Mortality rates in transplant recipients and transplantation candidates in a high prevalence COVID-19 environment.

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Abstract

Background

The risk of COVID-19 infection in transplant recipients is unknown. Patients on dialysis may be exposed to greater risk of infection due to an inability to isolate. Consideration of these competing risks is important before restarting suspended transplant programs. This study compared outcomes in kidney and kidney/pancreas transplant recipients with those on the waiting list, following admission with COVID-19 in a high prevalence region.

Methods

Audit data from all 6 London transplant centres were amalgamated. Demographic and laboratory data were collected and outcomes included mortality, intensive care (ITU) admission and ventilation. Adult patients who had undergone a kidney or kidney/pancreas transplant, and those active on the transplant waiting list at the start of the pandemic were included.

Results

121 transplant recipients (TR) and 52 waiting list patients (WL) were admitted to hospital with COVID-19. 36 TR died (30%), whilst 14 WL patients died (27% p=0.71). There was no difference in rates of admission to ITU or ventilation. 24% of TR required renal replacement therapy, and 12% lost their grafts. Lymphocyte nadir and D-dimer peak showed no difference in those who did and did not die. No other co-morbidities or demographic factors were associated with mortality, except for age (odds ratio of 4.3 [95% CI 1.8 – 10.2] for mortality if aged over 60 years) in TR.

Conclusions

Transplant recipients and waiting list patients have similar mortality rates after hospital admission with COVID-19. Mortality was higher in older transplant recipients. These data should inform decisions about transplantation in the COVID era.

Introduction

Immunosuppressed patients are thought to be at increased risk of death from the SARS-Cov-2 virus, when compared to the general population. Solid organ transplant recipients are not only immunosuppressed, but often have a number of co-morbidities, such as diabetes, which have been associated with worse outcomes following COVID-19 infection. London has had the highest prevalence of COVID-19 infections in the UK, and one of the highest per million population worldwide, with 6 966 deaths at the 1st May 2020[1]. All six kidney transplant centres in London suspended their programmes in March 2020, in response to the pandemic and anecdotal reports of poor outcomes in transplant recipients. As cases decline following public health measures, transplant programmes across the world are attempting to balance the risks of transplantation against the risks of patients remaining on haemodialysis. In centre haemodialysis requires thrice weekly attendance with a risk of viral spread by staff and other patients, as well as transportation to the dialysis site, which may increase the exposure to infected individuals.

This study considers the outcomes in all kidney transplant recipients admitted to hospital with COVID-19 from the start of the pandemic until the 27th April 2020, and compares this with all admissions of patients on the waiting list for transplantation from the same units. The primary aim was to determine the mortality rates for transplant recipients admitted to hospital with COVID-19, and to compare this with the rate for patients on the waiting list.

Methods

Audit data from March and April 2020 were collected from each of the six transplanting centres in London; Guys, Evelina and St Thomas Hospitals, the Imperial College Renal and Transplant Centre, the Royal Free Hospital, the Royal London Hospital, Great Ormond Street Hospital, and St Georges' Hospital. Ethical approval was not required. Participants were included if they had undergone a kidney or kidney/pancreas transplant and the graft was still functioning, and had been admitted to hospital. All were over 18 years except one paediatric transplant recipient, aged 4 years. Demographic data, comorbidities, blood results and outcome data were collected from patient records and anonymised. Data were also collected for patients who had been active on the waiting list prior to the pandemic, and were admitted with COVID-19.

Each centre advised both groups of patients to observe shielding, even if symptomatic, unless their condition was deteriorating, according to Government guidance[2]. Most of these patients did not undergo viral PCR testing, and therefore patients who were not admitted to hospital were not included in this analysis, since an accurate assessment of the total number of cases within the community would be impossible. Screening protocols for dialysis patients varied, and changed during the study period, so that the incidence of positive tests in those patients is similarly difficult to interpret.

Individual hospitals had their own criteria for escalation of treatment and admission to Intensive Care (ITU), but essentially those thought to have a low chance of survival were not admitted to ITU. Mortality was defined as all-cause mortality in hospital.

Statistical analysis was undertaken using Stata version 16 software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). All continuous variables

were normally distributed and comparative analyses were undertaken using Student's t test. Categorical variables were analysed using the Chi Squared test of association. Odds ratios were generated by univariate and multivariate binary logistic regression.

Results

121 kidney or kidney/pancreas transplant recipients (TR) were admitted to hospital during the study period, whilst 52 patients on the waiting list (WL) for a transplant were admitted. Of the TR group, 36 died (30%), whilst 14 WL patients died (27% p=0.71). There were 1239 waitlisted patients at the 6 London transplant centres at the 29th February 2020 (NHSBT personal communication) giving an overall mortality rate of 1.1%. The demographic data of the two groups are shown in Table 1, with a higher proportion of ethnic minority patients in the WL group; otherwise there were no significant differences between the groups. The mean time from transplant was 79 months, and 8.3% were kidney/pancreas transplant recipients, with the remainder being kidney only. 38 patients had received a depleting agent at induction (Alemtuzumab or Anti-thymocyte globulin), while the remainder had been given Basiliximab.

Table 2 shows the outcomes in each group. There were no significant differences in mortality, admission to intensive care or ventilation between the groups- the relative risk of death for transplant recipients compared with the waiting list group was 1.1 (0.65-1.86). Almost a quarter (24%) of TR required renal replacement therapy during their admission, and 12 of 102 recipients with recorded data lost their grafts (12%). Two patients received treatment with anakinra, one with hydrocortisone and one with tocilizumab, but no other experimental therapies such as hydroxychloroquine or remdesivir were used.

The symptoms at presentation are listed in Table 3, with fever, fatigue and cough being the most common, and fatigue and nausea occurring more commonly in transplant recipients. All but 8 TR had their calcineurin inhibitor or anti-metabolite modified or withdrawn.

There was no association between baseline haemoglobin, platelet count or white cell count, and mortality in either group. Similarly, lymphocyte nadir (0.6 v 0.65 x 10^9 for WL p=0.77, 0.54 v 0.9 X 10^9 for TR p=0.12) and D-dimer peak (4291 v 3356 mg/l for WL p= 0.6, 2058 v 1617 mg/l for TR p=0.62) had no association with mortality. However, peak D-Dimer levels were higher in WL (3567 v 1648mg/l p=0.03).

Other common variables showed no association with mortality in either group, except for age (Table 4), with an odds ratio of 4.3 (95% CI 1.8 – 10.2) for death if over 60 years in the TR group.

There was no difference in survival rates according to how recently the transplant took place (Table 5), although those within 6 months of transplantation were more likely to have received ventilatory support (6 of 22 ventilated v 4 of 64 not ventilated p=0.008, OR 5.6 (1.4-22.4).

Discussion

Our study, from an area with one of the highest prevalence rates of COVID-19 worldwide, has shown a mortality rate of 30% (and 12% risk of graft loss) for kidney transplant recipients admitted to hospital due to COVID-19. The mortality rate did not differ between transplanted recipients and patients awaiting transplant. The only significant association with mortality was age, in the transplant recipients, and importantly recent transplantation did not appear to confer an increased risk of death.

These data are particularly important as units consider strategies for transplantion in the COVID era, particularly in the context of a second surge. Whilst high mortality rates have been reported in patients on dialysis[3], many of these patients will be, by definition, unsuitable for transplantation due to age or multiple co-morbidities. A comparison with mortality rates in waiting list patients is therefore more appropriate to determine whether transplant recipients are at additional risk due to their immunosuppressive regimens. Of note, the study by the ISARIC COVID-19 investigators, which prospectively followed 16 749 patients admitted to UK hospitals with the virus, found a mortality rate of 33%, which is not dissimilar to the rate described in our study[4]. They also found that age was strongly associated with mortality.

In London by the 6TH May 2020, data from the national Renal Registry suggests that 175 transplant recipients had tested positive (but not necessarily admitted to hospital) for SARS Cov2, and 41 had died, while 977 patients undergoing in centre haemodialysis had tested positive and 197 had died[5].

The NHS Blood and Transplant Registry reported 38 974 kidney transplant recipients alive with a functioning graft in the UK on the 1st March 2020. By the 7th May 2020, 477 UK kidney transplant recipients had tested positive for COVID-19 (12.2%). In London, 1105 patients were on the waiting list for a kidney transplant at the 1st March 2020, of whom 155 have been reported as testing positive (14%)[6]. In light of our data showing 14 deaths from the waiting list group, this would suggest an overall mortality rate for waiting list patients is 1.3%.

As of the 22nd April, France reported 222 (16%) of 1398 dialysis patients with COVID-19 to have died, and 58 of 432 (13%) transplant recipients to have died. In Spain, the figures were 470 of 927 (51%) and 108 of 244 (44%) respectively on the 4th May 2020[3]. However, these

clearly include patients who were not admitted to hospital, and it is therefore impossible to know the true mortality rates, since many patients will have not been tested and some may have been asymptomatic.

A report from New York of 36 transplant recipients testing positive for SARS-Cov-2 suggested a mortality of 28%, although it was unclear how far after surgery these patients were[7]. Lymphopenia, especially low CD3 and CD4 T lymphocyte counts (and in 30% low CD8), was a feature, as was thrombocytopenia and raised D-Dimers. We found these features in both our groups of patients, but could not relate these to outcomes. Most of the New York patients were given hydroxychloroquine, and some were given other unproven therapies.

A report from Barcelona describes 26 transplant recipients, of whom 2 died and 1 lost their transplant; most were given antiviral therapy and hydroxychloroquine, as well as having 1 or more immunosuppressants withdrawn, although there were no episodes of rejection[8]. International comparisons are inevitably difficult, particularly as policies regarding testing, admission to hospital or ITU differ between countries.

Another recent report from Spain included 51 patients with renal disease and COVID-19 who required hospital admission; 26 were transplant recipients and 25 were on dialysis, with mortality rates of 23% and 28% respectively[9]. Again, most were treated with hydroxychloroquine.

Finally, a study of factors associated with 5 683 hospital deaths from COVID-19, found that organ transplantation carried a HR of 4.27 in a Cox proportional hazards model[10]. However, this is not unexpected, since this was in comparison to all remaining COVID cases, which would potentially include a healthier group.

Our study has a number of limitations. The numbers used in the comparisons, whilst larger than any other report, remain relatively small (particularly considering the recently transplanted), raising the possibility of a Type II error. Given that all programs in London ceased transplantation early during the pandemic, it is difficult to be definitive about the risk of transplanting in the context of continued COVID-19 prevalence. Indeed, one unit in the UK has experienced significant mortality in kidney transplant recipients prior to suspension of their programme in March (of the last 7 patients, 2 died and 2 others lost their graft- K Graetz personal communication). Nevertheless, a recent report from Oxford describes 24 patients who were transplanted during the COVID pandemic, with excellent outcomes (S Sinha personal communication). Our transplanted cohort included patients who had undergone deceased donor or living donor transplantation, whereas by definition our waiting list group were those who were due to undergo deceased donor transplantation only.

Similarly, it is difficult to draw any conclusions about the need for ventilator support or ITU admission, given the variable criteria for admission. The lack of association between age and mortality in the waiting list group may be a reflection of the small numbers, given that age appears to confer a significant risk of mortality in other studies[11].

In summary, this study has shown a low absolute mortality risk from COVID-19 in transplanted and wait-listed patients, but a high and similar mortality when admitted to hospital, of around 30%. No factors were found to be associated with mortality, other than age in those who had been transplanted. Timing of transplantation was unrelated to mortality. These data support continuation of transplant programs during the COVID era, but the lack of excess mortality from COVID-19 in wait-listed patients implies that there is no imperative for urgent transplantation from this perspective.

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Tables:

	Transplant Recipients (n=121)	Waiting list patients (n=52)	P value
Mean age yrs (SD)	56.2 (13.2)	54.4 (11.6)	p =0.4
Female Gender	45 (37 %)	19 (36.5%)	p=0.93
Non-white ethnicity	79/120 (65.8%)	44/52 (84.6%)	**p = 0.012**
Obesity (BMI>30 kg/m^2)	50/121 (41%)	13/37 (35%)	p=0.5
Diabetes	59 (48.8%)	29 (55.7%)	p=0.4
Hypertension	103/120 (85.8%)	43/52 (82.7%)	p =0.6
Chronic lung disease	6/82 (7.3%)	7/37 (18.9%)	p = 0.06
ACE Inhibitor use	35/97 (36%)	15/38 (39%)	p=0.714

Table 1. Demographic data of transplant recipients and patients active on the transplant waiting list, admitted to hospital with SARS-Cov-2 infection. Denominators vary due to missing data. Differences tested by Chi-square, except age (T-Test). BMI= Body Mass Index, SD= standard deviation

	Transplant recipients n=121	Waiting list patients n=52	p value (Chi^2 test)
Died	36 (30%)	14 (27%)	0.71
Ventilated	22/109 (20.2%)	7/45 (15.6%)	0.5
Admitted to ITU	30/101 (29.7%)	17/52 (32.7%)	0.7
Renal replacement therapy during admission	19/78 (24.4%)	N/A	

Table 2: Outcomes in transplant recipients and patients active on the transplant waiting list

	Transplant recipients	**Waiting list patients**	**P value**
Fever	86/110 (78%)	26/38 (68%)	0.3
Fatigue	53/94 (56%)	12/38 (32%)	**0.008**
Cough	78/112 (69%)	37/52 (71%)	0.498
SOB	Not recorded	23/30 (77%)	n/a
Nausea	19 / 50 (38%)	2/23 (9%)	**0.008**
Diarrhoea	28 / 88 (32%)	7/38 (18%)	0.091
Headache	9/63 (14%)	3/37 (8%)	0.280
Myalgia	17/44 (38%)	9/23 (39%)	0.586

T**able 3**: Symptoms at presentation: Patients in both groups did not have a complete set of data recording for symptoms.

	Whole cohort	**Died**	**Survived**	**P value**
Age	56.2 (SD 13)	64.6 (SD 8.6)	52.8 (SD 13.3)	**p<0.001**
Female Gender	37%	36.1%	38.9%	p=0.771
Time from transplant (months)	79 (SD 86.7)	93.2	75.9	p=0.335
Kidney pancreas transplant	8.3%	5.5%	10.3%	p=0.4
Deceased donor organ	81%	79.2%	80.6%	p=0.87
Azathioprine use	10.8%	13.9%	10.4%	p=0.578
Sirolimus Use	4.13%	0	6.5%	P=0.118
Non-white ethnicity	65.8%	64%	67%	p=0.737
Obesity	45%	27.3%	32.8%	p=0.629
T cell depleting agent at induction	35%	34.3%	34.7%	P=0.96
Diabetes	48.7%	55.6%	45.5%	P=0.317
Hypertension	84.8%	88.9%	82.9%	P=0.41

Table 4a.

	Whole cohort	**Died**	**Survived**	**P value**
Age	54.3	58 (SD 3.1)	52.9 (SD 1.9)	p=0.16
Female Gender	37.3%	28.5%	40.5%	p=0.4
Haemodialysis	86.1	87.5	85.7	p=0.9
Obesity	36.1%	37.5%	35.7%	P=0.9
Non-white ethnicity	84.3%	92.3%	81.1%	P=0.3
ACE Inhibitor use	39.5%	20%	46.4%	P=0.142
Diabetes	56.8%	64.2%	54.1%	P=0.51
Hypertension	82.4%	71.4%	86.5%	P=0.21
Smoker	10.8%	0	14.8%	P=0.197

Table 4b

Table 4: Potential risk factors for mortality in a) Transplant Recipients and b) Waiting list patients

	Died	Survived	P value (Chi^2)	Odds ratio (95% CI)
Within 3 months of transplant	4/36 (11%)	7/77 (9.1%)	0.7	1.25 (0.34 – 4.6)
Within 6 months of transplant	7/36 (19.4%)	9/77 (11.7%)	0.27	1.82 (0.62 – 5.4)

Table 5: Survival according to transplant timing