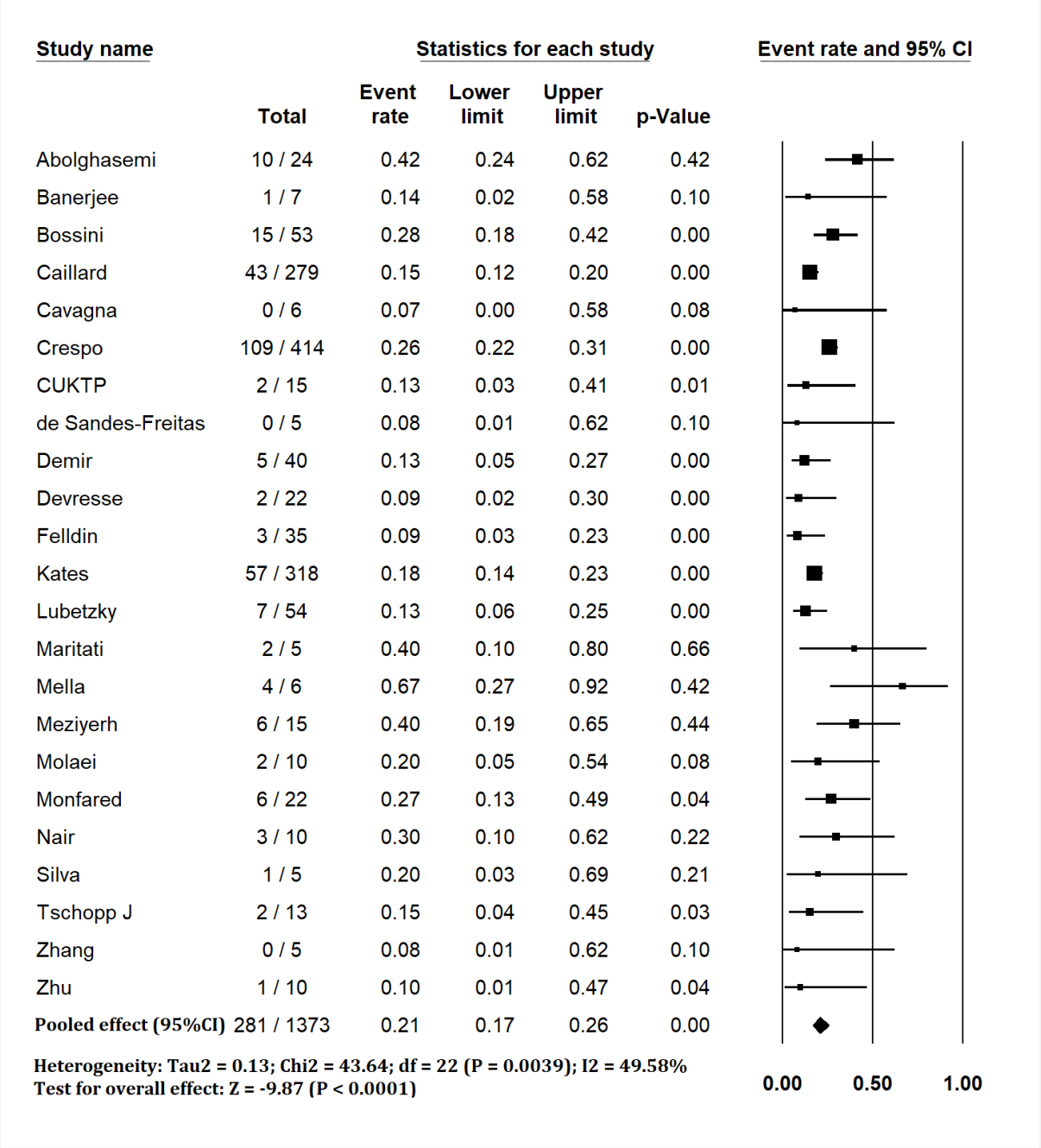

Figure 2. Forest Plot Showing Incidence of Mortality in Kidney Transplant Recipients With COVID-19

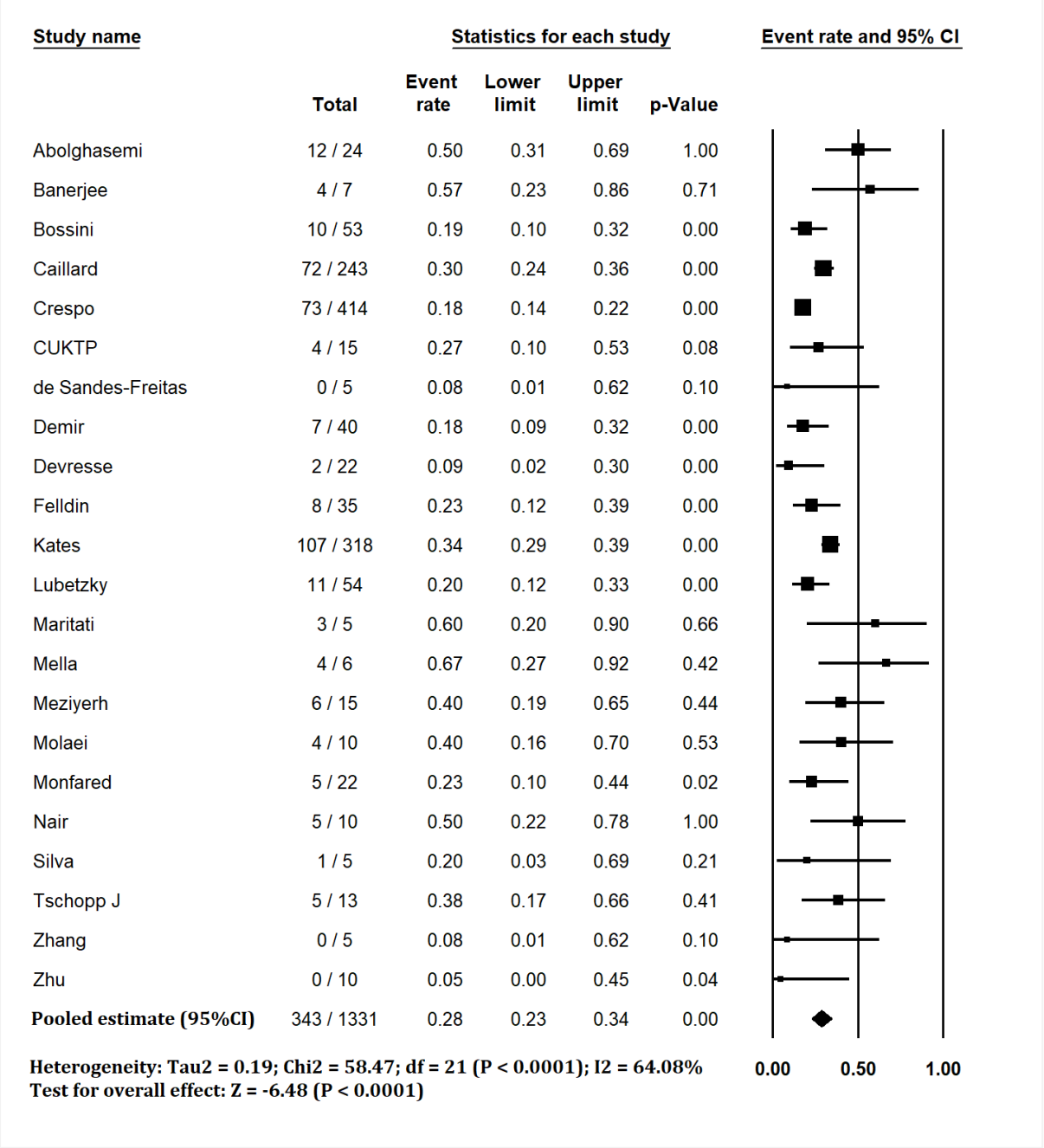

Figure 3. Forest Plot Showing Incidence of Critical Illness in Kidney Transplant Recipients With COVID-19

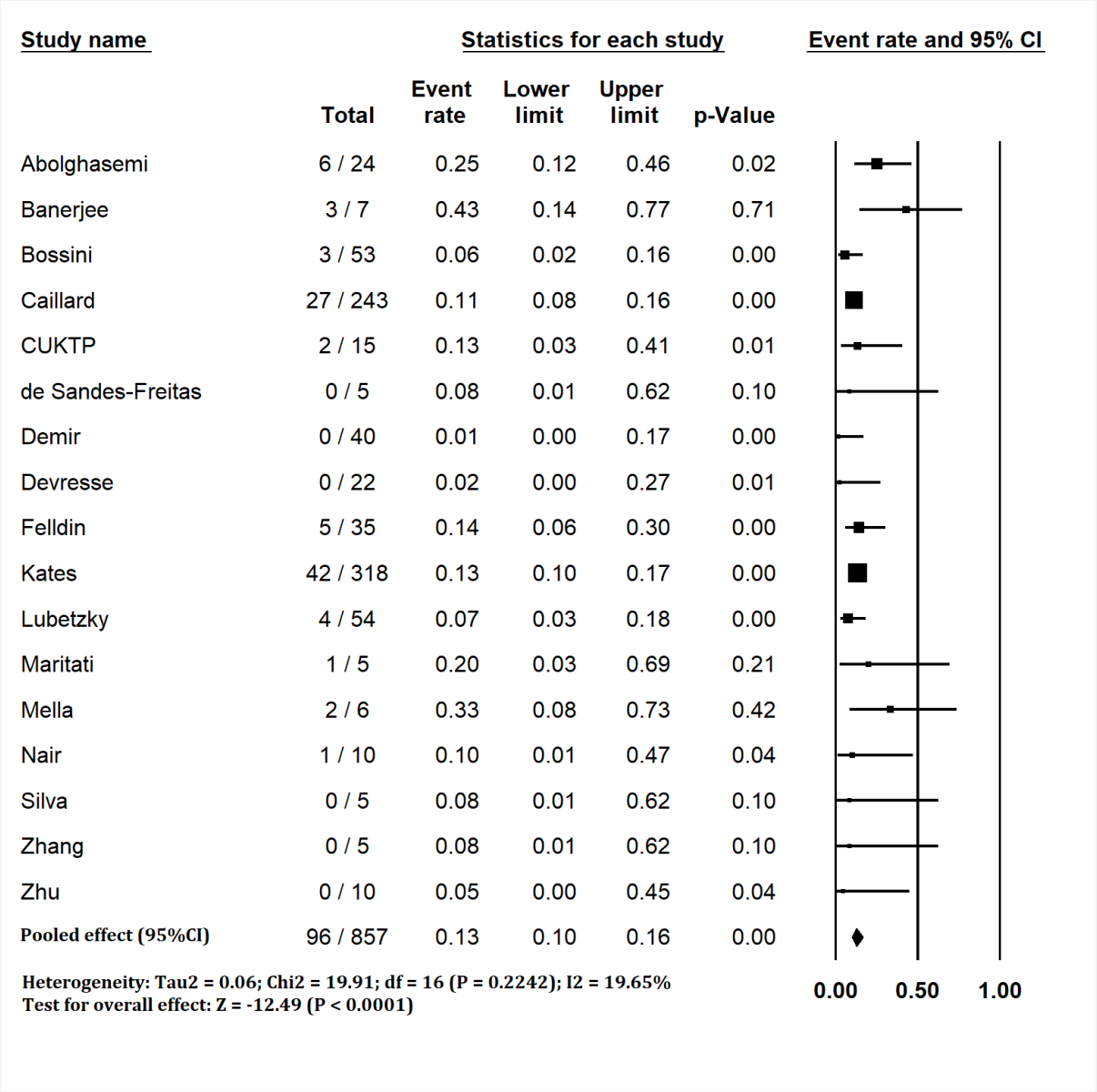

Figure 4. Forest Plot Showing Incidence of Need for Dialysis in Kidney Transplant Recipients With COVID-19.

APPENDIX – SUPPLEMENTARY MATERIAL

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)

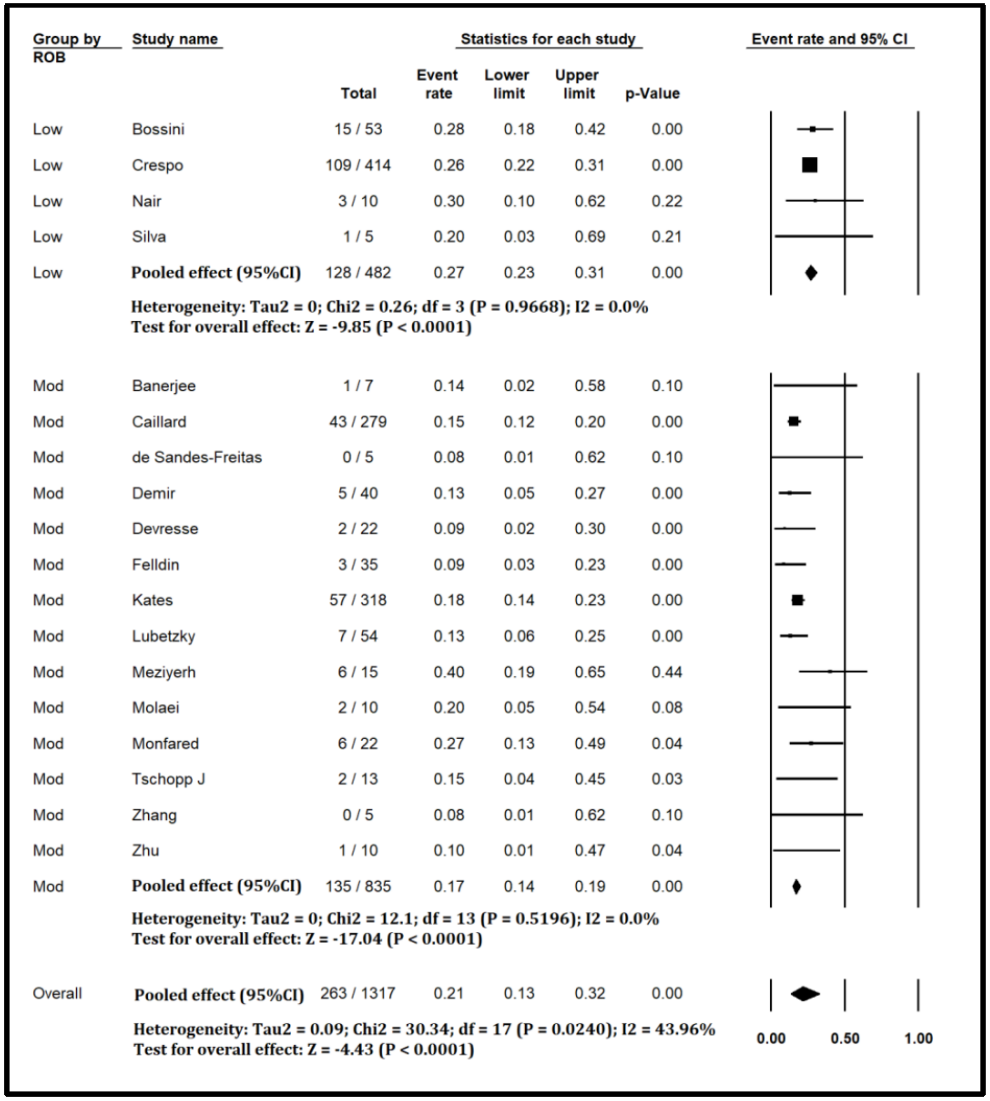

Figure S2. Forest Plot Showing Incidence of Critical Illness in Kidney Transplant Recipients With COVID-19 (excluding studies with high risk of bias)

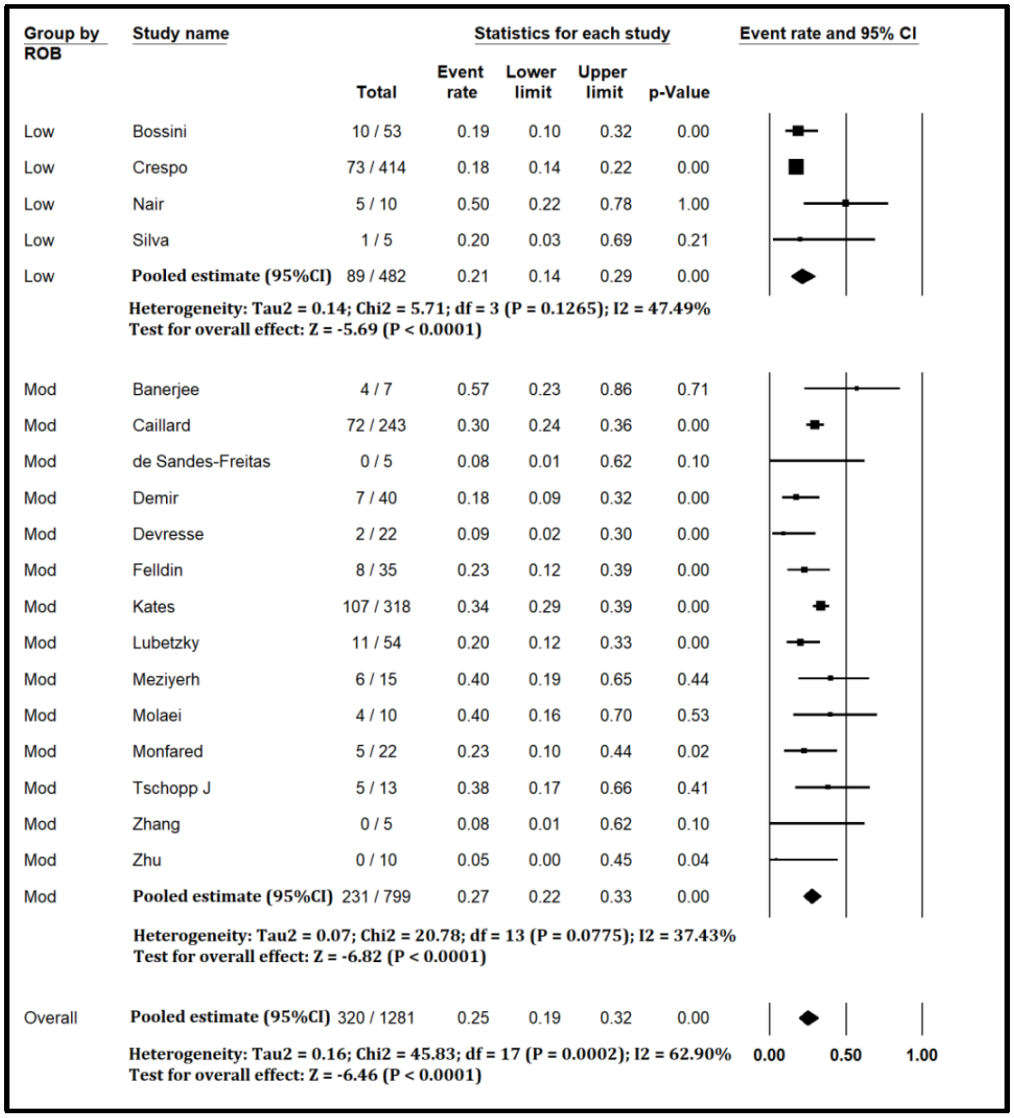

Figure S3. Forest Plot Showing Incidence of Need for Dialysis in Kidney Transplant Recipients With COVID-19 (excluding studies with high risk of bias)

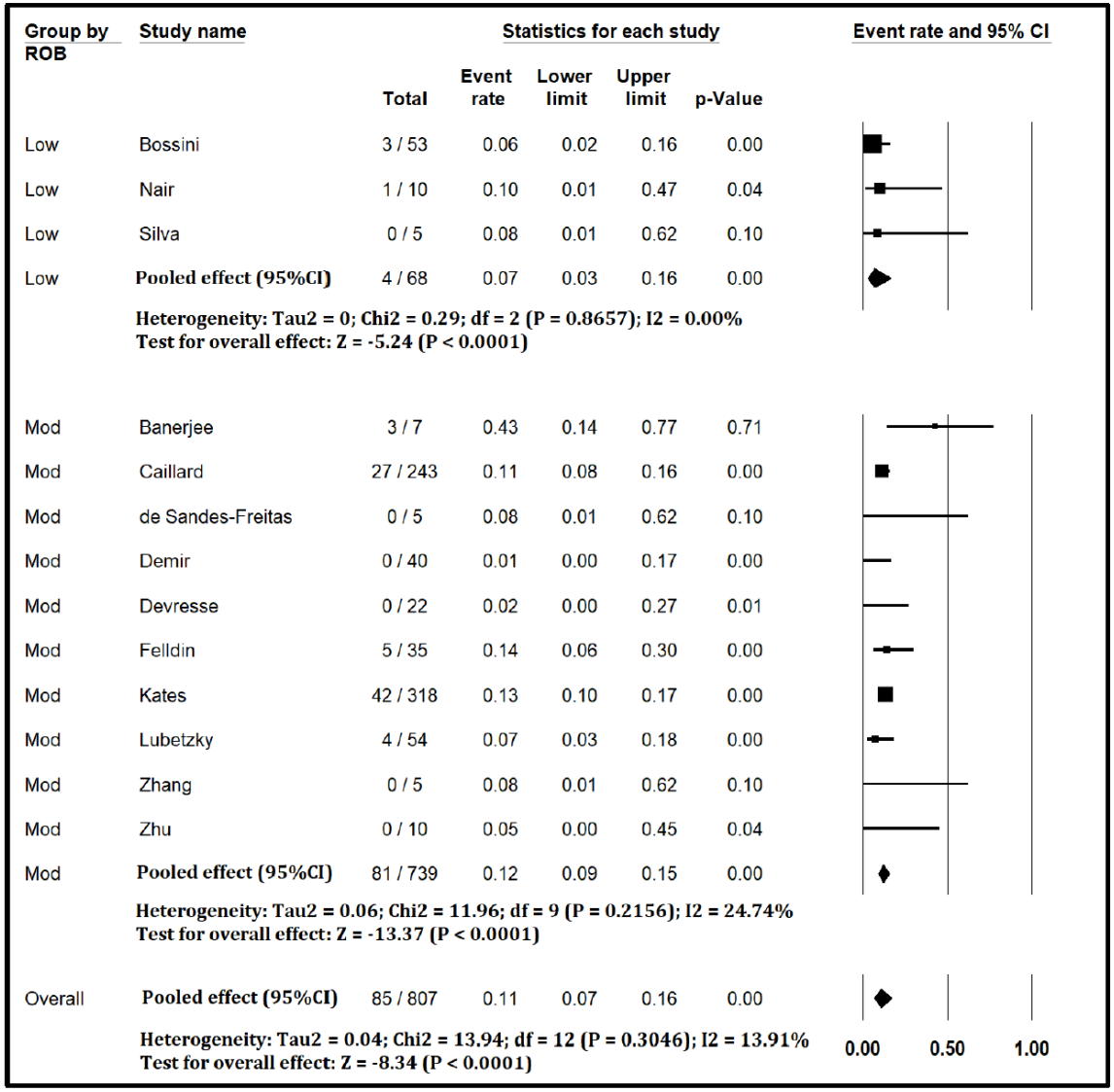

Table S2. Subgroup Analysis of Outcomes Based on the Geographical Distribution of Studies

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 S4. Funnel Plot for Mortality

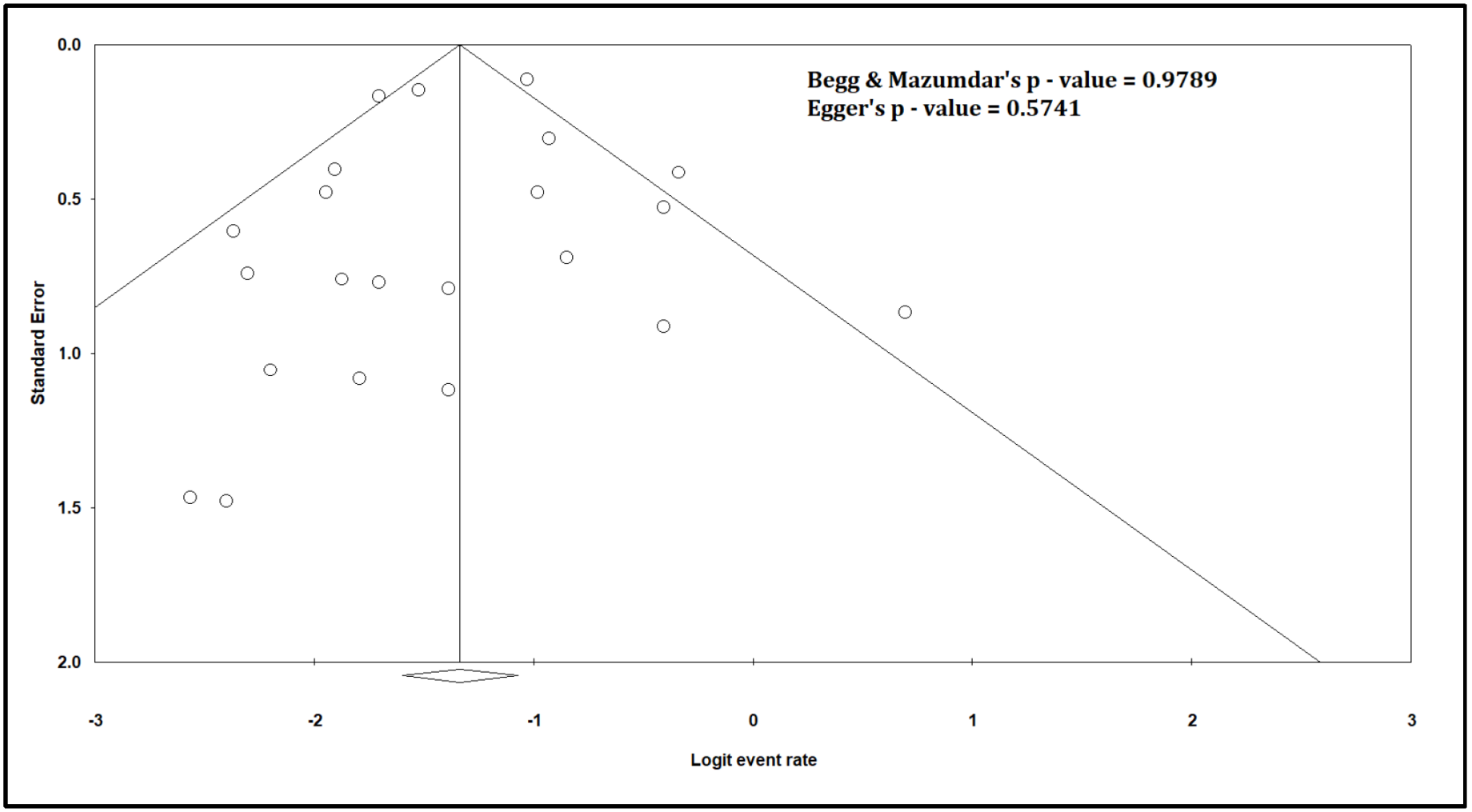

Figure S5. Funnel Plot for Critical illness

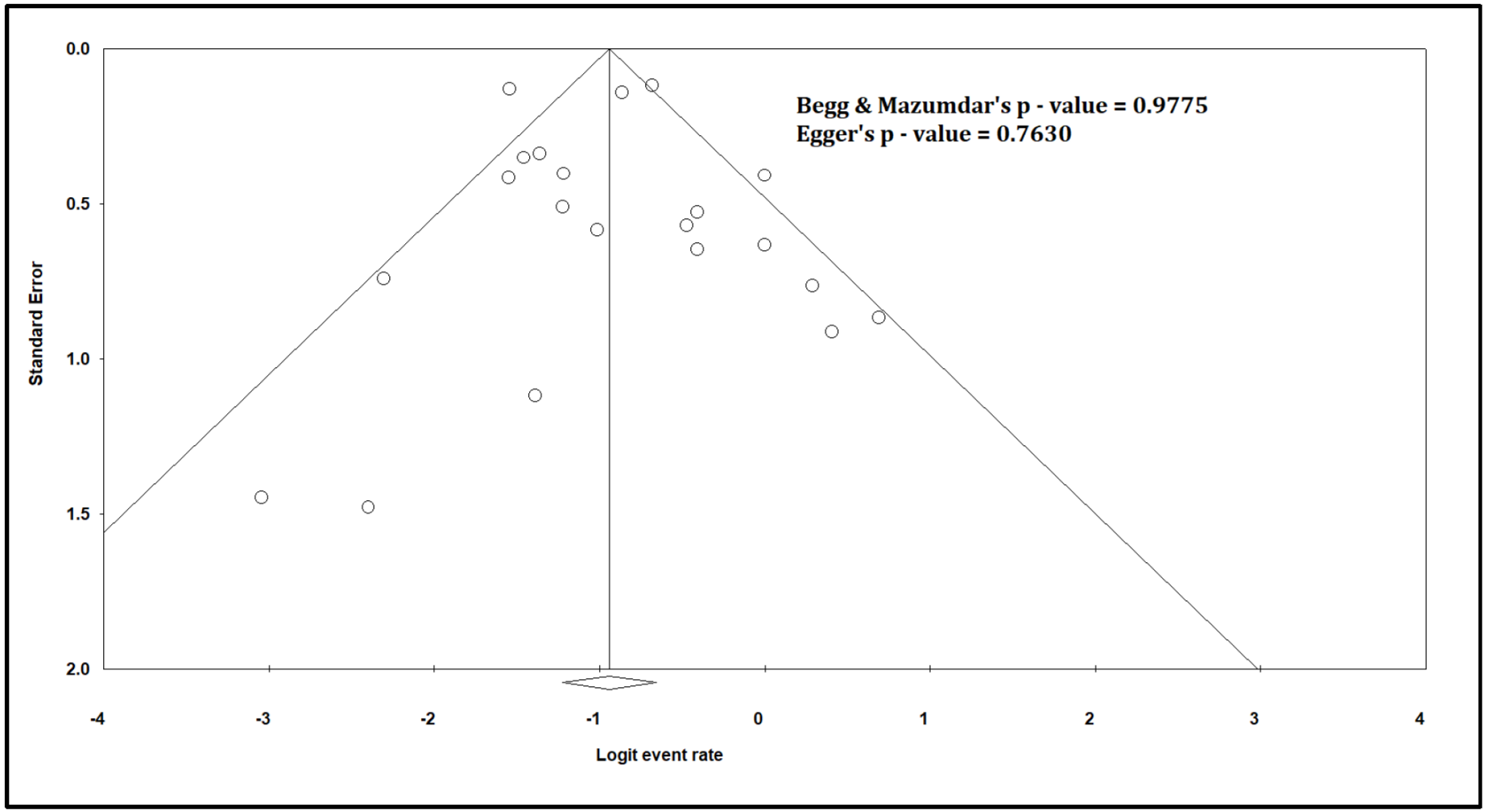

Figure S6. Funnel Plot for Need for Dialysis

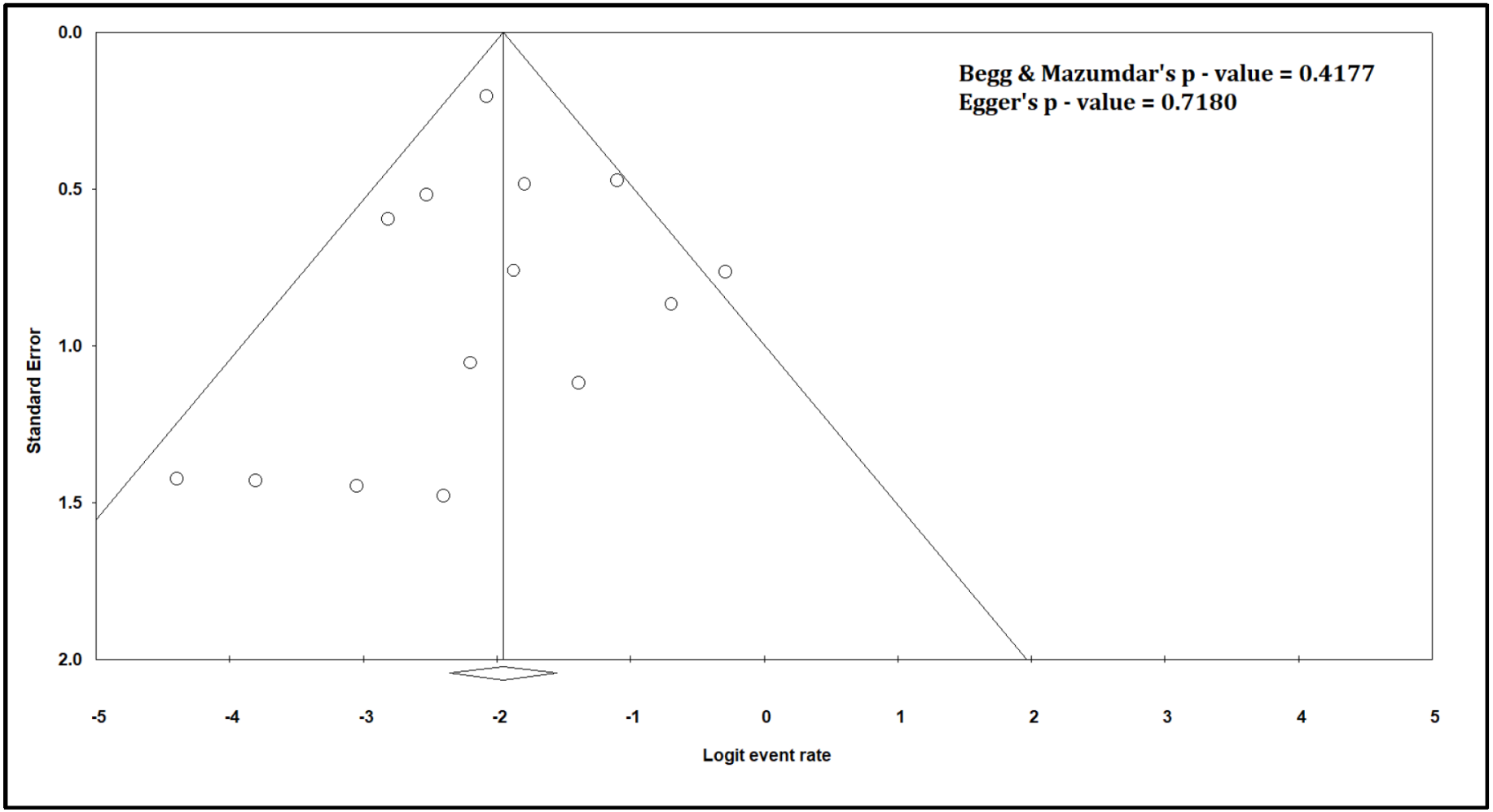

Table S3. Meta-regression of Factors Predicting Mortality

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

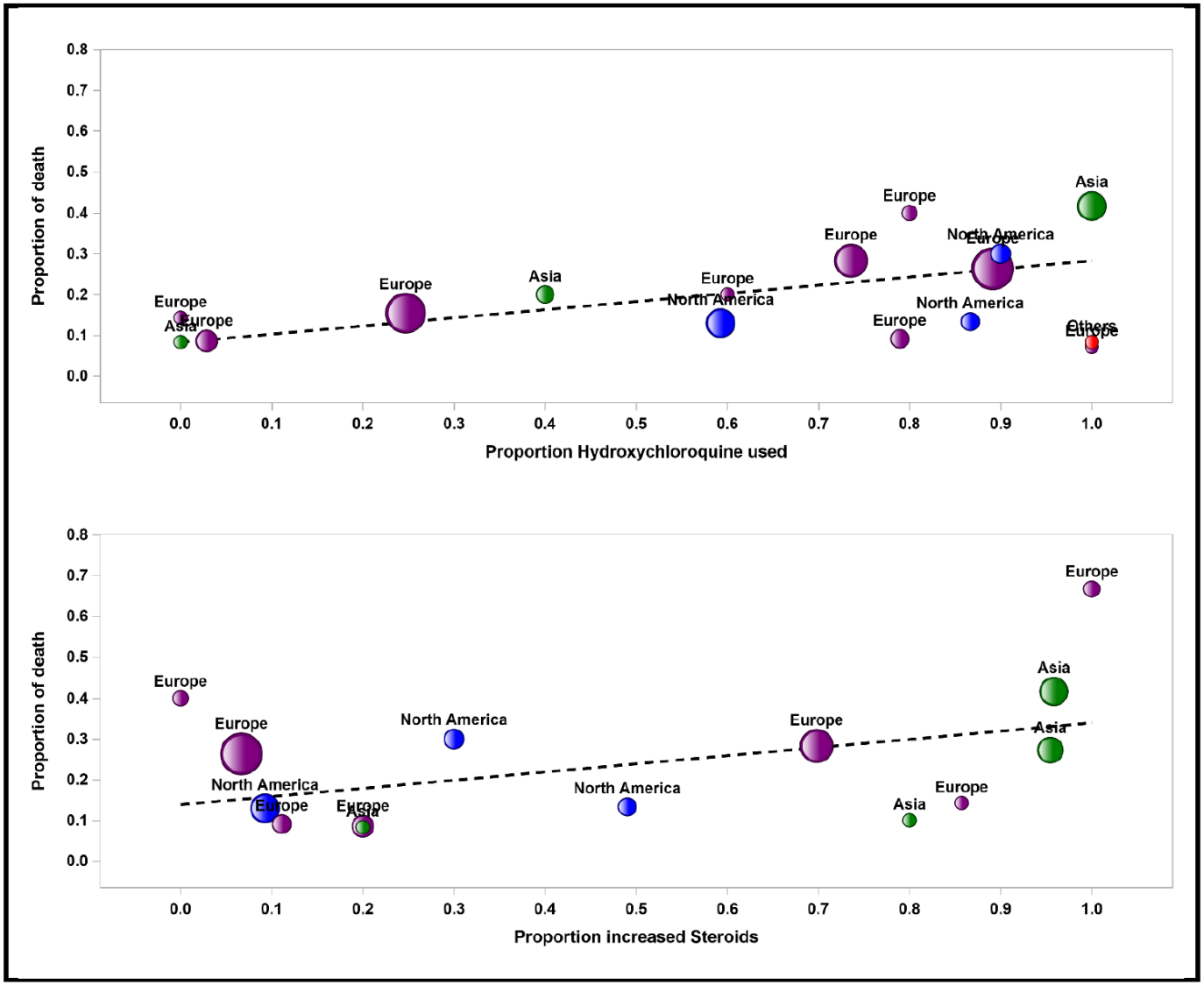

Table S4. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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