Systematic review and meta-analysis of COVID-19 and kidney transplant recipients, the South West London Kidney Transplant Network experience

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Systematic Review and Meta-analysis of COVID-19 and Kidney Transplant Recipients, the South West London Kidney Transplant Network experience

Cohort

1494 patients with kidney transplants

253 patients on transplant waitlist

1278 patients on hemodialysis (HD)

Incidence of symptomatic COVID- 19

23 (1.5%)

12 (4.7%)

123 (9.6%)

Case Fatality Ratio (CFR) in COVID-19

6 (26.1%)

1 (8.3%)

34 (27.6%)

META-ANALYSES
871 hospitalized patients from 16 studies: Europe, USA, South America, and Asia

CFR	24% [95% CI (19%, 28%)]
AKI	50% [95% CI (45%, 56%)]

CONCLUSION: Transplant patients were at lower risk of Covid-19 with comparable CFR to those on HD, on waitlist, and other hospitalised patients with Covid-19. Data supports continuation of kidney transplantation during Covid-19.

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Original article

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Abstract

Introduction

There is paucity of literature comparing outcomes of kidney transplant patients with Covid-19 to that of dialysis and waitlisted patients. This report describes our data, provides comparative analysis, together with meta-analysis of published studies and describes our protocols to restart the transplant programme.

Methods

Data were analysed on kidney transplant, dialysis and waitlisted patients tested positive for SARS-CoV-2 (naso-pharyngeal swab PCR) between March 1, 2020 and June 30, 2020 together with meta-analysis of 16 studies.

Results

23/1494 kidney transplant patients tested positive for SARS-CoV-2 compared to 123/1278 haemodialysis patients (1.5% vs 9.6%, p<0.001), 12/253 waitlisted patients (1.5% vs 4.7%, p=0.002). 19 required hospital admission, 6 died and 13 developed AKI. Overall case fatality ratio was 26.1% compared to patients on haemodialysis (27.6%, p=0.99) and waitlisted patients (8.3%, p=0.38). Within our entire cohort, 0.4% of transplant patients died compared to 0.4% of waitlisted patients and 2.7% of haemodialysis patients. Patients who died were older [Alive (median 71years) vs. Dead (median 59years), p=0.01].

In meta-analysis of 16 studies, including ours, pooled case fatality ratio was 24% [95%CI (19%, 28%)]; AKI proportion in 10 studies was 50% [95%CI (45%, 56%)], with some evidence against no heterogeneity between studies (p=0.02).

Conclusions

From our cohort of transplant patients, a significantly lower proportion of patients contracted COVID-19 compared to waitlisted and dialysis patients. The case fatality ratio was comparable to that of dialysis cohort and pooled case fatality ratio from meta-analysis of 16 studies. The pooled AKI ratio in the meta-analysis was similar to our experience.

Introduction

SARS-CoV-2, the virus that causes COVID-19 continues to cause significant mortality and morbidity across the world as the pandemic evolves. As of 27th July 2020, 300,111 people had tested positive for the virus in the UK and, of those tested positive, across all settings, 45,312 have died. The disease is primarily pulmonary but involvement of other organs, including the kidneys and heart during the course of illness is now well recognised. Kidney transplant recipients, due to their immunosuppressive burden and underlying co morbidities are thought to be at higher risk of acquiring the infection as well as developing severe disease requiring hospitalisation. We recently reported our initial experience of 7 renal transplant patients from 3 south London hospitals: 2 out of 7 patients were managed at home and one patient died[1]. All patients were managed with reduction of immunosuppression with no specific antiviral or anti-inflammatory therapies. In the same journal edition, Alberici et al published their early experience of 20 kidney transplant patients admitted with SARS CoV-2 pneumonia in which they described a 25% mortality in spite of additional treatment with various drugs that included Lopinavir/Ritonavir, Hydroxychloroquine, Dexamethasone and Tocilizumab[2]. Since these early reports, there have been several further reports of COVID-19 in kidney transplant patients describing overall case fatality ratios of 10-38% and 50-65% for patients requiring invasive ventilation. [3-19]

We and others have advocated for immunosuppression reduction as a primary therapeutic strategy for hospitalised kidney transplant patients with COVID-19 pneumonia with cessation of antiproliferative agents (Mycophenolate mofetil/Azathioprine) and continuation of CNIs either at same or reduced dose depending on severity of disease along with continuation of corticosteroids[1-3,6].

In this report, we describe 23 kidney transplant patients tested positive for SARS CoV2 from two tertiary care renal centres from South London Renal transplant Network, UK. This includes follow up data on 5 patients described in our previous report.

The aim of this analysis was to further characterise SARS-CoV-2 infected transplant patients, describe their management and outcome; compare the proportion of infections and case fatality ratios in transplant patients with waitlisted and total cohort of dialysis patients. In addition, we have performed meta-analyses on 15 published studies on COVID-19 in kidney transplant patients in addition to ours to derive case fatality/Acute Kidney injury (AKI) ratios in hospitalised kidney transplant patients with Covid-19.

Methods

Data were collected on all kidney transplant recipients tested positive for SARS-CoV-2 between March 1, 2020 and June 30, 2020 (First wave of Covid19 in the UK) and followed until October 15, 2020. The data collected included demographics, clinical and laboratory parameters and outcomes. In addition, we collected data on dialysis patients that included all the patients on dialysis and those on the transplant waitlist. Data were collected as part of routine clinical processes and downloaded for the study from Electronic Patient Records. The study was approved by NHS Research Ethics Committee 20/SW/0077 and Heath Research Authority IRAS 283130.

Continuous variables were summarized by their means, medians, standard deviation, IQR limits and ranges; categorical data were summarized as proportions.

Two-sample independent tests tailored to the nature of the variables were used to test the null hypothesis of no difference between transplant patients and those on the waiting list. 2x2 contingency table with and Fisher's exact tests were employed to assess the effect of dual Vs triple immunosuppression on the outcome of death.

Meta-analyses were performed to derive pooled proportions of deaths, AKI and AKI stage 3 among positive patients using the available data from 15 published studies and our data. The keywords used for PubMed search included: Covid 19, kidney transplant, mortality, AKI and outcomes for studies published between May 15 2020 and October 20, 2020. Amongst 157 returns we selected 15 studies that included at least 10 patients reporting mortality of hospitalised patients and/or acute kidney injury (AKI)[2,3,5,8-19]. Methods associated with analyses of proportions specific to binomial data, allow computation of exact binomial and score test-based confidence intervals. They also use appropriate methods for dealing with

proportions close to or at the margins where the normal approximation procedures often break down, by use of the binomial distribution to model the within-study variability or by allowing Freeman-Tukey double arcsine transformation to stabilize the variances. (We used *Metaprop* command implemented in Stata -StataCorp. 2019. ***Stata*** Statistical Software: Release ***16***. College Station, TX: StataCorp LLC).

Results

Clinical characteristics (Table 1)

23 transplant patients tested positive for SARS-CoV-2 during the study period out of a total cohort of 1494 kidney transplant recipients under follow up in two renal centres (1.5% of total transplant cohort). 4 were managed at home and 19 patients required hospitalisation. The mean age was 62±9.2 years, median age was 62 years (IQR 55-69 years) compared to median age of 51 years of overall transplant cohort. There were 17 males and 6 females. 6 (26%) patients were of black ethnicity, 9 white (39.1%), 4 south Asian (21.7%), one east Asian, 1 hispanic, 2- other. In comparison, ethnicity of our entire transplant cohort as reported previously as: black-7.7%, white- 73.8%, south Asian-15.4%[7]. 22 patients had hypertension, two patients had previous history of cancer, 8 had diabetes, one patient had HIV. The 19 hospitalised patients had a mean age of 64.2 ± 8.7 years, median age of 64 years, (IQR 59-72 years). Median follow up period was 183 days (range 169-199 days, IQR 173-192 days). The median transplant vintage (from transplant date to date of positive swab) was 1686 days (4.6 years) (range 47-12054 days, IQR 273-5326 days). 3 patients (2 hospitalised, one managed at home) were within 3 months since receiving transplant (53 days, 56 days and 47 days), 3 were between 3-12 months since their transplant and the rest (17) had received their transplant >12 months ago. None of the patients who died had their transplant within previous 6 months.

All patients had received Basiliximab induction. 15 patients including 4 managed at home were on dual maintenance immunosuppression and 8 patients were on triple immunosuppression. 2 of 19 hospitalised patients had received their transplant since February 2020.

Management

All hospitalised patients were managed with immunosuppression reduction and antiproliferative agents (Mycophenolate mofetil/Azathioprine) were stopped on admission in all the patients (n=19). Tacrolimus dose was reduced in mild to moderate cases (n=11) and stopped in severe cases where there was progressive clinical and radiological deterioration (n=8). Prednisolone dose was either unchanged (n=3) or increased (n=13) in all cases. Some of the patients were recruited in to Recovery trial (Randomised Evaluation of COVID-19 therapy, www.recoverytrial.net). As a part of this trial two patients received hydroxychloroquine and one received Dexamethasone. In addition, two patients received Tocilizumab. Out of 4 patients managed at home, one patient had his mycophenolate mofetil dose reduced by 50% with increase back to baseline dose after 2 weeks, remaining three patients were managed without any change to immunosuppression (Table 2).

All patients who had Tacrolimus dose reduced had the dose progressively increased such that by 2 weeks post discharge the levels were in therapeutic range (5-8ng/mL). Mycophenolate mofetil was re- introduced around 2-3 weeks post discharge provided patients were well with no fever or other symptoms of COVID-19 for at least 3 days and had a normal CRP.

Patient demographics, laboratory parameters and clinical outcomes are summarised in table 1. Age, admission to intensive care unit (ICU) and type of respiratory support required were the only variables significantly different in patients who died compared to those discharged home. Patients who died were significantly older (59.2±8.2 vs. 70.5±6.8 years; p=0.01 and required more ventilatory support (p=0.04). There were no significant differences between the two groups (living Vs died) with regards to co-morbidities, peak ferritin levels, C-reactive protein, baseline lymphocyte count or lowest lymphocyte count during admission (Table 1).

Outcome of infected patients (Tables 1, 2)

Duration of hospital stay, respiratory support, Acute kidney injury (AKI), Renal Replacement Therapy (RRT) and outcome of hospitalised patients (n=19) are described in table 2. 6/19 (31.57%) hospitalised patients died (Table 2). Out of the total cohort of 1494 transplant patients, 6 patients died and this represents 0.4% of total cohort.

12 out of 14 (85.7%) patients on dual immunosuppression survived and 2 (14.3%) died; Out of 9 patients on triple immunosuppression, 5 (55.6%) survived and 4 (44.4%) died. Although non-significant (P=0.16), RR of death on triple immunosuppression was 1.54 (0.91-3.28), OR 4.8 (0.71-29.3) (Table 3). There was no difference in proportion of patients on maintenance steroids between the two groups (living Vs died) (Table 1).

Among 6 patients who died, one patient was white, 2 black, 2 South Asian, 1 other. The ethnicity was not significantly different between the two groups (Survived and Died) but this may be due to small sample size. All patients who died had hypertension and 4 had diabetes.

Respiratory support (see Tables 1 and 2): Out of 19 hospitalised patients, 3 were managed on high flow nasal cannula (HFNC) or non-invasive ventilation (NIV), 6 (31%) were intubated and ventilated; remaining 10 were managed with oxygen delivered through nasal cannula or venturi mask. Of the intubated and ventilated patients, 3 out of 6 patients (50%) died. Of the 3 other patients who were discharged home, two had a functioning graft and one remained on dialysis. The patient who was discharged on dialysis had poor graft function before he had COVID-19 and was on haemodialysis pre admission. He was ventilated for a prolonged period of 57 days.

Acute Kidney Injury (AKI) (see Tables 1 and 2)**:** 13/23 patients (57%) developed AKI. 11 patients had stage 2-3 AKI [Stage 2 – 5 patients, Stage 3 = 6 patients] and 2 patients had stage 1 AKI. 4 patients needed RRT (HD or CVVHDF). AKI resolved in all but 3 patients. These 3 patients in whom transplant kidney function failed to recover, had poor baseline kidney function with CKD-EPI eGFR of <20 mL/min/1.73m^2. None of the patients underwent percutaneous kidney biopsy. Two patients continued on haemodialysis and one was

discharged with CKD stage 5 and commenced HD 5 months post discharge. Out of 2 patients who have remained on haemodialysis post discharge, one (patient 1 in table 2) underwent transplant nephrectomy 3- month post discharge due to severe rejection (clinical diagnosis). His nose and throat swabs for SARS-CoV2 PCR both before and during this admission were negative. He made good recovery from surgery and is currently on outpatient haemodialysis. The histology of kidney post-nephrectomy revealed severe vascular rejection with widespread cortical infarctions and a thrombus in main transplant artery.

At follow-up till 15th October 2020 (Median follow-up of 183 days), all discharged patients and those managed at home (n=17) have remained well with no readmissions apart from the patient described above. 3 patients have lost their graft function (all with baseline eGFR <20/ml/min/1.73m^2).

8/9 hospitalised patients discharged home (from one centre) with baseline positive naso-pharyngeal swab for SARSCoV-2 PCR were re swabbed 3-4 weeks post discharge. All of them had cleared the virus as shown by negative nose and throat swab results.

Comparisons with dialysis cohort and waitlisted patients

23 from a cohort of 1494 kidney transplant patients were tested positive for SARS-CoV-2 compared to 123/1278 haemodialysis patients (1.5% vs 9.6%, p<0.001), 12/253 waitlisted patients (1.5% vs 4.7%, p=0.002) and 8/170 peritoneal dialysis patients (1.5% vs 4.7%, p=0.01). (Table 4). Case fatality ratio was 26.1% for transplant patients, 8.3% for waitlisted patients, 27.6% for haemodialysis patients and 75.0% for peritoneal dialysis patients. There was no statistically significant difference in case fatality ratio of transplant patients compared to waitlisted patients, haemodialysis patients and peritoneal dialysis patients. (Table 4).

Meta-analyses

We performed meta-analyses of 15 published studies and our data to derive a pooled estimate of case fatality ratio (of hospitalised patients) and AKI in kidney transplant patients who tested positive for SARS-CoV-2, including a recent publication of TANGO international consortium. [2, 3, 5, 8-19] The total number of hospitalised patients included in these studies

were 871. The pooled case fatality ratio was 24% (95% CI 19%, 28%). The variability in the effect size attributable to between study heterogeneity was moderate **(**I^2=51.5%) consistent with some evidence against the null hypothesis stating no heterogeneity between studies (p = 0.01) (Fig 1A). The Montefiore 2 study[18], the third most influential in this analysis exhibited a case fatality ratio of 38% [95%CI (29%, 48%)], well above the pooled estimate of 24% [95%CI (19%, 28%)]. Excluding this study, the I^2drops to 34.3% with a p-value=0.09 indicating consistency with the magnitude of I^2 and with the null hypothesis of not much heterogeneity between studies. The pooled case fatality ratio in this analysis was 22% [95%CI (18%, 27%)] very close to our first analysis. Given the size and hence the precision of estimate in Montefiore 2 study (n=111) we opted to include all studies and provide evidence that pooled case fatality ratio of hospitalised kidney transplant patients with Covid- 19 is 24% [95% CI (19%, 28%)].

The analyses of AKI included 10 studies which reported AKI. The pooled proportion of AKI was 50% [95%CI (45%, 56%)]. There was no evidence to suggest heterogeneity between the studies, p = 0.27 and therefore, the data estimates that 50% [95%CI (45%, 56%)] of kidney transplant patients with Covid19 develop AKI (Fig 2A). We also separately analysed pooled proportion of severe AKI (Stage3 AKI or those requiring RRT). This analysis showed pooled proportion of stage 3 AKI of 18% [95%CI (12%, 25%)] (Fig 2B). However, there was evidence for presence of significant heterogeneity between studies P=<0.001. Re analysis after removal of Bologna study showed that high stage3 AKI percentage of 45% yielded results with pooled stage3/RRT requiring AKI estimate of 16% [95%CI (10%, 22%)] although the evidence against no heterogeneity between studies remained significant (p=0.02) with I^2= 56.96% (Fig 2C).

Discussion

In this report we have described 23 kidney transplant recipients who tested positive for SARS- CoV-2 between March 1, 2020 and June 30, 2020 (this includes the entire period of the first surge of COVID-19 in the London) with a median follow up of 183 days. 19 were hospitalised, 4 managed at home, 6 patients died (overall case fatality ratio of 26%, for hospitalised patients 31.6%). Out of 6 patients requiring intubation and ventilation, 3 died (50% mortality in ventilated patients). Age, requirement of ICU admission and respiratory support (NIV or invasive ventilation) were significantly different in patients who died compared to those who survived. In the meta-analysis of 16 available reports including ours the pooled case fatality ratio for hospitalised transplant patients with Covid-19 was 24% (95% CI 19%, 28%), pooled proportion of AKI (all stages) was 50% [95% CI (45%, 56%)] and that of AKI stage 3/requiring RRT was 16% [95% CI (10%,22%)].

A small proportion of our overall transplant patient cohort got COVID-19 (1.5%) compared to 9.6% haemodialysis patients, 4.7% peritoneal dialysis patients and 4.7% of waitlisted patients with an in-hospital case fatality ratio of 31.57%. A German multicentre study 10, 021 patients with COVID-19 admitted to 920 hospitals showed overall mortality of 22% and 53% mortality in those requiring mechanical ventilation[20]. An UK study of 20,133 patients admitted to 208 hospitals demonstrated an overall mortality of 26%[21] compared to pooled mortality of 24% in our meta-analyses. Our overall case fatality ratio of 26% is very similar to 27% mortality shown in UK data in renal transplant recipients (NHSBT weekly Covid19 reports). Transplant patients had comparable case-fatality ratios to that of haemodialysis patients. The case fatality ratio of waitlisted patients was lower compared to transplant patients but this difference did not achieve statistical significance. Waitlisted patients tend to be younger with fewer co morbidities compared to some of the older transplant patients and this may largely explain this difference. Older age was associated with poor prognosis with median age of 71 years for transplant patients who died compared to 59 years for those who survived. This is consistent with Spanish series by Perez-Saez et al who reported a HR of death of 3.1 for patients older than 60 years[22]. We observed 50% mortality of intubated patients and this compares favourably with 53% mortality of general medical patients with COVID-19 requiring invasive mechanical ventilation in the German study[20]. Similarly, Rinaldi et al found no difference in survival in transplant patients compared to

general population[17]. All the patients from our cohort who were discharged home have survived to date.

It is likely that baseline immunosuppressive burden plays a role in prognosis of COVID-19 as it does with other infections. Our units have a significant number of patients (approx. 60-70%) on long term dual immunosuppression[7]. There was a trend towards higher risk of death in patients on triple immunosuppression but, this did not achieve statistical significance probably due to small sample size. It needs to be seen in larger datasets if patients on triple immunosuppression are at higher risk of severe disease from SARS-CoV-2 compared to those on 2 drugs and if mycophenolate mofetil confers higher risk. We managed all the patients in line with NHS Blood and Transplant British Transplantation Society guidelines with immunosuppression reduction as main strategy along with supportive medical care (https://bts.org.uk/information-resources/covid-19-information/) and recruitment into national clinical trials. Some of our patients were enrolled into the RECOVERY trial and received Tocilizumab outside the trial on clinical grounds but the numbers are too small to draw any conclusions on effectiveness of these drugs. For current recommendations on management of transplant patients with COVID-19 which includes guidelines on use of dexamaethasone and Remdesivir in transplant patients with COVID-19 pneumonia the reader is referred to recent British Transplant Society (BTS)/UK renal association guidelines. (https://bts.org.uk/wp-content/uploads/2020/07/Clinical-management-of-transplants-and-immunosuppression-updated-9th-July.pdf). We would like to highlight here that some of the drugs used worldwide for COVID-19 such as Azithromycin and Lopinavir/Ritonavir show significant interaction with Tacrolimus causing toxicity and therefore, should be avoided where possible and if used, tacrolimus levels should be monitored closely.

We observed high percentage of Acute Kidney Injury (AKI) in these patients (68%) and 6 (31.5%) patients with stage 3 AKI. In comparison, the pooled proportion of AKI was 50% and that of stage 3AKI/AKI reporting RRT was 16%-18%. There was significant heterogeneity in studies reporting AKI as some reported all stages and some only reporting patients requiring RRT. We analysed these separately and included stage3/RRT requirement in one group as this indicates severe AKI. However, it must be noted that studies that reported patients requiring RRT only would have excluded patients with stage 3 AKI not needing RRT and

therefore, true number of stage3 AKI in these studies is likely to be higher than reported. Reassuringly, the AKI recovered in majority of the cases. Two patients who remained dialysis dependent had poor baseline kidney function (eGFR<20ml/min/1.73m^2) and their kidney function deteriorated further during their hospital stay. It is possible that these patients developed rejection upon immunosuppression reduction but we did not have transplant kidney biopsy results to prove this. On clinical grounds, we felt that treating COVID-19 pneumonia was the priority and therefore, felt that risk/benefit ratio did not favour doing a biopsy. During this period, we found an AKI risk of 26% in hospitalised patients with COVID-19 (204 out of 792 hospitalised patients in three hospitals from South London and Surrey developed AKI) (personal communication). A recent publication on all hospitalised patients found an AKI in 36.6% of patients and 31.1% had stage 3 AKI[23], very similar to stage 3 AKI that we observed in our transplant cohort.

Following discharge from hospital, patients were followed up in a dedicated COVID-19 outpatient setting for 4 weeks. In one of the two hospitals, we performed repeat SARS-CoV-2 nasal and throat swabs 3-4 weeks following discharge. All of the 8 patients tested had cleared the virus with negative follow up swab PCR results. The negative swab enabled us to de- isolate these patients and return them to their normal outpatient pathway provided they have been free from symptoms for at least 3 days. The recently published New York study reported that 8 out of 13 hospitalised patients re tested were negative (median re-test 29 days)[9]. Difference in management of immunosuppression may account for this difference; we stopped mycophenolate mofetil in all of our hospitalised patients whereas in this study 24 out of 39 patients (61%) discontinued mycophenolate mofetil. It needs to be seen if continuation of mycophenolate mofetil in transplant patients admitted with COVID-19 is associated with more prolonged viral shedding.

During the start of pandemic in the UK, between 1st February 2020 and 23rd March 2020 we performed 19 transplants of which 3 patients were tested positive for SARS-CoV-2. One patient had mild illness managed at home with regular outpatient reviews. Two out of these 3 patients developed COVID-19 pneumonia requiring hospitalisation. One of the hospitalised patients had delayed graft function (DGF) and rejection requiring methylprednisolone infusions, he spent 60 days in intensive care unit with 57 days of invasive ventilation. He was successfully discharged home stable on regular haemodialysis

as his graft failed. A limitation of our study is that we did not systematically screen all transplant recipients or dialysis patients at regular intervals. The data presented includes only symptomatic patients who reported to our centres and tested positive for SARS-CoV-2. Therefore, it is likely to under estimate true prevalence of SARS-CoV-2 infection in our cohort. However, it does capture all symptomatic infections requiring hospitalisation. It is worth noting that studies analysed showed case fatality ratio of 22%-38%, in spite of differences in management strategies, in particular with regards to the use of specific pharmacotherapy [2, 3, 5,6-19].

Our transplant programme was suspended on 23rd March 2020 due to increasing number of COVID-19 patients in South West London and unprecedented demand on critical care services. Based on our data analysis, clinical experience of managing transplant patients with COVID-19 and national guidelines, we reopened our transplant programme in the later part of June 2020. All the potential recipients received letters specific counselling and consenting along the lines of advice given by NHS blood and transplant (NHSBT) and Organ Donation and Transplantation (ODT) UK (https://www.odt.nhs.uk/covid-19-advice-for-clinicians/re-opening-of-transplant-programmes/). These guidelines were used to develop pathways that include access to 'green' theatres, dedicated outpatient clinic areas for follow up and plans for re- admission in to non COVID wards if needed.

We have now (Until 15th October 2020) performed 32 kidney transplants since our reopening. We have limited donor case selection to lower risk donors (DBD (Donation after Brainstem Death) donors age <60 years, DCD (Donation after Cardiac Death) donors age <50 years, no significant AKI in the donor (minimising the risk of DGF and prolonged hospital stay), no extended criteria donors). National policy is to only offer organs from donors who did not die of COVID-19 and after obtaining negative SARS-CoV2-PCR test (naso-pharyngeal swab and endotracheal aspirate). We have reactivated lower risk patients who are aged <65 years, BMI <30 kg/m^2 with low to medium cardiovascular risk, not expected to require critical care admission during their inpatient stay. For living donor transplants, the donor and the recipient 'shield' for 14 days pre transplant with SARS-CoV-2 testing (nasal and throat swabs for PCR) at Day -14 and Day -2. We intend to expand donor and recipient acceptance criteria in a phased manner.

In conclusion, from our large cohort of transplant patients, small proportion got COVID-19 with proportion of infection significantly lower than that of waitlisted patients and those on dialysis. The overall case fatality ratio (26%) was comparable to that of dialysis cohort and patients on wait list. 31% required intubation and ventilation of which 50% died. Within our entire cohort, significantly lower proportion of transplant patients died of COVID-19 compared to haemodialysis and peritoneal dialysis patients. The case fatality ratio of hospitalised transplant patients with Covid-19 was 31.57%. The older age and severity of illness were associated with mortality. We observed high proportion of AKI (68%) but the majority recovered. Meta-analysis of 16 studies including ours revealed pooled case fatality ratio of 24% for hospitalised patients, pooled AKI proportion of 50% and pooled proportion of severe AKI of 16-18%. We have successfully re-started our transplant programme with defined donor and recipient criteria to minimise the risk and optimise the outcomes.

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Disclosures

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Supplementary material

The PRISMA checklist document is available at KI Reports website.

References

1. Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. Kidney Int 2020;97:1076-82.
2. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int 2020;97:1083-8.
3. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation. N Engl J Med 2020;382:2475-7.
4. Vistoli F, Furian L, Maggiore U, et al. COVID-19 and kidney transplantation: an Italian Survey and Consensus. J Nephrol 2020;33:667-80.
5. Nair V, Jandovitz N, Hirsch JS, et al. COVID-19 in kidney transplant recipients. Am J Transplant 2020;20:1819-25.
6. Kronbichler A, Gauckler P, Windpessl M, et al. COVID-19: implications for immunosuppression in kidney disease and transplantation. Nat Rev Nephrol 2020;16:365-7.
7. Phanish MK, Hull RP, Andrews PA, et al. Immunological risk stratification and tailored minimisation of immunosuppression in renal transplant recipients. BMC Nephrol 2020;21:92.
8. Montagud-Marrahi E, Cofan F, Torregrosa JV, et al. Preliminary data on outcomes of SARS-CoV-2 infection in a Spanish single center cohort of kidney recipients. Am J Transplant 2020.
9. Lubetzky M, Aull MJ, Craig-Schapiro R, et al. Kidney allograft recipients, immunosuppression, and coronavirus disease-2019: a report of consecutive cases from a New York City transplant center. Nephrol Dial Transplant 2020;35:1250-61.
10. Columbia University Kidney Transplant P. Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York. J Am Soc Nephrol 2020;31:1150-6.
11. Zhu L, Gong N, Liu B, et al. Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China. Eur Urol 2020;77:748-54.
12. Cravedi P, Suraj SM, Azzi Y, et al. COVID-19 and Kidney Transplantation: Results from the TANGO International Transplant Consortium. Am J Transplant 2020.
13. Elias M, Pievani D, Randoux C, et al. COVID-19 Infection in Kidney Transplant Recipients: Disease Incidence and Clinical Outcomes. J Am Soc Nephrol 2020;31:2413-23.
14. Craig-Schapiro R, Salinas T, Lubetzky M, et al. COVID-19 Outcomes in Patients Waitlisted for Kidney Transplantation and Kidney Transplant Recipients. Am J Transplant 2020.
15. Pierrotti LC, Reusing Junior JO, Freire MP, et al. COVID-19 among kidney-transplant recipients requiring hospitalization: preliminary data and outcomes from a single-center in Brazil. Transpl Int 2020.
16. Katz-Greenberg G, Yadav A, Gupta M, et al. Outcomes of COVID-19-positive kidney transplant recipients: A single-center experience. Clin Nephrol 2020.
17. Rinaldi M, Bartoletti M, Bussini L, et al. COVID-19 in solid organ transplant recipients: no difference in survival compared to general population. Transpl Infect Dis 2020:e13421.
18. Azzi Y, Parides M, Alani O, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. Kidney Int 2020.
19. Caillard S, Anglicheau D, Matignon M, et al. An initial report from the French SOT COVID Registry suggests high mortality due to Covid-19 in recipients of kidney transplants. Kidney Int 2020.

20. Karagiannidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med 2020.
21. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
22. Perez-Saez MJ, Blasco M, Redondo-Pachon D, et al. Use of tocilizumab in kidney transplant recipients with COVID-19. Am J Transplant 2020.
23. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209-18.

Tables and Figure Legends

Table 1.

Title: Patient demographics, Co-morbidities, Immunosuppressive drugs, hospital management (critical care admission, type of respiratory support and renal replacement therapy).

Legend: Data for hospitalised patients is for 19 patients. Rest of the data is for 23 patients. Age, requirement of respiratory support and intensive care unit admission were significantly different between the 2 groups (Alive Vs Died). SD=standard deviation, Q1-Q3=Quartile 1 to Quartile 3, DCD=Deceased Cardiac Donor, DBD=Deceased Brain Donor, MMF=Mycophenolate Mofetil, CRP=C-Reactive Protein, ITU=Intensive Therapy Unit, RRT= Renal Replacement Therapy, ACEi=Angiotensin Converting Enzyme inhibitor, ARB=Angiotensin receptor blocker.

Table 2.

Title: Duration of hospital stay, respiratory support, Acute Kidney Injury (AKI), Renal replacement Therapy (RRT, requirement and type) and outcome of hospitalised patients (n=19) and non- hospitalised patients (n=4)

Legend: Y=yes, N=No, St=Stage (of AKI), HD= Haemodialysis, CVVHDF=Continuous veno-venous haemodiafiltration, HFNC=High flow nasal cannula, NIV=Non-invasive ventilation, Intensive therapy unit,

Table 3.

Title: The effect of baseline Dual Vs Triple immunosuppression on mortality.

Legend: RR (relative risk) of death in patients on triple immunosuppression was 1.54 but there was no statistical difference between the groups (Fisher's exact test). OR=Odds ratio

Table 4.

Title: Proportions of infections, deaths in transplant, waitlisted, haemodialysis and peritoneal dialysis patients

Legend: (A) Proportions of infections and case fatality ratio of transplant patients (1) compared to patients on transplant waitlist (2), haemodialysis (3) and peritoneal dialysis patients (4).

(B) There was a significant difference in infection risk in transplant patients compared to patients on waitlist and haemodialysis (1 Vs 2, P=0.002, 1 Vs 3, p=<0.001). There was no significant difference in case fatality ratio between transplant patients and other groups.

Comparisons were performed between aggregated proportions. Only p-values lower than 0.05/12=0.0042 are considered significant (shown in green) due to Bonferroni correction for multiple comparisons.

Figures 1A and 1B

Meta-analyses of Covid-19 in transplant patients- Case fatality ratio

The pooled case fatality ratio was 24% (95% CI 19%-28%). There was moderate heterogeneity between the studies **(**I^2=51.5% (variation in effect size attributable to heterogeneity), Heterogeneity chi^2 = 30.90 (d.f. = 15), p = 0.01). The New York Montefiore2 study, the third most influential in this analysis exhibited a case fatality ratio of 38% [95%CI (29%, 48%)], well above the pooled estimate of 24% [95%CI (19%-28%)]. (Fig 1A)

We then analysed 14 studies excluding this study and with this analysis the I^2 drops to 34.3% with a p-value=0.09 consistent with the null hypothesis of not much heterogeneity between studies. The pooled case fatality ratio in this analysis was 22% [95%CI (18%, 27%)]. (Fig 1B)

Figure 2A

Meta-analyses of COVID-19 in transplant patients- AKI (All stages)

The pooled proportion of AKI was 50% [95%CI (45%, 56%)]. There was no significant heterogeneity between the studies, chi^2 = 11.02 (d.f. = 9), p = 0.27; I^2 (variation in effect size (ES) attributable to heterogeneity) = 18.37%. Therefore, the pooled proportion of AKI is 50% [95% CI (45%, 56%)].

Figure 2B and 2C

Meta-analysis of COVID-19 in transplant patients- AKI (Stage3/RRT requirement)

The pooled proportion of severe AKI (Stage3/requiring RRT) was 18% [95%CI (12%, 25%)] (Fig 2B). However, there was a significant heterogeneity I^2= 66.27%, P=<0.001. Re analysis after removal of Bologna study that showed high stage3 AKI percentage of 45% yielded results with pooled stage3/RRT requiring AKI estimate of 16% [95%CI (10%, 22%)] but the heterogeneity, although improved, remained significant with I^2= 56.96%, P=<0.02 (Fig 2C). Therefore, it appears from these analyses that pooled proportion of severe AKI is 16-18%.

	TYPE/CATEGORY	23	17(73.9%)	6(26.1%)	independent test (P value)
Age(Years)	Mean (SD) Median (Q1-Q3) Range	62 (9.2) 62(55-69) 45-78	59.2 (8.2) 59(54-64) 45-73	70.5 (6.8) 71(68-76) 59-78	**0.01**
Gender	Female Male	6 (26%) 17 (74%)	5(29%) 12(71%)	1(17%) 5(83%)	0.99
Ethnicity	Black East Asian Other South Asian White	6(26.1%) 1(4.4%) 2(8.7%) 5(21.7%) 9(39.1%)	4(23.5%) 1(5.9%) 1(5.9%) 3(17.7%) 8(47.1%)	2(33.3%) 0(0%) 1(16.7%) 2(33.3%) 1(16.7%)	0.615
Immuno-Suppressive Drugs	2 3	14(61%) 9(39%)	12(71%) 5(29%)	2(33.3%) 4(66.6%)	0.162
Transplant type	DBD DCD Living Donor	17 (73.9%) 4 (17.4%) 2 (8.7%)	12(70.6%) 3(17.7%) 2(11.8%)	5(83.3%) 1(16.7%) 0(0%)	0.99
Tacrolimus	Yes	21(91.3%)	15(88.2%)	6(100%)	0.99
Cyclosporine	Yes	1(4.4%)	1(5.9%)	0(0%)	0.99
Azathioprine	Yes	2(8.7%)	2(11.8%)	0(0%)	0.99
MMF	Yes	13(56.6%)	9(52.9%)	4(66.7%)	0.66
Prednisolone	Yes	16(69.6%)	11(64.7%)	5(83.3%)	0.621
Cancer	Yes Missing	2(8.7%) 3(13%)	1(5.9%) 3(17.7%)	1(16.7%) 0(0%)	0.521
Diabetes	Yes	8 (34.8%)	4(23.5%)	4(66.7%)	0.131
Chronic Lung Disease	Yes Missing	0(0%) 3(13%)	0(0%) 3(17.7%)	0(0%) 0(0%)	NA
Hypertension	Yes	21 (91.3%)	15(88.2%)	6(100%)	0.99
Platelets	Mean (SD) Median (Q1-Q3) Range Missing	213(50.1) 206(178-238.5) 144-337 3(13%)	221.1(53) 213.5(186-251) 157-337 3(17.6%)	193.8(39.9) 193(157-230) 144-246 0(0%)	0.30
White Cell Count	Mean (SD) Median (Q1-Q3) Range Missing	6.6(1.9) 6.6(5.3-7.4) 3.2-10.3 3(13%)	6.4(1.9) 6.5(5.1-7.3) 3.2-10.3 3(17.6%)	7.1(2.0) 6.7(6.4-9.1) 3.9-9.5 0(0%)	0.563

Baseline Lymphocyte count	Mean (SD) Median (Q1-Q3) Range Missing	1.5(0.9) 1.4(1.1-1.9) 0.3-4.2 3(13%)	1.7(0.9) 1.6(1.2-2) 0.3-4.2 3(17.6%)	1.2(0.7) 1.1(0.5-1.7) 0.4-2.3 0(0%)	0.303
Haemoglobin on admission	Mean (SD) Median (Q1-Q3) Range Missing	113.1(20.6) 116.5(99-130) 67-149 3(13%)	115.6(22.7) 117.5(101-131) 67-149 3(17.6%)	107.2(14.5) 105(97-109) 93-134 0(0%)	0.283
Lymphocyte nadir during admission	Mean (SD) Median (Q1-Q3) Range Missing	0.7(0.9) 0.4(0.2-0.8) 0.2-4.1 3(13%)	0.8(1) 0.4(0.2-0.8) 0.2-4.1 3(17.6%)	0.5(0.4) 0.25(0.2-0.7) 0.2-1.1 0(0%)	0.334
Highest ferritin during admission	Mean (SD) Median (Q1-Q3) Range Missing	1691.7(1901.5) 781(544-2469) 462-6959 8(35%)	1598.1(2004.4) 781(549-1320) 538-6959 6(35%)	1949(1833.2) 1506(503-3395) 462-4321 2(33%)	0.896
Highest CRP during admission	Mean (SD) Median (Q1-Q3) Range Missing	186.7(106.1) 178.5(122-230) 31-497 5(22%)	161.1(83.4) 160.5(114.5-212) 31-320 5(29%)	237.8(135.3) 217(147-233) 116-497 0(0%)	0.223
RRT during admission	No Yes	15 (78.9%) 4 (21.1%)	12(85.7%) 2(14.3%)	3(60%) 2(40%)	0.272
ITU admission	No Yes	10(52.6%) 9 (47.4%)	9(69.2%) 4(30.8%)	1(16.7%) 5(83.3%)	**0.05**
On ACEi/ARB	No Yes Missing	9 (39.1%) 10 (43.5%) 4 (17.4%)	7(41.2%) 7(41.2%) 3(17.7%)	2(33.3%) 3(50%) 1(16.7%)	0.99
Breathing support	Nasal cannula/mask Invasive Ventilation NIV/HFNC	10(52.6%) 6(31.6%) 3 (15.8%)	9(69.2%) 3(23.1%) 1(7.7%)	1(16.7%) 3(50%) 2(33.3%)	**0.045**

Table 1

Pt	Hosp stay (Days)	Resp support	Place of management	AKI(Y/N) Stage	RRT Yes/No	Comments and Outcome
1	12	Nasal cannula and mask	Renal ward	Y, St 3	Y (Intermittent HD)	Discharged Home, Alive to date, Graft failed, Transplant nephrectomy-90 days post discharge
2	12	Intubation and ventilation	Intensive (Critical) Care Unit	Y, St 3	Y (CVVHDF)	Died
3	5	Intubation and ventilation	Intensive (Critical) Care Unit	Y, St 2	N	Discharged Home, Alive to date with functioning graft, renal function back to baseline
4	7	Nasal cannula	Medical ward, palliative care	Y, St3	N	Died
5	12	HFNC, NIV, Intubation and ventilation	Renal ward, respiratory ward, Intensive (Critical) Care Unit	Y, St2	N	Died
6	5	Nasal cannula and venturi mask	Renal ward	Y, St3	N	Discharged home, Alive to date, poorly functioning graft
7	8	Nasal cannula	Renal ward	N	N	Discharged Home, Alive to date, functioning Graft
8	7	Nasal cannula and venturi mask	Renal ward	Y, St2	N	Discharged Home, Alive to date, functioning Graft, renal function back to baseline
9	80	NIV, Intubation and ventilation (57 days of invasive ventilation)	Renal ward, Intensive (Critical) Care Unit	Y, St3	Y (CVVHDF and intermittent HD)	Discharged home, Alive to date, Graft failed
10	13	Nasal Cannula	Renal ward	Y, St2	N	Discharged Home, Alive to date, functioning Graft, renal function back to baseline
11	4	Nasal Cannula	High Dependency Unit	N	N	Discharged Home, Alive to date, functioning Graft
12	5	Nasal Cannula	Renal ward	Y, St1	N	Discharged home, Alive to date, functioning Graft, renal function back to baseline

13	5	NIV	ITU	Y, St1	No	Died
14	4	Nasal Cannula/Venturi mask	High Dependency unit	N	N	Discharged home, Alive to date, functioning Graft
15	5	HFNC (Refused intubation)	ITU	Y, St2	N	Died
16	11	NIV	ITU	N	N	Discharged Home, Alive to date, functioning Graft
17	23	Intubated and ventilated	ITU	N	N	Discharged Home, Alive to date, functioning Graft
18	2	Nasal canula	ward	N	N	Discharged Home, Alive to date, functioning Graft
19	21	Intubated and ventilated	ITU	Y, St3	Y	Died
20	0	None	Home	N	N	Alive, no change in immunosuppression, no graft dysfunction
21	0	None	Home	N	N	Alive, MMF dose halved, No graft dysfunction
22	0	None	Home	N	N	Alive, no change in immunosuppression, no graft dysfunction
23	0	None	Home	N	N	Alive, no change in immunosuppression, no graft dysfunction

Table 2

Immunosuppression (Whole cohort, n=23)		Alive	Died	P	RR of death	OR
Dual	14	12(85.7%)	2(14.3%)			
Triple	9	5 (55.6%)	4 (44.4%)	0.16	1.54(0.91-3.28)	4.8 (0.71-29.3)

Table 3

4 (A)

	Transplant patients (1)	Patients on transplant waitlist (2)	Haemodialysis patients (3)	Peritoneal dialysis patients (4)
Total cohort (numbers)	1494	253	1278	170
COVID-19 positive (numbers)	23	12	123	8
Proportion of COVID-19 positive out of all	1.5%	4.7%	9.6%	4.7%
Deaths (numbers)	6	1	34	6
Case fatality ratio (% of deaths out of COVID-19 positive)	26.1%	8.3%	27.6%	75.0%
Proportion of deaths (% of deaths out of all)	0.4%	0.4%	2.7%	3.5%

4(B)

	GROUP COMPARISONS (as above in 4A)					
	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Proportion of COVID-19 positive out of all	0.002	<0.001	0.01	0.011	0.999	0.033
Case fatality ratio (% of deaths out of COVID-19 positive)	0.380	0.999	0.032	0.185	0.004	0.010

Table 4

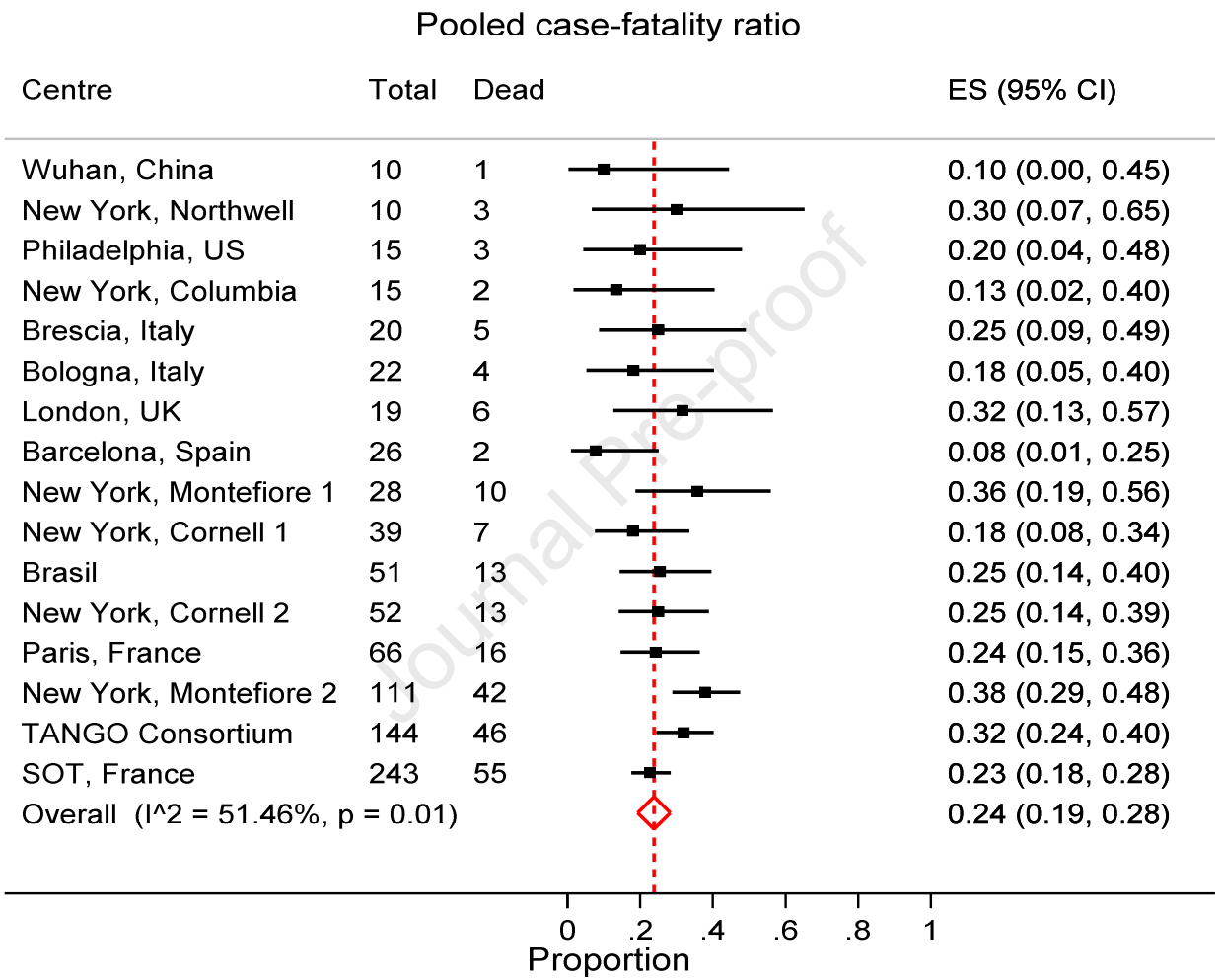


Figure 1A

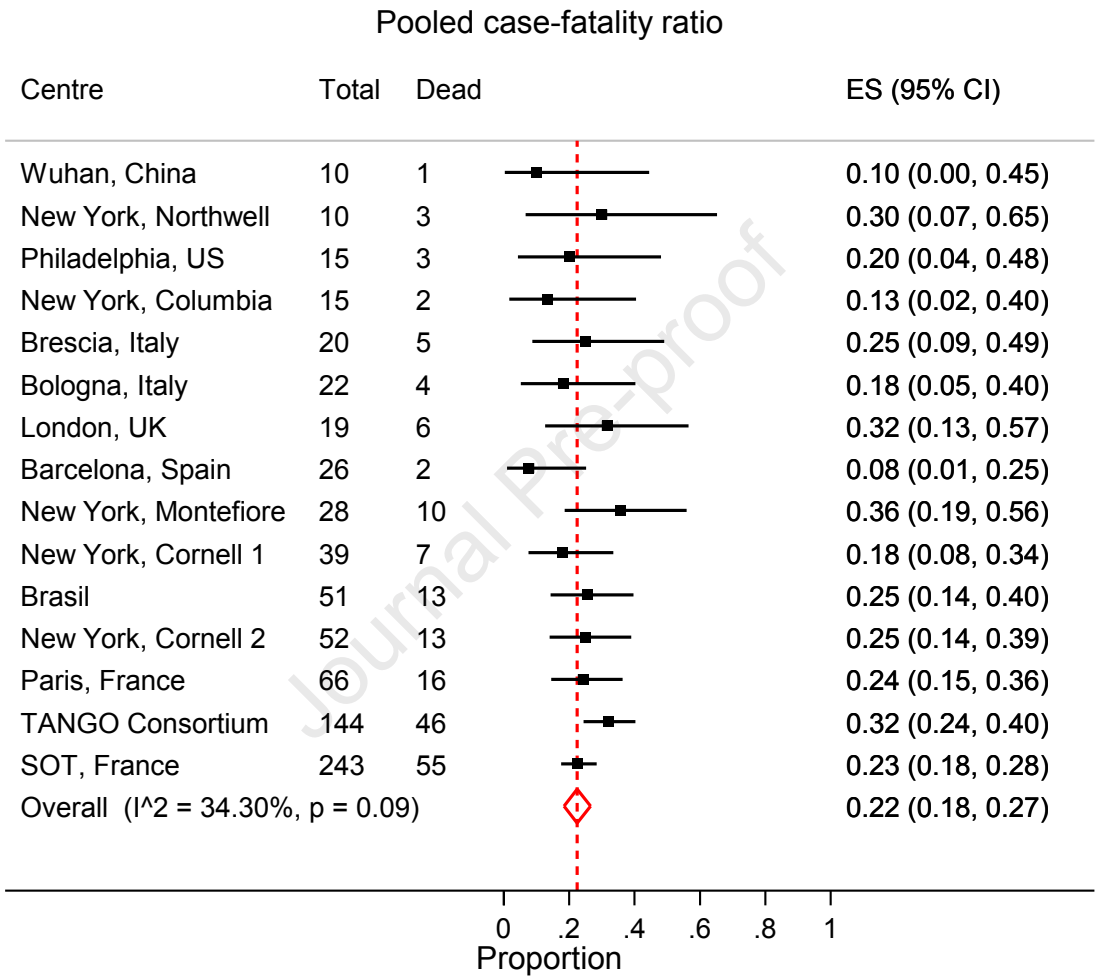


Figure 1B

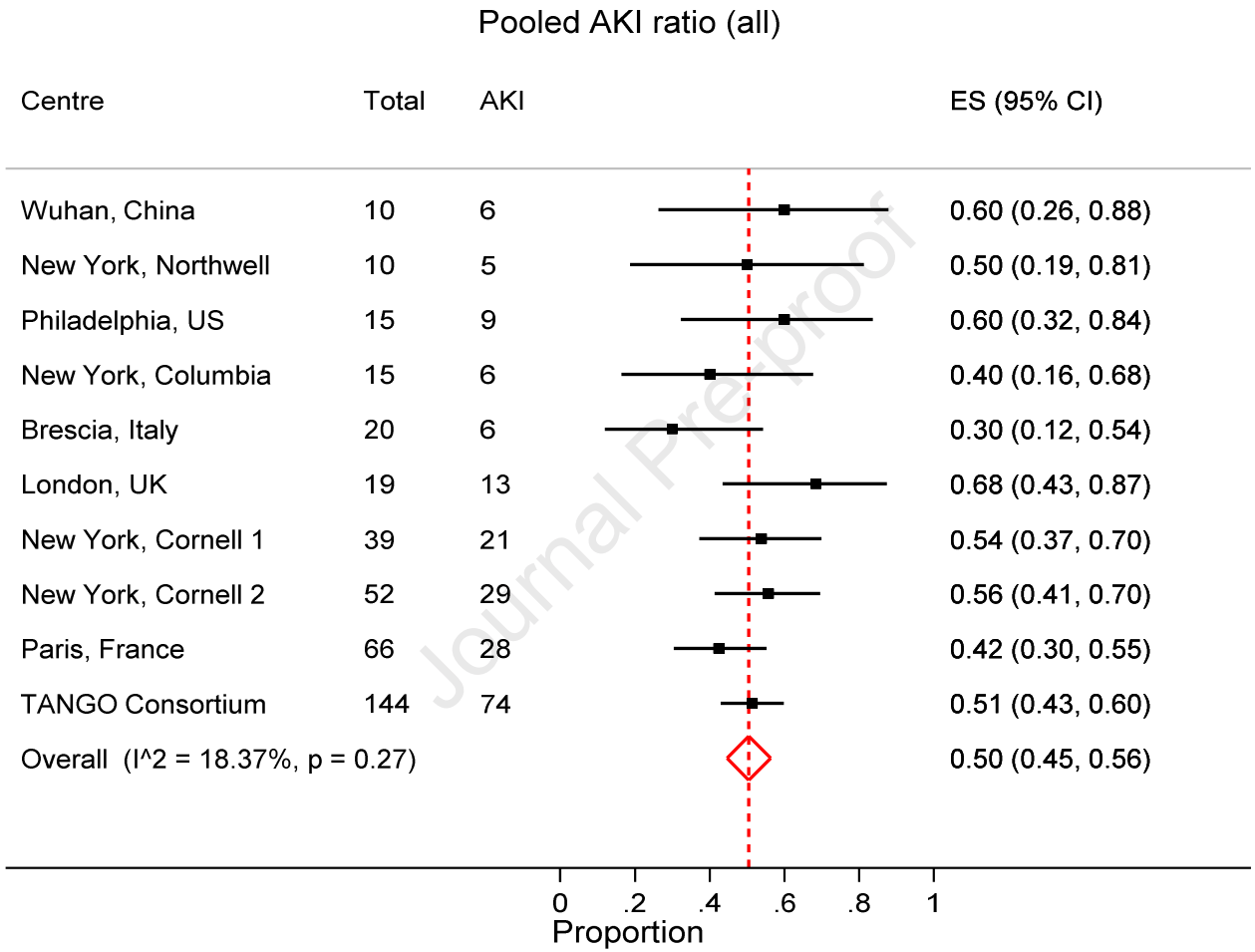
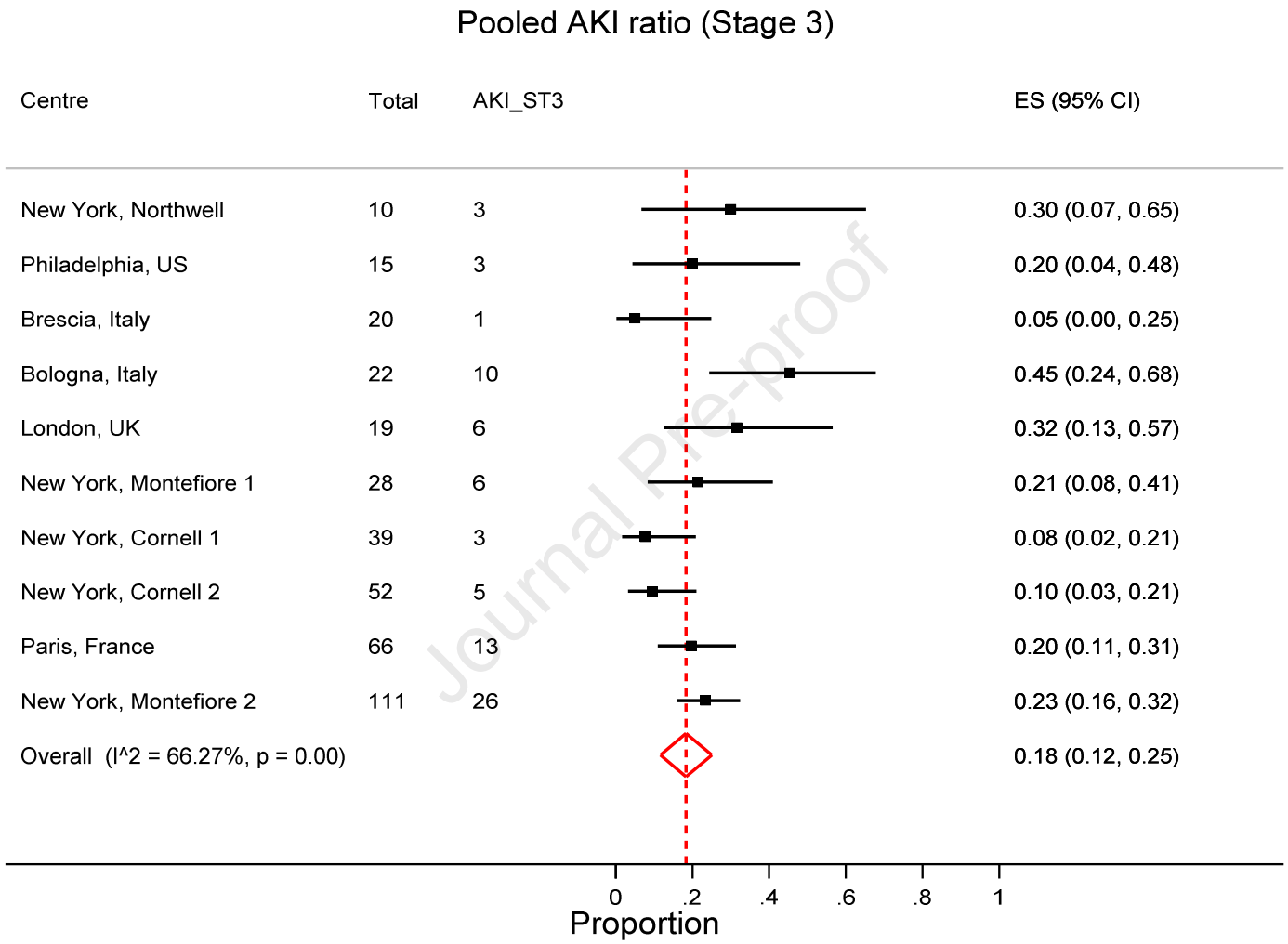


Figure 2A



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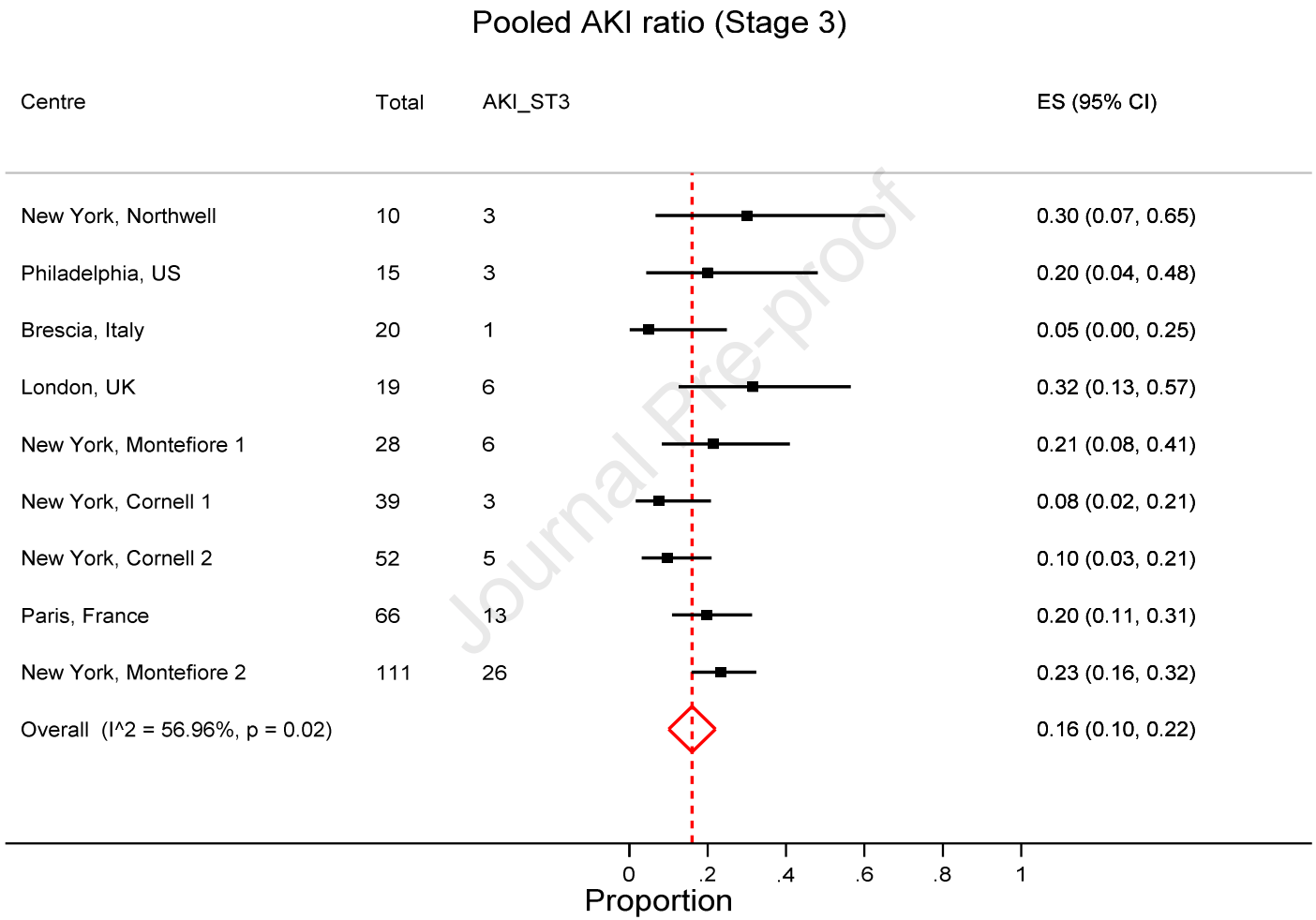

Figure 2C