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Observational Study

Outcomes of early hospital readmission after kidney transplantation: perspectives from a Canadian transplant centre

Early Hospital Readmissions Post Kidney Transplant

Abstract

BACKGROUND

Early hospital readmissions (EHR) post-kidney transplantation range in incidence from 18-47%, and thus are important and substantial healthcare quality indicators. EHR can adversely impact clinical outcomes such as graft function and patient mortality, as well as healthcare costs. EHR have been extensively studied in American healthcare systems, but these associations have not been explored within a Canadian setting. Due to significant differences in the delivery of healthcare and patient outcomes, results from American studies cannot be readily applicable to Canadian populations. A better understanding of EHR can facilitate improved discharge planning and long-term outpatient management post kidney transplant.

AIM

To explore the burden of EHR on kidney transplant recipients and the Canadian healthcare system in a large transplant centre.

METHODS

This single centre cohort study included 1,564 kidney transplant recipients from January 1st, 2009 to December 31st, 2017, with a one-year follow-up. We defined EHR as

hospitalizations within 30 or 90 days of transplant discharge, excluding elective procedures. Multivariable Cox and linear regression models were used to examine EHR, late hospital readmissions (LHR) - defined as hospitalizations within 31-365 days for 30day EHR and within 91-365 days for 90-day EHR, and outcomes including graft function and patient mortality.

RESULTS

In this study, 307 (22.4%) and 394 (29.6%) kidney transplant recipients (KTR) had 30-day and 90-day EHR, respectively. Factors such as previous cases of rejection, being transplanted in more recent years, having a longer duration of dialysis pre-transplant and having an expanded criteria donor were associated with EHR post-transplant. The cumulative probability of death censored graft failure, as well as total graft failure, was higher among the 90-day EHR group as compared to patients with no EHR. While multivariable models found no significant association between EHR and patient mortality, patients with HER were at increased risk of LHR, poorer kidney function throughout the first year post-transplant, and higher hospital-based care costs within the first year of follow-up.

CONCLUSION

EHR are associated with suboptimal outcomes after kidney transplant and increased financial burden on the healthcare system. The results warrant the need for effective strategies to reduce post-transplant EHR.

Key Words: Kidney transplantation; Early hospital readmissions; Post-transplant outcomes

Famure O, Kim ED, Li Y, Huang JW, Zyla R, Au M, Chen PX, Sultan H, Ashwin M, Minkovich M, Kim SJ. Outcomes of Early Hospital Readmission after Kidney

Transplantation: Perspectives from a Canadian Transplant Centre. *World J Transplant* 2023; In press

Core Tip: EHRs post-transplant are associated with suboptimal patient outcomes and increased financial burden on the healthcare system. The 90-day window for defining EHR, in addition to the frequently used 30-day period, provides a novel opportunity to evaluate the risks for kidney transplant recipients

INTRODUCTION

Kidney transplantation is widely accepted as the best treatment option for the majority of patients with end-stage renal disease;[1] however, it carries a risk of complications and subsequent hospital readmissions in the post-transplant period.[2] Early hospital readmissions (EHR), commonly defined as any new hospitalization occurring within 30 days after initial transplant discharge, is an indicator of healthcare quality and an important outcome measure after transplantation.[2,3] In the U.S., approximately 30% of kidney transplant recipients (KTR) have EHR, with rates ranging from 18 to 47% between transplant centres.[4,5] More recently, a single-centre Brazilian study reported an EHR incidence of 27% among 1175 KTR from 2011 to 2012,[3] while a population-based Canadian study reported a cumulative EHR incidence of 21% among 5437 KTR from 2002 to 2014.[2]

The relatively high incidence of post-transplant EHR is concerning since EHR have been associated with severe reduction in health status and substantial healthcare costs. Several kidney transplant studies observed an increased risk of graft failure, patient mortality, and suboptimal graft function with EHR.[6-10] EHR were also associated with more late hospital readmissions (LHR), defined as subsequent readmissions within the first year of transplantation after the EHR time frame. Furthermore, EHR had a mean cost of approximately 10,000 USD per KTR, which can create a significant burden on healthcare delivery systems.[2]

Factors that interfere with post-transplant recovery and increase the risk of EHR include patient demographics (e.g., older age, African American race), pre-existing comorbidities (e.g., obesity, diabetes, heart disease, chronic obstructive pulmonary disease), transplant characteristics (e.g., expanded criteria donor transplants, lack of induction therapy, longer initial hospital stay, surgical complications), and frailty, a measure of physiologic reserve in aging populations.[7,8, 11-13] Alternately, EHR could potentially reflect deficits in discharge planning and outpatient management, calling for improvements in transplant care practices.[8]

While EHR have been studied extensively in American transplant settings, there is a paucity of EHR data collected in Canadian transplant populations. One Canadian study recently examined secular trends in post-transplant EHR incidence; however, it did not report on the impact of these findings on patients and healthcare delivery systems.[2] Due to significant differences in the delivery of healthcare services and patient outcomes between American and Canadian transplant centres [2], results from American studies cannot be readily extrapolated to Canadian populations.[2]

STUDY AIMS

The objectives of our study were to examine the impact of EHR on graft outcomes, patient mortality, LHR, and hospital costs in a Canadian transplant setting. We also considered how the impact on outcomes would change with an expanded EHR definition that included hospitalizations within 90-days of transplant discharge. With this information, we hope to generate knowledge that may be useful in developing strategies to reduce post-transplant EHR.

MATERIALS AND METHODS

Design and Setting

We conducted a single-centre observational cohort study at the University Health Network (UHN) in Toronto, Ontario. Approval was obtained from the Research Ethics Boards of both institutions.

Population and Sample

We included all adult (age ≥ 18 years) KTR who received a kidney transplant from 1 January 2009 to 31 December 2017 (with follow-up until 31 December 2018) at the Toronto General Hospital, University Health Network (UHN). KTR were excluded if they: (*a*) were multi-organ transplant recipients, (*b*) were transplanted at another transplant facility, (*c*) experienced primary graft non-function, or (*d)* experienced graft loss, death, or had their last follow-up before the study origin (i.e., 30 days after discharge from their transplant hospitalization).

Data Collection

Patient data was obtained from electronic hospital health records in the Organ Transplant Tracking Record (OTTR) and subsequently stored in the in-centre research database, the Comprehensive Renal Transplant Information System (CoReTRIS).[14] CoReTRIS consists of recipient, donor, transplant, treatment, and follow-up data for all kidney transplant recipients at UHN since January 2000 and has been audited for completeness and accuracy. All participants provided informed written consent for their health record information to be stored, collected, and used in CoReTRIS.

Exposure and Outcome Classification and Assessment

The main exposure of interest was EHR, defined as any hospitalization occurring within 30 days after discharge from the transplant hospitalization. We also examined an extended window of 90 days after discharge. The hospitalization must have been documented, either as an electronic summary in OTTR or as a paper discharge summary faxed from a non-UHN hospital. Hospitalization data was captured by a team of research assistants using a systematic review of medical records. Any discrepancies during data collection were later validated and resolved by a trained clinician.

The primary clinical outcome of interest was the composite of graft failure or death with graft function. Graft failure and death with graft function were also

examined separately as our secondary outcomes. The time of origin for the analyses was defined as either 30 days or 90 days after transplant discharge, therefore, we excluded KTR who experienced death, graft failure, or were lost to follow-up prior to this time. Other clinical outcomes included (1) graft function, which was measured using estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, at 6-months and 1-year post-transplant, and (2) LHR, defined as any hospitalization occurring between 31 and 365 days for 30day EHR, or 91 to 365 days for 90day EHR. The financial outcome of interest was the average cost of hospital-based care (inpatient and outpatient) per KTR over the first year of follow-up. This included all billed patient expenditures at each department of all hospitals that are part of UHN. Inpatient and outpatient cost data were provided by the UHN Accounting Centre, and evaluated using a single-centre perspective.

Potential Confounders

To assess the independent association between the exposure and outcomes, covariates were chosen based on the literature and clinical experience. Recipient factors (i.e., age, sex, race, body mass index (BMI) at time of transplant discharge, smoking history, diabetes mellitus, chronic lung disease, cardiovascular disease, baseline eGFR, and time on dialysis), donor factors (i.e., donor age, BMI at time of donation, donation type, expanded-criteria status), and transplant factors (i.e., peak panel reactive antibody (PRA), delayed graft function, acute rejection within 30 days of discharge, and transplant era) were considered in multivariable analyses.

Statistical Analysis

Categorical variables were described using frequencies and percentages. Continuous variables were described using mean (± standard deviation [SD]) if normally distributed and median (interquartile range [IQR]) if skewed. Baseline characteristics were compared between patients who experienced EHR and patients who did not experience EHR, using chi-square tests for categorical variables, Student t-

tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for skewed continuous variables. The Kaplan-Meier product limit method was used to assess time from 30 days post-discharge to graft failure, death or their composite by EHR status. Multivariable Cox proportional hazards models were used to estimate the independent association of EHR with graft failure, mortality, and LHR. Linear regression models were used to estimate the association between EHR and graft function during 1-year of post-transplant follow-up. Multiple imputation by chained equations method was used to address the missingness of all outcome variables.[15] A two-tailed *P* values < 0.05 were considered statistically significant. Data management and analyses were performed using Stata/MP 12.0 (StataCorp, College Station, TX). Statistical review of the study was performed by a biomedical statistician (Y.L. from Toronto General Hospital).

RESULTS

A total of 1,564 KTR were eligible for inclusion in the study cohort. Application of the pre-specified exclusion criteria resulted in a final study cohort of 1,368 KTR for 30-day EHR analyses (**Figure 1**). A final study cohort of 1,333 KTR was used for the 90-day EHR analyses, as five KTR experienced death, graft failure, or were lost to follow-up between 31 and 90-days post-transplant. For the 30-day EHR analysis, the median follow-up time was 5.11 years (IQR: 3.16, 7.59), with 329 cases of graft failure, 145 cases of death, and 439 cases of LHRs in the first year starting from 30 days after transplant discharge. For the 90-day EHR analysis, the median follow-up time was 5.05 years (IQR: 3.12, 7.52), with 324 cases of graft failure, 140 cases of death, and 368 cases of LHR in the first year starting from 90 days after transplant discharge.

Baseline recipient, donor, and transplant characteristics of both study cohorts are summarized in **Table 1**. The 30-day EHR study population was 60.0% male and 46.7% white. The 90-day EHR study population was 60.2% male and 47.4% white. A total of 307 (22.4%) and 394 (29.6%) KTR experienced 30-day and 90-day EHR, respectively. KTR who experienced an EHR were more likely to have a longer duration of dialysis,

an expanded donor criteria donor, a previous case of biopsy-proven acute rejection, and be transplanted between 2015-2017. Particularly, KTR with 90-day EHR were older, more likely to have a history of diabetes, spent a longer time on dialysis before transplant, had older donors, and similarly to 30-day EHR, were more likely to have a previous case of rejection and be transplanted between 2015-2017. Other characteristics were similar between the EHR and non-EHR groups.

The 30-day and 90-day EHR groups had greater cumulative probabilities of LHR within one year (Log rank $P < 0.001$, **Figure 2C** and **Figure 2D**) compared to the non-EHR group. Only the 90-day EHR group displayed a higher probability of death censored graft failure (Log rank $P = 0.02$ [**Figure 2F**]) as well as the composite outcome of graft failure and death (Log rank $P < 0.01$ [**Figure 2H**]), vs. the non-EHR group.

Thirty-day and 90-day EHR were independent predictors of LHR (HR 1.73 [95%CI: 1.40, 2.13] for 30-day EHR; HR 1.58 [95%CI: 1.27, 1.97] for 90-day EHR, [**Table 2A**]). Neither 30- nor 90-day EHR were associated with the other outcomes of interest in the multivariable Cox models. In multivariable linear regression models (**Table 2B**), 30- and 90-day EHR were associated with lower graft function at 3 mo (HR -2.60 [95%CI: -4.90, -0.30]) and 12 mo (HR -3.11 [95%CI: -5.62, -0.60]) for 30-day EHR; and lower function at 3 mo (HR -3.08 [95%CI: -5.17, -0.99]), 9 mo (HR -2.81 [95%CI: -5.24, -0.39]), and 12 mo (HR -3.77 [95%CI: -6.15, -1.38]) for 90-day EHR.

The mean cost of hospital-based care per KTR in the first year post-transplant is shown in **Figure 3**. In the first 3 mo, the mean cost of care for KTR with an EHR was nearly three times higher than for those without EHR (**Figure 3A**). After 3 mo, the mean cost of care for the EHR group declined to levels comparable to the non-EHR group, with an exception at month 7. Similarly, the mean number of readmissions for the EHR group decreased after the first 3 mo post-transplant, though the EHR group had more readmissions than the non-EHR group overall (**Supplementary Figure 1**). When the cost of hospital-based care was examined cumulatively, the mean post-transplant cost was consistently higher for the EHR group than the non-EHR group (**Figure 3B**).

DISCUSSION

In our patient cohort, the incidence of 30-day and 90-day EHR was 22.4% and 29.5%, respectively. The 30-day EHR incidence was lower than those reported in the American studies by Luan *et al.* (36%) [8] and McAdams-DeMarco *et al.* (31%) [9]. This may be related to differences in the study population, as well as specific threshold and institutional criteria for admitting KTR rather than outpatient care. Our results were comparable with the 30-day EHR incidence of 21% that was reported in a recent population-based Canadian study.[2] However, Naylor *et al.* found that 30-day EHR rates can vary even across different transplant centres within the province of Ontario, ranging from 16% to 27%.[2]

After accounting for potential confounders, 30-day and 90-day EHR were shown to be an independent predictor of LHR at 1-year post-transplant, and poorer graft function. Our results corroborate recent observational studies that associated EHR with negative clinical outcomes among KTR and other high-risk patient populations.[7, 16-21] More specifically, Luan *et al.* and McAdams-DeMarco *et al.* also demonstrated that EHR are associated with a higher risk of LHR and graft failure in KTR.[8,9] However, contrary to these studies, we did not find a statistically significant association between EHR and patient mortality. Additionally, while most studies focused on the impact of 30-day EHR,[9] we expanded our EHR definition and were able to demonstrate that hospitalizations occurring within the first 3 mo after transplantation discharge are also associated with rehospitalizations up to 1 year post-transplant.

The relationship between EHR and inferior patient outcomes can be explained in several ways. Post-transplant conditions or complications that necessitate EHR could directly result in clinical events like graft failure or frequent hospital readmissions.[8] Alternately, KTR with EHR may already possess pre-existing medical comorbidities (e.g., diabetes mellitus, cardiovascular disease) that increase the likelihood of adverse clinical events after transplantation. In our study, the EHR-group were more likely to have an expanded criteria donor and a history of acute rejection, which have been previously linked with mortality, graft failure, and hospitalizations after kidney

transplant.[5,22] EHR are also associated with frailty, which is a marker of suboptimal transplant outcomes.[12, 23-26] This factor may become increasingly important over time with an aging and subsequently a more co-morbid KTR population.[7] Moreover, patients transplanted in the more recent era (2015-2017) were more likely to have EHR as compared to earlier transplant years. The transplant program at our centre has been expanding its pool of patients among both recipients and donors in more recent years, to include more medically complicated patients such as expanded criteria donors.

EHR not only affect patient outcomes but are also detrimental from a financial perspective. We observed that, on average, twice as much money was spent on EHR patients as compared to non-EHR patients. Hospital readmissions increase the financial burden on the healthcare system, costing 1.8 billion CAD annually (11% of annual inpatient costs).[27] Moreover, the average cost of a second hospitalization is often greater than the first [27], which is particularly relevant to our finding that EHR increase the risk of LHR. Our analysis only focused on costs at a single transplant centre, thus the financial consequence might have been more significant if expenditure at other tertiary care centres and community-based hospitals were also taken into consideration.

Due to the risks and costs associated with EHR, there is considerable interest in clinical monitoring and prevention of EHR. However, despite the growing evidence in the literature, there are no specific clinical practice guidelines to manage and monitor KTR with EHR. After transplant discharge, KTR at the UHN Kidney Transplant Program are followed weekly for the first month, biweekly from months 2 to 3, monthly from months 4 to 6, bimonthly from months 7 to 12, every 3 to 4 mo from 13 to 24 mo, and then every 6 to 12 mo beyond 24 mo. [28] Like many other centres, a number of KTR with stable kidney function from the UHN program are transferred from the hospital-based transplant unit to community-based general nephrology centres within the first year post-transplant. Thus, although there are standard practices in place for KTR management in general, there are no standardized strategies that are tailored specifically for those KTR at risk of EHR.

KTR who are at increased risk of EHR may benefit from multifaceted interventions that include (1) better educational strategies to improve medication knowledge and support capacity for self-care, (2) collaborative care provided by transplant and general nephrologists, and (3) more frequent follow-up visits for an extended period of time.[2,9,29] Further investigation of these interventions would be required to determine the feasibility and efficiency of reducing EHR in KTR. Previous studies have suggested that up to half of hospital readmissions for KTR are preventable and can be reduced by early intervention.[30] Exploring the characteristics of KTR with preventable EHR can inform the development and evaluation of prediction tools, which will aid clinicians in identifying high-risk patients.[31]

With this study, we were able to extend the previous work on EHR and long-term outcomes of KTR to a Canadian healthcare context. Our methodology involved a standardized and comprehensive collection of patient and hospitalization data for a relatively large study population of over 1000 KTR.[14] Moreover, we benefited from exploring the use of 90-day EHR (in addition to the previously used 30-day EHR definition) for the assessment of outcomes. Nevertheless, some limitations to our study also warrant discussion. First, the generalizability of our findings may be limited by the single-centre study design. Second, this study was based on observational data and so, we cannot confirm that changes in EHR would improve long-term outcomes. Third, non-UHN readmissions may have been missed since we relied on UHN clinical notes to determine readmissions within the first year. However, it is unlikely that many events were missed since patients are instructed to contact the transplant centre if they are admitted to any facilities outside of UHN and hospitalization events are checked with each patient at every clinic visit. Finally, while patient and hospitalization data could be verified with patient charts and electronic records, our cost data was solely obtained from the UHN financial services and, therefore, was difficult to verify independently. However, these cost data are used for hospital planning and budgeting so are sufficient for their intended purpose in our study.

CONCLUSION

In summary, EHR after kidney transplantation were associated with a greater risk of LHR at 1-year post-transplant, suboptimal kidney function, and higher hospital-based care costs. The 90-day window after discharge from transplant hospitalization, in addition to the frequently used 30-day post-transplant period, marks a novel opportunity to evaluate the risks for KTR. Further studies are required to determine which EHR are preventable and implement reliable tools that can reduce EHR after kidney transplantation.

ARTICLE HIGHLIGHTS

Research background

Early hospital readmissions (EHR) post-kidney transplantation adversely impact clinical outcomes such as graft function and patient mortality, as well as healthcare costs. A better understanding of EHR can facilitate improved discharge planning and long-term outpatient management post kidney transplant.

Research motivation

Associations between EHR and suboptimal clinical outcomes post kidney transplant have not been extensively studied in a Canadian healthcare setting. We sought to explore the burden of EHR on kidney transplant recipients and the Canadian healthcare system in a large transplant centre.

Research objectives

The objectives of our study were to examine the impact of EHR on graft outcomes, patient mortality, late hospital readmissions, and hospital costs in a Canadian transplant setting.

Research methods

This was a single centre cohort study of 1,564 kidney transplant recipients (KTR) transplanted between 2009-2017. Analyses were separated by patients with no EHR, patients with EHR within 30 days of transplant, and those with EHR within 90 days of transplant. Multivariable Cox and linear regression models were used to examine EHR, late hospital readmissions (LHR) and outcomes including graft function and patient mortality.

Research results

EHR post kidney transplant are associated with subsequent LHR, suboptimal kidney function and a higher burden on the healthcare system.

Research conclusions

EHR post kidney transplant are associated with suboptimal patient outcomes and higher burdens on the healthcare system.

Expanding the window of readmissions to 90 days post-transplant reveals an important target for reducing the risk of suboptimal outcomes.

Research perspectives

A better understanding of EHR can contribute to the development of prediction tools to identify those KTR at risk of EHR, and thus a standardized approach to manage and target these patients.

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