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ORIGINAL ARTICLE

Retrospective Study

Risk stratification of renal transplant recipients using routine parameters: Implication of learning from SARS-CoV-2 into transplant follow-up program

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a global pandemic that is associated with a high risk of morbidity and mortality among recipients of solid organ transplantation. In the course of acute SARS-CoV-2 infection, various laboratory markers have been identified as predictors for high risk of mortality.

AIM

To risk stratify renal transplant recipients (RTxR) using general demographic parameters, comorbidities and routine laboratory markers for the severity of the disease and its outcomes. We believe that learning about these routinely monitored parameters can help us plan better strategies for the RTxR follow-up program.

METHODS

This present study includes RTxR who acquired SARS-CoV-2 infection from March 2020 to February 2021. We recorded the basic demographics, comorbidities and routine laboratory markers. We investigated the impact of SARS-CoV-2 infection on RTxRs and risk-stratified the progression of disease severity and outcomes in terms of recovery or mortality.

RESULTS

From 505 RTxRs in our renal transplant follow-up program, 29 (7.75%) RTxRs had PCR-positive SARS-CoV-2 infection. We recorded 8 deaths from SARS-CoV-2 infection giving an overall mortality rate of 1.6% but a significant 27.6% mortality in SARS-CoV-2 positive recipients. Age more than 68 years, non-Caucasian ethnicity and male gender were associated with a significant drop in survival probability; $P \leq 0.001$. < 0.001 and < 0.0001 respectively. 87.5% of the deceased were diabetic; $P \leq 0.0.0001$. Estimated glomerular filtration rate of less than 26 mL/min/1.73 m^2, serum albumin less than 20 g/L, Hemoglobin less than 9.6 g/L and serum calcium less than 1.70 mmol/L were all associated with significantly increased risk of mortality; $P = 0.0128$, < 0.001, < 0.0001 and 0.0061 respectively.

CONCLUSION

This study has identified some routinely used modifiable parameters in predicting a higher risk of mortality and morbidity. This knowledge can be used in RTxR follow-up programs by addressing these parameters early to help reduce the morbidity and mortality in RTxRs.

Key Words: SARS-CoV-2 mortality; Renal transplant recipients; Glomerular filtration rate; Anemia; Albumin; Calcium; Reducing morbidity and mortality; Renal transplant follow-up program

Core Tip: In this present study, we aim to risk stratify renal transplant recipients (RTxR) using general demographic parameters, comorbidities and routine laboratory markers for the severity of the disease and its outcomes. We believe that learning about these routinely monitored parameters can help us to plan better strategies for RTxR follow-up program.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in December 2019[1] and subsequently declared a global pandemic on March 11, 2020[2]. So far it has resulted in more than 767 million cases worldwide with more than 6.9 million deaths[3]. The severity of the disease is related to various risk factors and associated comorbidities including older age, obesity, diabetes, pre-existing cardiac and pulmonary disease and conditions that affect the immune system[4-6].

The recipients of solid organ transplantation (SOT) are known to be more vulnerable to opportunistic infections[7] including several common respiratory virus infections[8], due to a weakened T-cell mediated immune response[9]. Globally, the recipients of SOT were included among patients at increased risk for severe illness from SARS-CoV-2[10, 11]. The reported mortality among Renal Transplant Recipients (RTxRs) from SARS-CoV-2 varied between 10% to 33%, in different studies across the world[12-17]. This increased risk of mortality is not only because of immunosuppression but also secondary to associated comorbidities[5,6]. In the course of acute SARS-CoV-2 infection, various laboratory markers have been identified as predictors for high risk of mortality including lymphopenia, high C-reactive protein levels, D-dimer, lactate dehydrogenase and ferritin[18-20]. However, some of the other routinely monitored parameters have not been studied in detail in RTxRs when compared with the general population. These include blood pressure control[21], Haemoglobin (Hb)[22], serum albumin[23], serum calcium levels[24] and function of the renal allograft, being measured as estimated glomerular filtration rate (eGFR)[25]. In this present study, we investigate these routine parameters with an aim to risk stratify RTxRs in high or low-risk groups using general demographic parameters, comorbidities and routine laboratory markers. The aim is to identify relevant routinely done parameters to identify high-risk RTxRs at an early stage. We believe that identification and correction of these parameters can significantly reduce long-term morbidity and mortality in RTxRs from SARS-CoV-2 as well as non-SARS-CoV-2 related infections.

MATERIALS AND METHODS

In this retrospective observational study, we analysed the data of our renal transplant follow-up program. At the time of the present study, we had 505 RTxRs registered under the follow-up program at St Georges University Hospitals NHS Foundation Trust, London, United Kingdom. Since the start of the pandemic in March 2020, on the advice of National Health Services England, National Health Services Blood and Transplant and the British Transplantation Society, we

recommended shielding for all our RTxRs in our follow-up program. In this present study, we included all RTxR who acquired SARS-CoV-2 infection from March 2020 to February 2021. It included both symptomatic and asymptomatic patients. There were 29 patients in our RTxRs follow-up program who acquired SARS-CoV-2 infection during this period which were included in study group cohort A; leaving 476 patients in the control group, cohort B. We recorded the basic demographics, comorbidities and routine laboratory markers. We compared these two groups to identify any significant factors responsible for predisposing RTxRs to the severity of SARS-CoV-2 infection. We then further investigated 29 RTxRs with SARS-CoV-2 infection to stratify the progression of disease severity and outcomes in terms of recovery or mortality. We subdivided patients in cohort A into A1 (n = 21) where they recovered from SARS-CoV-2 infection and A2 (n = 8) which resulted in mortality. We used Prism 9 and MedCalc statistical software programs for the data analyses. Baseline characteristics were compared using a t-test, Fisher exact test, Chi-square test or Mann-Whitney U-test where appropriate. Box-Whisker plots were used to describe means, standard deviations and standard error of means. Survival probabilities were recorded for individual risk factors. Univariate and multivariate analyses were performed to record the impact of various factors on each other. Survival analysis was carried out using Kaplan–Meier estimates and for differences in survival, a log-rank test was used.

RESULTS

From 505 RTxRs in our renal transplant follow-up program 29 (7.75%) RTxRs had PCR-positive SARS-CoV-2 infection (cohort A), leaving 476 patients in control cohort B. We recorded 8 deaths in cohort A giving a mortality rate of 1.6% for the overall follow-up population but a significant 27.6% mortality in SARS-CoV-2 positive patients. There was no death recorded in cohort B during the same period.

General demographic and risk of SARS-CoV-2

The patients who acquired SARS-CoV-2 infection were from a significantly older age group with a mean (SD) and median interquartile range (IQR) of 63.24 (12.57) and 65 (56-71.5) compared to rest of the group; $P \leq 0.001$ (Table 1, Figure 1). In intra-cohort A analysis, where all patients were exposed to SARS-CoV-2 infection, the mean (SD) and median (IQR) age in years in cohort A1 and A 2 were 60.85 (12.5) and 64 (64-69.5) compared with 69.5 (9.5) and 68 (68-77); $P = 0.0986$ (Figure 2). However, on further analysis of survival probability, a direct correlation was noted between older age and mortality (Figure 3). There was a significant drop in survival probability recorded once patients crossed 68 years of age; $P \leq 0.001$. When comparing gender distribution as a risk of SARS-CoV-2 infection there was no significance recorded between cohort A and B; $P = 0.3056$. However, when the risk of mortality was compared in the SARS-CoV-2 infection-positive group, there was a higher risk of mortality among male patients, with 75% of the deceased patients being male; $P \leq 0.0001$ (Table 1). Non-Caucasian ethnicity was associated with high mortality risk once infected with SARS-CoV-2; $P \leq 0.001$ (Figure 4). The survival probability was worst in older patients from Middle Eastern ethnicity followed by Black, Asian and White ethnicities (Figure 5).

Clinical comorbidities and SARS-CoV-2 risk analysis

The overall prevalence of diabetes in our RTxR follow-up patients was 20%. Of the patients who acquired SARS-CoV-2 infection, 55% were diabetic (Cohort A) with 87.5% among deceased (Cohort A2); $P \leq 0.0.0001$ (Figure 6). This suggests diabetes is a major risk factor for SARS-CoV-2-related mortality in renal transplant patients. We further analysed survival probability depending on the recipient's age and diabetic status and found a direct correlation between old age, diabetes and mortality (Figure 7). The mean (SD) body mass index (BMI) kg/m^2 of the overall RTxR population was 26.60 (4.81). There were no significant differences recorded in BMI across the RTxR population (Figure 8). There was no impact of BMI on mortality. In our RTxR follow-up cohort hypertension and history of ischemic heart disease were also not independently significant risk factors for mortality; $P = 0.8221$ and $P = 0.7622$ respectively.

Common laboratory markers and SARS-CoV-2 risk analysis

We analysed some of the routinely monitored laboratory investigations to identify the severity of SARS-CoV-2 infection. We analysed the latest laboratory markers just prior to SARS-CoV-2 infection to avoid any impact of acute infection on these markers. We investigated the patient's renal allograft function recorded as an eGFR in mL/min/1.73 m^2). The mean (SD) and median (IQR) in cohort A1 and A2 were 47 (21) and 41 (41-56.5); and 25.75 (7.5) and 26.5 (26.5-30) respectively, $P = 0.0128$ (Figure 9). The poor functional quality of the renal allograft was directly related to a higher risk of mortality (Figure 10). The second marker we investigated was serum albumin level. The mean (SD) and median (IQR) of serum albumin in g/L of all RTxR patients was 36.81 (4.36) and 38 (35-39) which was within the normal range (Figure 11). On review, there was a significant difference between serum albumin levels of patients who recovered from SARS-CoV-2 infection as compared to those who died; $P \leq 0.0001$. There was also a significant relation noted between low albumin levels and a high risk of mortality, particularly when serum albumin was less than 20g/L $P \leq 0.001$. The mean (SD) and median (IQR) (Hb g/L) of overall RTxR were 126.9 (18.07) and 127 (115-140) compared to 106.4 (20.8) in group A and 101 (93-124) in group A2; $P \leq 0.001$ (Figure 12). On further comparison between patients who recovered (A1) with patients who died (A2), a significant difference was recorded; $P \leq 0.0001$. Looking at survival probability Hb less than 7 was associated with higher mortality. Finally, we looked at serum calcium levels across our RTxR. The mean (SD) and median (IQR) values of serum calcium in mmol/L of the overall RTxR cohort were 2.39 (0.14) and 2.41 (2.3-2.4). There was a significant difference in serum calcium recorded between all RTxR and SARS-CoV-2 positive; $P \leq 0.001$ and also between patients who recovered and those who died; $P = 0.0061$ (Figure 13). We found a significant correlation between low serum

Table 1 Demographic factors and risk of severe acute respiratory syndrome coronavirus 2 infection in renal transplant recipients, (%)

Demographic	Cohort A (*n* = 29), SARS-CoV-2 infection	Cohort B (*n* = 476), no infection	Significance
Age			
Mean (SD)	63.24 (12.57)	55.70 (13.63)	< 0.001
Median (IQR)	65 (56-71.5)	57 (46-66)	
Gender			
Male	14 (48.27)	276 (57.8)	0.3056
Female	15 (51.73)	200 (42.2)	
Ethnicity			
White	7 (24.13)	252 (52.94)	
Black	8 (27.58)	90 (18.9)	
Asian	13 (44.82)	126 (26.47)	< 0.001[a]
Others	1 (3.44)	8 (1.6)	
Cohort A1		Cohort A2	
(Recovered; *n* = 21)		(Died; *n* = 8)	
Age			
Mean (SD)	60.85 (12.5)	69.5 (9.5)	0.0986
Median (IQR)	64 (64-69.5)	68 (68-77)	
Gender			
Male	8 (38)	6 (75)	< 0.001
Female	13 (62)	2 (25)	
Ethnicity			
White	5 (23.8)	2 (25)	
Black	7 (33.33)	1 (12.5)	
Asian	9 (42.85)	4 (50)	< 0.001[b]
Others	0	1 (12.5)	

[a]Asian ethnicity is associated with a significant risk of severe acute respiratory syndrome coronavirus 2 infection.
[b]Non-Caucasian ethnicities are associated with a significant risk of severe acute respiratory syndrome coronavirus 2 mortality.

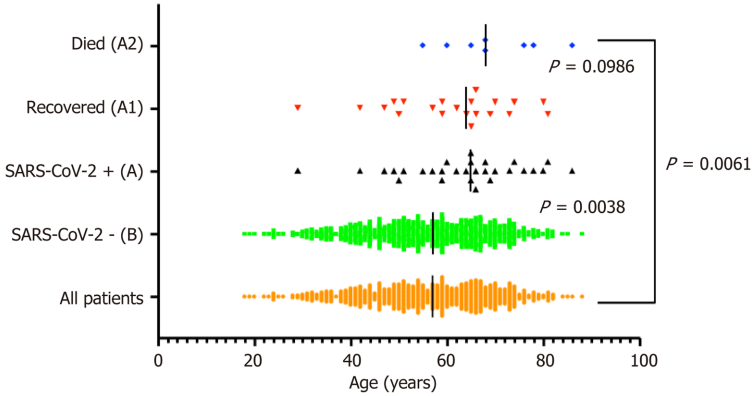

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Figure 1 Median age across various cohorts.

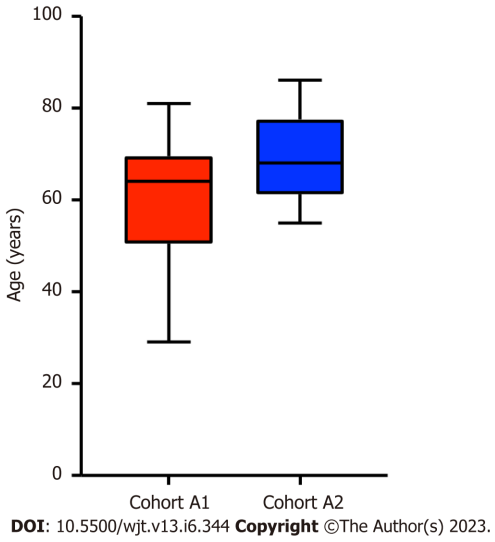

Figure 2 Intra-group age analysis A1 *vs* A2.

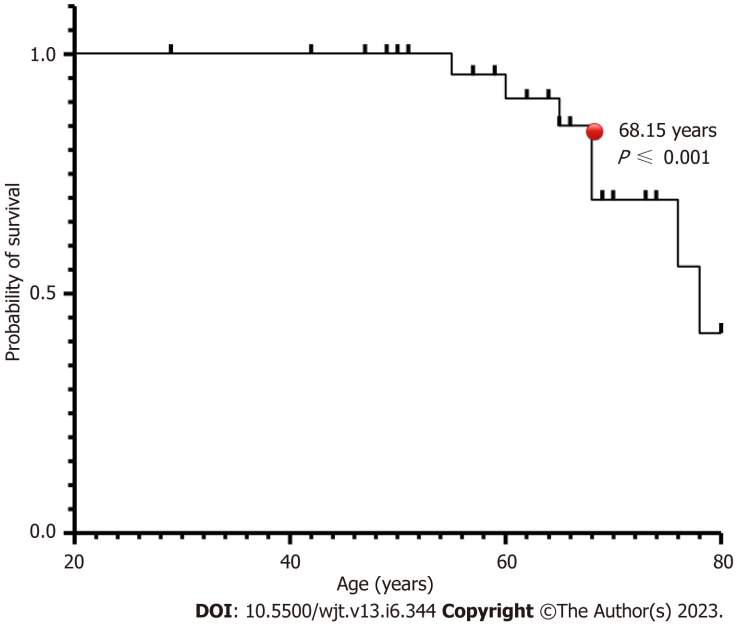

Figure 3 Age-related survival probability.

calcium levels and mortality once the level falls below 1.70 mmol/L < 0.001.

DISCUSSION

The recipients of solid organ transplantation are more vulnerable to opportunistic infections due to immunosuppressant medication. They demonstrate reduced resistance to infection, rapid progression of pathology, atypical clinical presentations and high risk of morbidity and mortality[26]. In addition to these factors, recovery from infection is dependent on various factors including the general well-being of the recipient and associated comorbidities. In renal transplant recipients, the functional status of the renal allograft also plays a vital part in the recovery phase, particularly when medication dosage is dependent on renal function. In addition to this, treatment regimens may be complicated by drug interactions and the need to maintain immunosuppression to prevent rejection. This complex interconnection between high-risk of infection, allograft function, limited treatment choices and associated comorbidities makes post-transplant infections the leading cause of morbidity and mortality[27]. During SARS-CoV-2 pandemic, the reported mortality among renal transplant recipients was as high as 33%[17]. In various general population studies, greater than 75 years of age, male gender and BMI greater than 40 are associated with significant mortality[28]. In our study, the mean (SD) age of recipient mortality was 69.5 (± 9.5) with a significantly increased risk of mortality after age 68 years and above. This

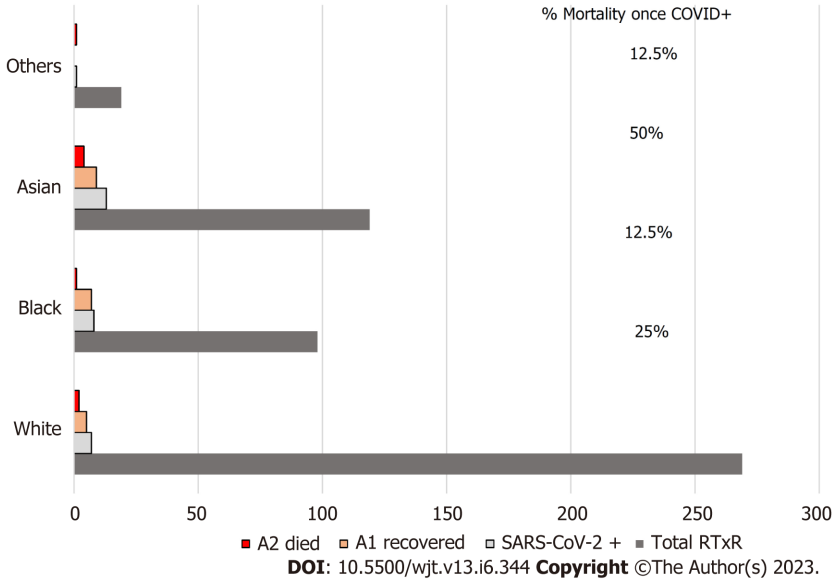

Figure 4 Ethnicity across various cohorts.

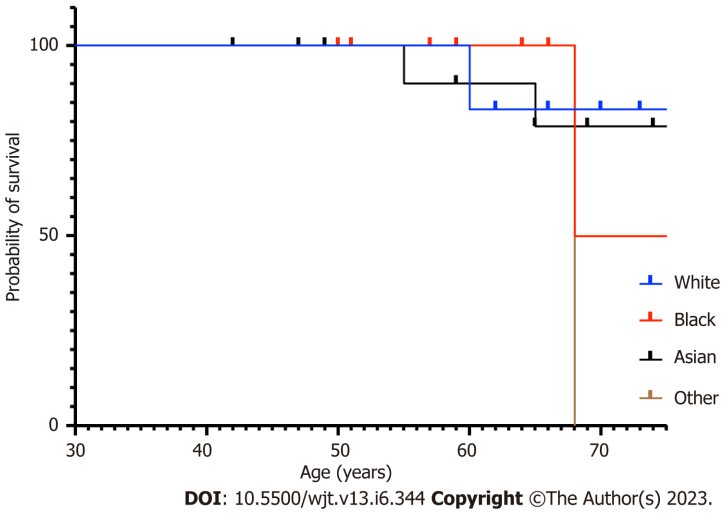

Figure 5 Survival probability with age and ethnicity.

finding is comparable to other studies in the renal transplant population[11,17,28] (Figure 14). These findings confirm that renal transplant recipients are at high risk of mortality at an earlier age when compared to the general population. We recorded a higher rate of mortality among male patients. This is also comparable with other published data[11,17,27,29]. Comparing BMI, there was no significant difference recorded in various groups in our study. The mean (SD) BMI in our mortality group was 27.20 (4.97) which is comparable to other published studies in the transplant population[11,17,29]. In general population studies, there was a high risk of mortality recorded in patients with a BMI greater than 40, but this BMI range is uncommon in renal transplant recipients. Surprisingly, we did not find any significant impact of hypertension and ischemic heart disease on mortality in our study population. This finding contrasts with general population studies[28,30,31] as well as other renal transplant studies[11,17,29] where there is a high risk of SARS-CoV-2-related mortality. The mean (SD) and median (IQR) systolic BP in our RTxR population were 130.8 (14.56) and 128 (120-139) with diastolic BP 79.22 (9.9) and 80 (71-87). This showed good BP control of our RTxR population. We had a higher number of patients with diabetes compared to other studies. This demonstrates that the demographics of renal transplant recipients vary widely across the globe and even within the United Kingdom. In contrast to other studies where acute inflammatory markers were studied in RTxR, we looked at routine laboratory parameters in predicting the outcome of RTxR after getting SARS-CoV-2 infection. We compared this to routine laboratory parameters when RTxR were free of SARS-CoV-2 infection. This helped to determine baseline parameters. There are limited studies of such parameters in the transplant population, so we compared our results with published data on the non-transplant population[14]. We noted that anaemia, hypercalcemia and hypoalbuminemia are associated with high-risk mortality in our study. These findings are similar to other published studies in non-transplant patients (Figure 15). We also noted that low GFR in RTxRs is also associated with high mortality risk. When we compared the impact of these parameters on mortality using multiple

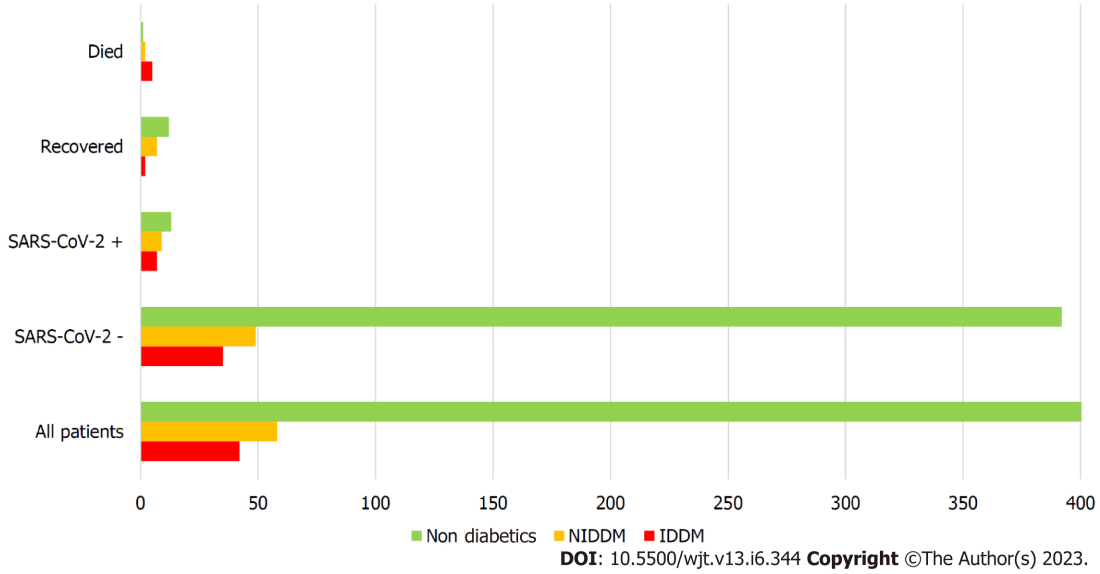

Figure 6 Diabetic status across various cohorts.

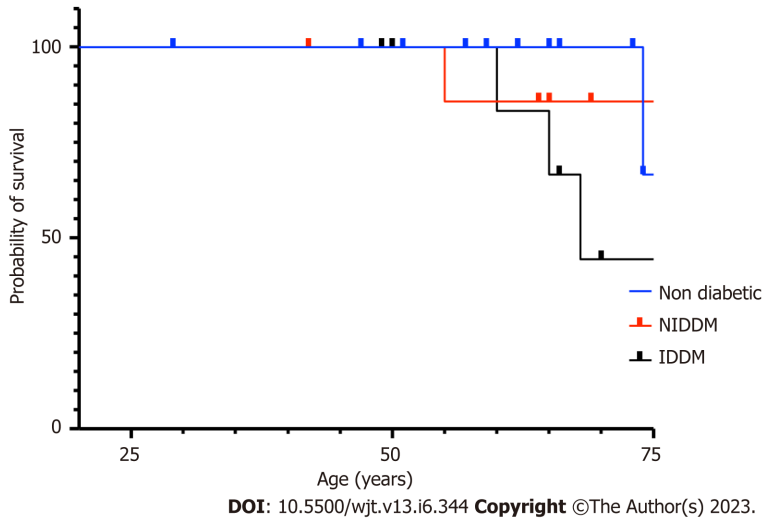

Figure 7 Survival probability with age and diabetic status.

logistic regression, we found a direct correlation (Figure 16). Identifying the impact of these parameters on mortality may be an important finding. The majority of these factors can be picked up on simple routine tests and do not require specialist investigations. Some of these factors are correctable with simple interventions. These can be addressed at an early stage during the RTxRs follow-up program with an aim to bring them to the normal range, where possible. This in return can significantly reduce morbidity and mortality in RTxRs.

CONCLUSION

It would be very easy and cost-effective to incorporate the findings of this study into any post-operative follow-up pathway and protocol for RTxRs. These simple parameters can help to risk stratify RTxRs into high and low-risk categories. In addition to this, despite having a failing renal transplant, early intervention to improve a patient's anaemia, hypercalcemia and hypoalbuminemia could reduce their risk of morbidity and mortality. Early identification of at-risk sub-groups within those already identified as being high-risk, can further reduce the risk of infection-associated mortality, with timely interventions.

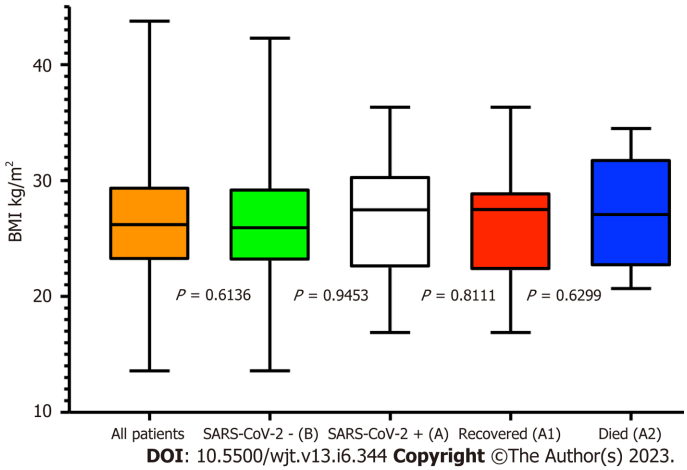

Figure 8 Body mass index range across various cohorts. BMI: Body mass index; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

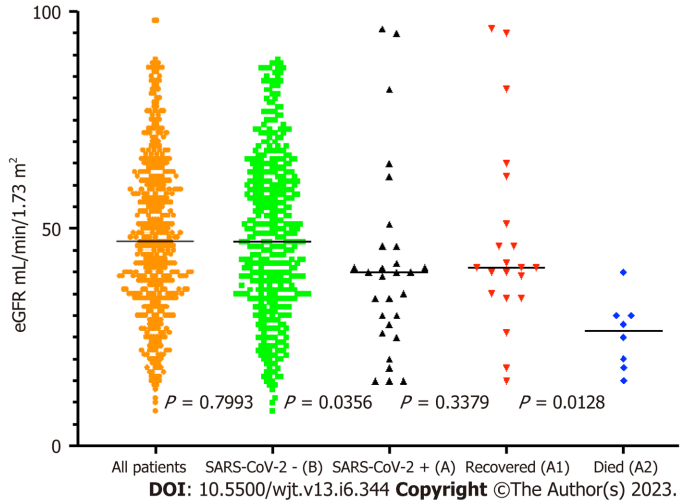

Figure 9 Median estimated glomerular filtration rate across various cohorts. eGFR: Estimated glomerular filtration rate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

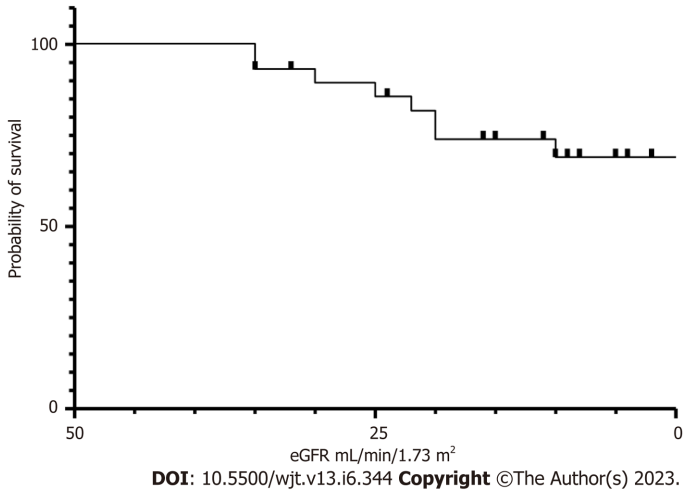

Figure 10 Survival probability dependent on graft estimated glomerular filtration rate. eGFR: Estimated glomerular filtration rate.

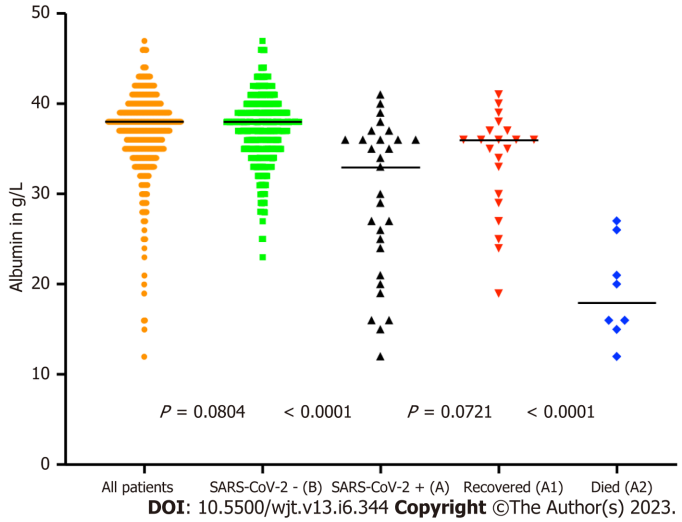

Figure 11 Albumin (g/L) across various cohorts. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

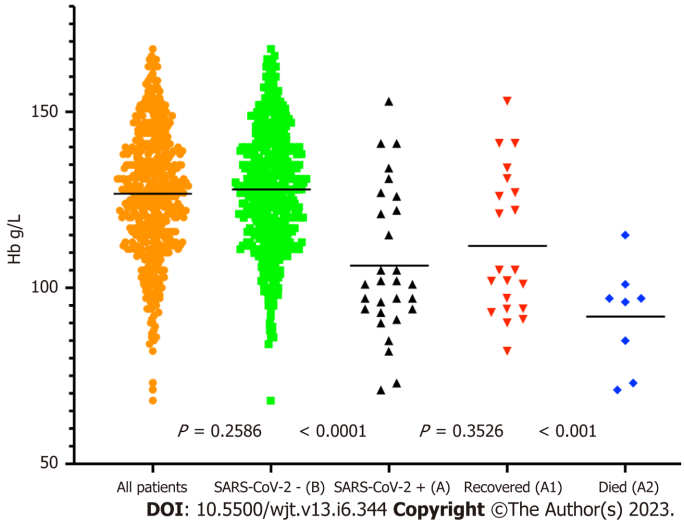

Figure 12 Hb distribution among various cohorts. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

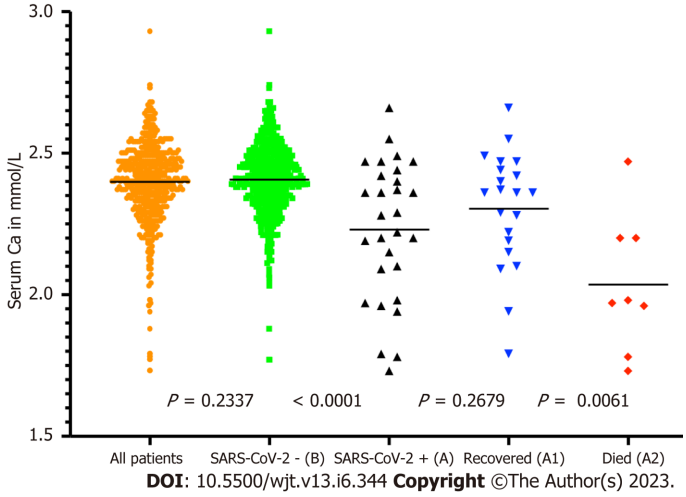

Figure 13 Serum Ca distribution across various cohorts. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

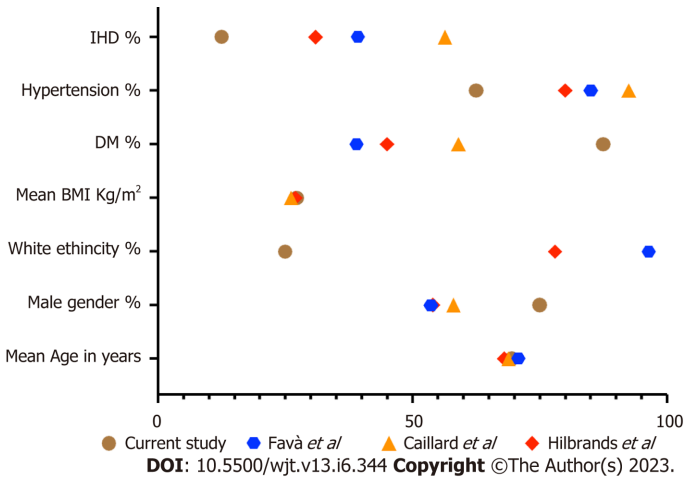

Figure 14 Comparison of current study demographics with published data. IHD: Ischemic heart disease; DM: Diabetes mellitus; BMI: Body mass index.

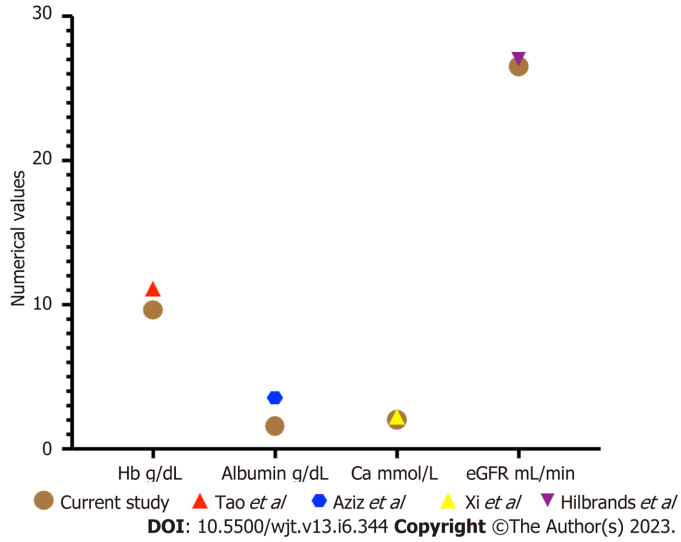

Figure 15 Comparison of current study routine lab parameters with published data. eGFR: Estimated glomerular filtration rate.

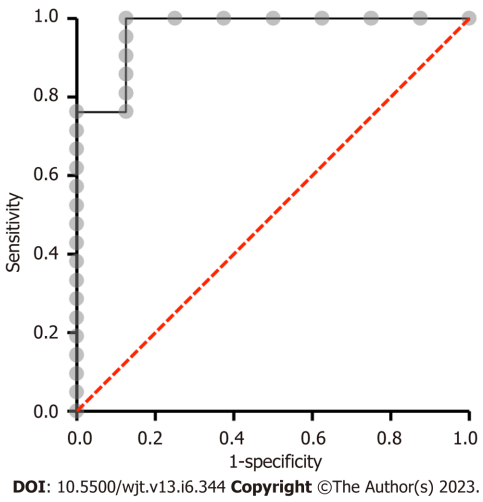

Figure 16 Multiple logistic regression: Mortality with Haemoglobin, Estimated glomerular filtration rate, Albumin and Ca.

ARTICLE HIGHLIGHTS

Research background

Various studies have been done to separately study routine laboratory markers to stratify patients with high risk of morbidity and mortality but very little is known in renal transplant patients.

Research motivation

This study provides a new way of looking at the significance of routine laboratory tests with an aim to risk stratify renal transplant recipients into high-risk sub-groups.

Research objectives

This study will help in shaping new policies and guidelines by providing individualized shielding advice, self-isolation guidance and booster coronavirus disease 2019 vaccination. Moreover, this will also help to plan better follow-up strategies for transplant patient. Addressing and correcting these parameters during a follow-up program can reduce the risk of morbidity and mortality in renal transplant recipients (RTxR).

Research methods

Retrospective observational study to analyze the data of our renal transplant follow-up program for various routine parameters and their impact of patient outcomes.

Research results

This study has identified some routinely used modifiable parameters in predicting a higher risk of mortality and morbidity.

Research conclusions

This knowledge can be used in RTxR follow-up programs by addressing these parameters early to help reduce the morbidity and mortality in RTxRs.

Research perspectives

This knowledge can be used in RTxR follow-up programs by addressing these parameters early to help reduce the morbidity and mortality in RTxRs.

FOOTNOTES

Author contributions: Ghazanfar A and Abbas M contributed to study design, data analysis, manuscript writing; Ghazanfar A and Hussain Md W contributed to data collection; Kayal M contributed to manuscript writing support.

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Informed consent statement: Online assessment confirmed that no patient consent or ethical approval from NHS HRA/REC was required.

Conflict-of-interest statement: Authors have no conflict of interest related to the content of this publication.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at email address a.ghazanfar@nhs.net.

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