

# Distance from treatment facility and risk of death from cardiovascular and infectious causes in renal transplant patients

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## ABSTRACT

We investigated whether patients receiving RTx who live farther from their attending nephrologist are more likely to die than those who live closer. A random sample of 167 patients who undergone RTx between 1996 and 2004 was examined. We calculated the distance between each patient's residence and the practice location of their attending nephrologist. We used Cox proportional hazards models to examine the adjusted relation between distance and clinical outcomes (death from all causes, rejection episodes, infectious causes, and cardiovascular complications) over a follow-up period of upto 6 years. During the follow-up period (median: 3.3, range: 1.0-6.5 years), 22% of patients died. Compared with patients who lived within 50 km of their nephrologist, the adjusted hazard ratio of death was 1.04 among those who lived 50.1-150 km away, 1.16 for those who lived 150.1-300 km away, and 1.19 for those who lived more than 300 km ( $P$  for trend  $<0.001$ ). The risk of death from infectious causes increased with greater distance from the attending nephrologist ( $P$  for trend  $<0.001$ ). The risk of developing acute rejection episodes did not increase with distance from the attending nephrologist ( $P$  for trend = 0.2). The risk of death from cardiovascular causes increased with distance from the attending nephrologist ( $P$  for trend  $<0.05$ ). Compared with patients who lived within 50 km of their nephrologist, the adjusted hazard ratio of death among those who lived  $>300$  km away was 1.75 for infectious causes and 1.39 for cardiovascular causes. We conclude that mortality and morbidity associated with RTx was greater among patients who lived farther from their attending nephrologist, as compared with those who lived closer.

**Key words:** Cardiovascular, infection, renal transplant

## Introduction

Little is known about the association between residency and living at a distance from the transplant center to deaths after renal transplantation. An increasing risk of death from cardiovascular and infectious causes after renal transplantation has been well recognized in the transplant community. This excess of deaths compared with that of expected age-matched population has been attributed to

increased numbers of co-morbidities. Subsequent analyses suggesting that most of the deaths so prevented were cardiovascular or infectious in nature. One explanation for increased prevalence of both these complications might be that the frail immunocompromised patients with a number of underlying medical conditions might not withstand the co-morbidities associated with acute infections and acute cardiovascular events. Hence, an increased risk of death might be expected in these groups. An increasing mortality might not occur in the immediate post-operative years after the transplantation but might last for a prolonged period.

The patients who live far from the centers where they undergo transplantation could face a barrier to optimal follow-up care. Distance may also limit the ability of transplant centers to collect data that allow for monitoring, and thereby improve long-term outcomes. The reputations of some centers may entice patients to travel greater distances. Some local centers may not transplant high-risk patients, who must then travel to more distant centers like ours to undergo transplantation.

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In this study, we investigated whether patients receiving renal transplantation who live farther from their attending nephrologist are more likely to die than those who live closer. To better understand factors that could affect distance between home and transplant center, we examined how patient and transplant center characteristics were associated with distance. Distance between home and transplant center may be determined by the location of the center closest to the patient's home. We also examined the association of distance with patient and kidney allograft survival especially the cardiovascular and infectious mortality.

## Patients and Methods

A random sample of 167 patients who undergone RTx between 1996 and 2004 was examined. We calculated the distance between each patient's residence location and the practice location of their attending nephrologist. Data from our local registry were used for this study, which was approved by the local research ethics review board. We studied adult patients, aged 18-70 years, who initiated renal replacement (chronic dialysis or transplantation) between January 1996 and December 2004. The zip code for each patient's residence location at the time of their first presentation to our unit was obtained from the medical file. The geographical coordinates for each 5-digit zip code were determined using the Egyptian 5-digit zip code Database. The distance between each patient's residence and his/her transplant center was then estimated as the distance between the centroids of the zip codes using the great circle formula (Equation by Weisstein *et al.*)<sup>[1]</sup>

Distance to the transplant center was classified using categories corresponding to the 0-50 km, 50.1-150 km, 150-300 km, and higher than 300 km and the numbers of transplant patients in each category were tabulated.

## Statistical analysis

Cox multivariate regression analysis was performed to determine the likelihood of cardiovascular and infectious complications seen in renal transplant patients among different distance categories after adjustment for the following potential confounders: patient age, sex, cause of ESRD (diabetes, hypertension, glomerulonephritis, and other causes), insurance status, ambulatory status, co-morbid conditions (coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, malignancy, and chronic obstructive pulmonary disease), body mass index, estimated glomerular filtration rate, and blood group. In cases for which data were missing, a category of unknown was created and entered into the model. Subgroups of patients

who were progressively more likely to be good transplant candidates were defined by combinations of age younger than 50 years, absence of diabetes, and absence of major co-morbidity (coronary disease, heart failure, and cancer). Patients who received pre-emptive kidney transplants were also included in the analyses.

Tests for interaction were performed using cross-product terms in the Cox proportional hazards models. The proportional hazards assumption was tested using log-negative-log plots of the within-group survivorship probabilities vs log-time as well as time-dependent covariates in the Cox model. Statistical significance was set at  $P < 0.05$ , and all statistical tests were two-sided. All eligible patients with a valid zip code and initiating renal transplant during the study period were included in the analyses. We used those hazards models to examine the adjusted relation between distance and clinical outcomes (death from all causes, rejection episodes, infectious causes, and cardiovascular complications) over the follow-up period of upto 6 years.

## Results

### Patient characteristics

The participants were classified into the following groups based on distance to the closest transplant center. Of those changing distance categories during follow-up, 17 patients (10% of the total) remained within 50 km of the transplant center, 62 patients (37%) within 50.1-150 km, 51 patients (30.5%) within 150.1-300 km, and 37 patients (22%) more than 300 km [Table 1].

### Clinical outcomes

Table 2 shows the associations of distance between patient homes and transplant centers and transplant outcomes. During the follow-up period (median: 3.3 year, range: 1.0-6.5), 22% of patients died. The rate of death was slightly higher among those who lived farther from the transplant center (four patients within 50 km of the transplant center, seven patients within 50.1-150 km, 12 patients within 150.1-300 km, and 14 patients more than 300 km,  $P < 0.01$ ). Compared with patients who lived within 50 km of their nephrologist, the adjusted hazard ratio of death among those who lived 50.1-150 km away was 1.04, 1.16 for those who lived 150.1-300 km away, and 1.19 for those who lived more than 300 km from their nephrologist ( $P$  for trend  $< 0.001$ ). The risk of death from infectious causes increased with increasing distance from the attending nephrologist ( $P$  for trend  $< 0.001$ ). The risk of developing acute rejection episodes did not increase with distance from the attending nephrologist ( $P$  for trend = 0.2). The risk of death from cardiovascular causes increased with distance from the attending nephrologist

**Table 1: Demographic and clinical characteristics of patients by distance closest to the center from renal transplant center in kilometer**

<i>n</i> =167 (%)	Within 50 km <i>n</i> =17 (10%)	50.1-150 km <i>n</i> =62 (37%)	150.1-300 km <i>n</i> =51 (30.5%)	More than 300 km <i>n</i> =37 (22%)
Age, years	39.2±10.5	41.5±12.1	42.8±11.1	40.1±10.6
Sex, male ( <i>n</i> , %)	9 (53)	33 (53)	27 (53)	20 (54)
Cause of ESRD ( <i>n</i> , %)				
Diabetes mellitus	7 (41)	25 (40)	20 (39)	14 (38)
Hypertension	3 (17.7)	12 (19)	9 (17.6)	7 (19)
Glomerulonephritis	2 (11.8)	8 (13)	7 (13.7)	5 (13.5)
Others	5 (29.4)	17 (27)	15 (29)	11 (29.7)
BMI>30 ( <i>n</i> , %)	6 (35)	21 (34)	17 (33)	13 (35)
Blood group ( <i>n</i> , %)				
A	6 (35)	22 (35)	17 (33)	13 (35)
B	3 (17.6)	10 (16)	8 (15.7)	6 (16)
AB	1 (6)	3 (5)	3 (6)	2 (5)
O	7 (41)	27 (43.5)	23 (45)	16 (43)
Non-ambulatory ( <i>n</i> , %)	1 (5.9)	3 (4.8)	3 (5.8)	2 (5.4)
Initial modality ( <i>n</i> , %)				
Pre-emptive	4 (23.5)	15 (24.1)	12 (23.5)	9 (24.3)
Hemodialysis	12 (70.6)	43 (69.4)	36 (70.5)	26 (70.2)
Transplantation	1 (5.9)	4 (6.4)	3 (5.9)	2 (5.4)
Insurance status ( <i>n</i> , %)				
Yes	7 (41)	25 (40.3)	20 (39.2)	15 (40.5)
No	10 (59)	37 (59.7)	31 (60.8)	22 (59.5)
eGFR at dialysis initiation, mean (SD)	9.2 (4.1)	8.9 (5.2)	8.7 (4.7)	8.2 (4.4)

BMI: Body mass index, CAD: Coronary heart disease, PVD: Peripheral vascular disease, CVD: Cerebro-vascular disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, GFR: Glomerular filtration rate

**Table 2: Associations of distance between patient homes and transplant centers and transplant outcomes**

Outcome	Hazard ratio	<i>P</i>
Death with functioning graft		
50.1-150 km	1.04	<0.001
150.1-300 km	1.16	<0.001
Above 300 km	1.19	<0.001
Death from infectious causes	1.75	0.001
Death from cardiovascular causes	1.39	0.001
Risk of acute rejection	0.96	0.2

(*P* for trend <0.05). Compared with patients who lived within 50 km of their nephrologist, the adjusted hazard ratio of death among those who lived >300 km away was 1.75 for infectious causes and 1.39 for cardiovascular causes.

Tests for interaction demonstrated that sex and insurance status all significantly modified the relation between distance from the transplant center and the likelihood of development of cardiovascular complications after transplantation (*P* < 0.001). Therefore, we performed analyses that examined the association between time to complications and distance from the closest transplant center after stratifying on these potential confounders. The time to complication was not significantly lower among remote patients for any of these subgroups than for those living closer. We also found a positive association between high body mass index and distance between home and center (*r* = 0.67, *P* < 0.001). Distance between

home and center was not much different between patients with diabetes as primary cause of ESRD and those with glomerulonephritis or cystic kidney disease as primary cause of ESRD. Similarly, a test for interaction showed that the proportion of remote patients significantly modified the association between distance from the transplant center and the likelihood of infectious complications (*P* < .001). When results from those above 150 km were pooled together, the hazard ratio for the likelihood of infectious complications was 1.05 (95% CI, 0.95-1.15).

## Discussion

The prevalence of end-stage renal disease has significantly increased in developing countries such as Egypt. Diabetes mellitus is still the leading cause of ESRD, while numbers of hypertensive patients among that population have significantly risen. Hemodialysis is available in most parts of the country. Continuous ambulatory peritoneal dialysis and renal transplantation programs have been performed in few nephrology centers. Costs for dialysis and renal transplantation are still unaffordable for most patients with ESRD. Since the cost burden has significantly increased as elucidated by Soliman *et al.*,<sup>[2]</sup> nephrology transplant services are concentrated in few centers mostly in Cairo (capital) and delta (lower Egypt) while patients in upper Egypt have to travel long distances to catch these services (up to 1000 km).

Most patients undergoing renal transplantation in our center lived more than 50 km away from the transplant center. This might be a potential barrier to follow-up after operation. We found that mortality and morbidity associated with renal transplantation was greater among patients who lived farther from their attending nephrologist, as compared with those who lived closer. The likelihood of developing cardiovascular and infectious complications among patients living farther away was greater than those residing within 50 km of the kidney transplant center.

Distance to care has been cited as an important variable in several utilization studies. Gelberg *et al.*<sup>[3]</sup> showed that distance to care was important in determining the number of regular health care visits a person had in a year, with greater distance resulting in fewer regular check-up visits. However, distance is not significant in determining the number of chronic care and acute care visits. Furthermore, Kim *et al.*<sup>[4]</sup> showed that living in a remote area appears to be a clinically relevant risk factor for mortality among patients with end-stage renal disease in Canada. When expressed as absolute risk, there is a substantial increase (1.7 excess deaths per 100 persons per year) owing to the high mortality associated with kidney failure. This risk is about three-times greater than the excess risk of death associated with diabetes mellitus in Canadian general population.

Little is known about the association between residence location and outcomes for renal transplant patients, as they require life-long supervision by a specialist. Although renal programs around the world deliver services to people who live in remote areas through the use of satellite hemodialysis units, few studies<sup>[5,6]</sup> have examined how residence location affects clinical outcomes among patients after renal transplantation. Tonelli *et al.*<sup>[7]</sup> examined a random sample of 7034 subjects initiating dialysis in Canada between 1996 and 2000. They used Cox proportional hazards models to examine the relation between residence location and the likelihood of kidney transplantation from deceased donors over a median period of 2.4 years. The adjusted likelihood of undergoing a kidney transplant from a deceased donor varied substantially between geographical regions. In contrast, the likelihood of transplantation within regions was not affected by distance from the closest transplant center.

These results are expected because multiple studies from the USA and other countries indicate that remote and rural dwellers are less likely to access primary care and specialized medical services often experience worse clinical outcomes.<sup>[8-12]</sup> Our analyses included all patients commencing renal transplantation in our center during

the study period and adjusted for differences in age, sex, and co-morbid conditions. Our findings therefore point to a significant difference in transplant medical care among remote regions in Egypt. Despite its potential to serve as a barrier to kidney transplantation, data on how remote residence location influences access to essential medical service are sparse.

A study from the USA found that post-transplantation clinical outcomes were similar for those living closer to and farther from a transplant center. They used data from the United States Renal Data System to examine distance between home and transplant center for 92,224 adults undergoing kidney transplantation from 1995 to 2003. Compared to whites (median distance: 28.5 miles), African Americans (11.5 miles) and Asians (13.5 miles) lived closer to their centers, whereas Native Americans lived farther away (90.1 miles). Hispanics lived closer (14.7 miles) than non-Hispanics (24.3 miles). Even after adjusting for center density, they found substantial regional variability, with median distance of 15.1 miles for patients living in the northeast and 40.6 miles for those in the southeast. Distance was also associated with center size, median zip code income, listing on more than one deceased donor waiting list, and other factors, but greater distance (adjusted for these other factors) was not associated with worse patient or graft survival. They concluded that substantial variability in geographical access to kidney transplantation could have important implications for long-term care.<sup>[13]</sup>

Our work showed that compared with patients who lived within 50 km of their nephrologist, the adjusted hazard ratio of death among those who lived >300 km away was 1.75 for infectious causes and 1.39 for cardiovascular causes. Therefore, mortality and morbidity associated with renal transplantation was greater among patients who lived farther from their attending nephrologist, as compared with those who lived closer. The increased risk of death from cardiovascular and infectious causes among our renal transplantation patients in remote areas may indicate that these serious diseases are not managed quickly or appropriately in remote hemodialysis units where nephrologists do not frequently attend. We did not have data on the management of either cardiovascular accidents or infections in those units; thus, these suggestions are speculative.

Increased cardiovascular and infectious complications in our study can also be explained by lower income in those who lived away from our center lying in Cairo. Our data are supported by the study of Kalil *et al.*,<sup>[14]</sup> who examined the impact of socioeconomic factors on long-term outcome after renal transplantation. They studied the effects of



family income among 202 patients transplanted between 1976 and 1982 who had an allograft that functioned for at least 1 year. They found that patients with low income have reduced renal allograft survival. Compared with patients with an adequate income, recipients of medical assistance at the time of transplantation were more likely to return to dialysis after 1 year, or after 5 years of graft function. Our results provide good support for the hypothesis that higher risk patients travel greater distances to be transplanted. Obesity is arguably a well-known risk factor for transplant outcomes. We found positive association between high body mass index and distance between home and center. Distance between home and center was not much different between patients with diabetes as primary cause of ESRD (considered high risk group) and those with glomerulonephritis or cystic kidney disease as primary cause of ESRD.

Our study has several limitations. First, we excluded participants without a valid residential zip code; however, these individuals accounted for only 11 patients. Second, the method we used to calculate distance necessitates some approximations. We attempted to reduce the effect of this imprecision by categorizing distance from the transplant center into relatively broad categories, reducing the risk of misclassification. Finally, although we studied all eligible patients who performed renal transplantation in our center during the study period, it is possible that patients residing in remote areas are less likely to receive a renal transplant than those living closer. Although we cannot exclude this possibility, we believe that it is unlikely to have influenced our conclusions.

## Conclusion

We can conclude that mortality and morbidity associated with RTx was greater among patients who lived farther from their attending nephrologist, as compared with those who lived closer. We found evidence that the likelihood of cardiovascular and infectious complications after kidney transplantation was higher among remote or far living patients treated for kidney failure in Egypt. These data

suggest that efforts are needed to improve follow-up of renal transplant patients in far residence location.

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