Additional Burden of Intensive Care to Rehospitalizations Following Kidney Transplantation

A Study of Rate, Causes, and Risk Factors

Marzieh Lak,[1] Ali Reza Jalali,[1] Seyede Fateme Badrkhahan,[2] Mojgan Hashemi,[3] Mehdi Azizabadi Farahani,[3] Babak Kardavani,[4] Hafez Ghaheri,[4] Mohammad Mehdi Naghizadeh[4]

[1]Nephrology and Urology Research Center, Baqiyatallah Medical Sciences University, Tehran, Iran
[2]Shahrekord Medical Sciences University, Shahrekord, Iran
[3]Clinical Research Unit, Baqiyatallah Medical Sciences University, Tehran, Iran
[4]Medicine and Health Promotion Institute, Tehran, Iran

Keywords. kidney transplantation, intensive care units, hospitalization, patient readmission, health care costs

Original Paper

Introduction. Little information exists on the burden of intensive care unit (ICU) to the posttransplant rehospitalizations of kidney allograft recipients. We do not clearly know the extent of the need for ICU during rehospitalizations and causes of readmissions. In this study, we aimed to assess ICU admissions of kidney transplant recipients, to determine the risk factors of ICU admissions in rehospitalized patients, and to evaluate the additional burden of ICU admission.

Materials and Methods. A total of 581 posttransplant rehospitalizations of kidney transplant recipients were assessed for ICU admission. Clinical characteristics of the patients and the length of hospital stay, transplantation-admission interval, hospitalization costs, and mortality rate were reviewed.

Results. Twenty-five rehospitalized kidney transplant recipients (4.3%) had been admitted to ICU with kidney dysfunction (36.0%), cerebrovascular accident (24.0%), sepsis (16.0%), brain tumor (8.0%), brain abscess (4.0%), diabetic ketoacidosis (4.0%), trauma (4.0%), and hemodynamic shock (4.0%). The risk factors of referral to ICU were higher age (P = .001) and hospitalization for cerebrovascular accident (P = .001) and malignancy (P = .004). Additional burdens were 1.8, 3.3, and 11.4 times as high as the rehospitalization burden for the length of hospital stay, hospitalization costs, and mortality rate, respectively.

Conclusions. Age and some special causes of hospitalizations are risk factors of ICU admission of kidney transplant recipients, and this occurs in about 5% of rehospitalizations. Admission to ICU adds considerably to the burden of rehospitalizations, warranting measures to prevent conditions that lead to the need for intensive care in these patients.

IJKD 2008;2:212-7
www.ijkd.org

INTRODUCTION

Now, after achieving acceptable results of kidney transplantation clinical outcomes, a great shift of patients with the end-stage renal disease (ESRD) to those undergoing kidney transplantation is seen. However, one thing which slows down this promotion is the limitation in financial resources.[1] In this regard, minimization of rehospitalizations and its associated costs has been changed into our high-priority goals,[2,3] transplant centers try to identify the major determinants increasing costs to understand how those can be controlled, modified,

or decreased.[4] Readmissions after transplantation is one of the topics gaining attention,[5] because more than half of the kidney transplant recipients experience it during the first posttransplant year,[6] and in some cases, even multiple readmissions may happen.[7] Hence, as the minimization of healthcare costs mandates the focus on rehospitalizations, it is also essential to assess all factors that may add the costs of it.

Of several published studies relevant to hospital-based healthcare utilization after kidney transplantation, very few have focused on admissions to the intensive care unit (ICU).[8] As expected, and also based on some evidence, ICU admission is an additional burden for rehospitalizations.[9,10] To expand our knowledge regarding ICU admission in the case of posttransplant rehospitalizations, we aimed to answer these questions: first, what proportion of all rehospitalizations need ICU admission, and what are the main causes? Second, during the rehospitalizations, what are the risk factors of the need for ICU? And third, how much is higher the costs, length of stay, and mortality if the patient needs admission to ICU during posttransplant hospitalizations?

MATERIALS AND METHODS

Patients and Definitions

We conducted a retrospective study on 581 rehospitalizations of kidney allograft recipients from 2000 to 2006 in Baqiyatallah Hospital, in Tehran, Iran. The hospital has an internal ICU and a surgical ICU each with 10 beds. The internal ICU treats a heterogeneous adult population excluding cardiac patients. Rehospitalization was defined as a hospital admission that occurred for any reason after discharge from the initial transplantation hospitalization. Admission to ICU was considered as any admission to the internal or surgical ICU at the onset of hospitalization and during hospital stay.

Studied Risk Factors

Patients' age, sex, level of education, marital status, cause of ESRD, length of hospital stay, transplantation-admission interval (ie, the time interval between the initial transplantation and the rehospitalization afterwards), hospitalization charges, and mortality data were extracted from patients' hospital records. Diagnoses recorded at discharge were classified into broad categories of infection, graft rejection due to infection, graft rejection due to other causes, ischemic heart disease, cerebrovascular accident, diabetes mellitus, malignancy, and miscellaneous etiologies such as posttransplant diabetes mellitus, benign prostatic hyperplasia, posttransplant hypertension, anemia, intestinal necrosis, transient thrombotic purpura, and cholestasis.

Intensive Care Unit

Data regarding ICU admission including the use of mechanical ventilation was extracted from the ICU charts. The acute physiology and chronic health evaluation scores of ICU-admitted patients were not available. The clinical signs for which the patients were referred to ICU were categorized into focal neurological signs, unconsciousness, deep coma, and respiratory distress. Moreover, the final diagnosis in the ICU was recorded.

The costs of rehospitalization were considered from the societal perspective. It is noteworthy that all of the hospitalization costs of the kidney transplant patients in Iran are paid by the government and the patient and the insurance companies pay nothing for the costs. The hospitalization cost was defined as the total costs charged by the hospital for rehospitalization including the costs of hoteling, medications, surgical procedures, laboratory tests, imaging tests, and miscellaneous costs. In this study, the hospitalization costs included direct medical costs but not the indirect costs such as those related to productivity loss (ie, sick leave due to disease). Since the costs of hospitalizations were recorded in different years, it was necessary to adjust them for the inflation rates, so that comparing the costs across different years would make sense. Considering 2006 as our adjustment reference year, the costs recorded between 2000 and 2005 were adjusted with those of 2006, assuming an annual inflation rate of 10%. To make the final costs internationally comparable, the costs in Iranian Rials were converted to purchase power parity or international dollar (PPP $). The conversion rate for PPP $ was based on a recently published Iranian study calculating PPP $ to be equal to 2727 Rials according to the information from of the Central Bank of Iran and the World Bank database.[11]

Statistical Analyses

Data were analyzed using the SPSS software

(Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). In order to determine the proportion of all rehospitalizations with ICU admission and the main causes, frequency tables were used. To determine the risk factors of receiving intensive care among all rehospitalizations, ICU-admitted patients and other rehospitalized kidney transplant recipients were compared using the Mann-Whitney test and the Chi-square test. *P* values less than .05 were considered significant.

RESULTS

Rehospitalizations

Of 581 rehospitalized patients with a mean age of 40.2 ± 13.7 years, 393 (68%) were men. The cause of ESRD among rehospitalized patients included unknown etiology in 236 (40.6%), hypertension in 121 (20.8%), diabetes mellitus in 115 (19.8%), urologic disease in 66 (11.4%), glomerulonephritis in 40 (6.9%), and miscellaneous etiologies in 3 (0.5%). Most of the patients (96.2%) had received their transplants from a living unrelated donor, while living related and cadaver donors were the source of the transplant in 2.3% and 1.5%, respectively. Twenty-five of the 581 rehospitalized patients (4.3%) needed ICU admission during their hospital stay. Table 1 shows ESRD etiology and the primary diagnosis of rehospitalization in patients with and without ICU admission.

Causes of End-Stage Renal Disease (ESRD) and the Final Diagnoses in Rehospitalized Kidney Transplant Recipients Admitted or not Admitted to Intensive Care Unit (ICU)

Parameter	ICU (n = 25)	No ICU (n = 556)	*P*
ESRD cause			
Diabetes mellitus	6 (24.0)	109 (19.6)	.48
Hypertension	6 (24.0)	115 (20.7)	.65
Glomerulonephritis	1 (4.0)	39 (7.0)	.73
Urologic disorder	3 (12.0)	63 (11.4)	.62
Unknown	6 (24.0)	230 (41.4)	.31
Others	3 (12.0)	0	.67
Admission cause			
Infection	5 (20.0)	191 (34.4)	.14
Graft rejection due to infection	2 (8.0)	66 (11.9)	.56
Graft rejection due to other causes	7 (28.0)	165 (29.7)	.86
Ischemic heart disease	0	5 (0.9)	.63
Cerebrovascular accident	6 (24.0)	0	.001
Diabetes mellitus	1 (4.0)	12 (2.2)	.54
Malignancy	2 (8.0)	6 (1.1)	.004
Others	2 (8.0)	111 (20.0)	.14

According to the symptoms, ICU referral were due to unconsciousness in 11 (44.0%), focal neurological signs in 8 (32.0%), deep coma in 2 (8.0%), and respiratory distress in 4 (16.0%). The ICU diagnoses were delirium (due to creatinine rise during graft rejection) in 9 (36.0%), cerebrovascular accident in 6 (24.0%), sepsis in 4 (16.0%), brain tumor in 2 (8.0%), and brain abscess, diabetic ketoacidosis, pneumothorax, and hemodynamic shock each in 1 (4.0%). Mechanical ventilation was necessary in 8 patients (32.0%). Eight deaths (32.0%) occurred among the 25 ICU-admitted patients with the mortality causes being sepsis in 3 (37.5%), cerebrovascular accident in 2 (25.0%), and kidney dysfunction, hemodynamic shock, and diabetic ketoacidosis each in 1 (12.5%).

Risk Factors of Intensive Care Unit Admission

There was no significant difference between the ICU-admitted patients and other rehospitalized kidney transplant recipients in terms of sex distribution, ESRD cause, and transplantation-admission interval. The mean age was 49.4 ± 11.3 years in the ICU-admitted patients and 39.8 ± 14.1 years the other rehospitalized patients (*P* = .001).

The 25th, 50th, and 75th percentiles of the length of hospital stay were 7, 15, and 20 days for the ICU-admitted patients and 5, 8, and 13 days for the patients not admitted to ICU, respectively (*P* = .05). The same percentiles for hospitalization costs were PPP $ 3119, PPP $ 5969, and PPP $ 14 694 in the ICU-admitted patients, respectively. These values were PPP $ 1024, PPP $ 2319, and PPP $ 7838 in the other rehospitalized patients, respectively. The mean hospitalization costs were PPP $ 9075 and PPP $ 2725 in the two groups, respectively (*P* = .05). Inpatient mortality was more frequent among ICU admitted than other rehospitalized patients (*P* = .001). The amount of additional burden was 1.8, 3.3, and 11.4 times for the length of hospital stay, hospitalization costs, and inpatient mortality frequency, respectively.

DISCUSSION

During the posttransplant rehospitalizations, 4% of our kidney allograft recipients required intensive care because of kidney failure (36%), cerebrovascular accident (24%), sepsis (16%), brain tumor (8%), etc. The higher length of hospital stay,

hospitalization costs, and inpatient mortality in those admitted to ICU is an unquestionable fact, but the amount of additional burden imposed by ICU admission of kidney transplant recipients needs to be re-emphasized where minimization of costs and complications is the issue. We found that the burden of intensive care is 1.8 to 11.4 higher than other readmissions of kidney transplant recipients in terms of the length of hospital stay, hospitalization costs, and inpatient mortality. We did not find any other study to compare the mentioned rates with the literature. It has only been shown that the rate of ICU admissions during the whole posttransplant period ranges from 0.8% to 34%.[9,12] A part of this wide range may be the due to the difference in ICU settings which may or may not include cardiac care and postoperative care.[9,11,12] The differences in referral patterns to ICU by transplant physicians and availability of ICU beds in different settings may provide further explanations.[13] Different follow-up periods in the reported studies may be also an important factor.

In our study, most of those kidney transplant recipients who were admitted to ICU mainly had kidney dysfunction (graft rejection due to infectious or noninfectious causes), while neurological complications such as stroke, brain tumor, and brain abscess were less frequent causes of admission. Notwithstanding that some reports pointed to the common occurrence of stroke (8%) among kidney transplant patients,[14] others showed that nonneurological causes such as infections and sepsis as a main cause of the need for ICU during posttransplantation phase.[10,12,15]

In our study, the median of the time interval between the initial transplantation and the need for ICU rehospitalization was about 6 months, without any difference with those admissions without the need for ICU care. This interval has been also variable, from 3 to 4 months to 23 to 35 months.[9,10,12,15] This difference may be secondary to duration of waiting list before transplantation, duration of ESRD, and degree of medical comorbidities in transplanted subjects.

The additional burden of ICU admission was eleven-fold in terms of mortality rate. This may be lower in some transplantation centers as 16% to 32% rates have been reported so far.[9,10,12] According to the literature, the need for mechanical ventilation and the use of vasoactive drugs may affect the mortality of kidney transplant recipients in ICU.[10] Every 1 of 3 ICU-admitted patients in our study needed respiratory ventilation support. This rate was higher (more than half of the patients) in the study of Kirilov and colleagues.[12] The cause of admission may be also another important contributing factor. It is generally believed that the mortality rate of kidney transplant patients admitted to ICU is higher than that of other ICU-admitted patients.[9,12] in our country, the mortality rate in general ICUs has been reported to be from 22% to 38%.[16-18]

Our study demonstrated that the high age of the kidney transplant recipients increases the risk of ICU admission. This is in line with some other reports indicating that though a small proportion of all kidney transplant recipients are the elderly, they make up 26% of all posttransplant patients readmitted to ICU.[9] An increased need for ICU during posttransplant rehospitalizations may be expected when we think of the increasing trend in of long-term complications among kidney transplant recipients, which is itself partly due to improvements in patient and graft survival.[19]

This study also indicates that the additional costs imposed to the healthcare system by posttransplant ICU admissions was about 3.3 times higher than general rehospitalizations. A part of this additional cost is due to the additional length of hospital stay of ICU which is about 1.8 times longer than that of other departments. Admission to ICU, according to the literature as well as our results, is the largest contributor to the costs of posttransplant rehospitalizations.[20]

Considering the high burden associated with the need for ICU for kidney transplant patients, attention to the risk factors of any causes leading to ICU need. Regarding malignancies, cancer surveillance regimens and posttransplant screening should be used.[21,22] The Clinical Practice Guidelines Committee of the American Society of Transplantation published guidelines for outpatient evaluation of adult and pediatric kidney transplant candidates.[23] Included in these guidelines are recommendations for cancer screening and early detection. Compliance of transplant teams in incorporating standard cancer prevention recommendations into the initial evaluation should be increased. Regular cancer prevention and screening strategies have been developed and should be taking into action.

Studies in the general population have led to the development of cancer screening guidelines in transplant recipients.[24] The efficacy of preventive strategies should also be assessed.[25]

According to this study, another important issue in kidney transplant recipients is prevention of cerebrovascular accidents. Preventive strategies for cerebrovascular accidents have been less frequently published, and some of them have not been proved to be effective.[26-28] In addition, although graft rejection was not a risk factor in our study, most of the ICU-admitted patients had a diagnosis of graft rejection. In this case, different guidelines exist and the role of medications compliance and monitoring of blood level of medications is very important.[29,30] Controlling the drugs might be the easiest prevention strategy.

Several factors may affect the prognosis of ICU-admitted patients, best measured by such standard scores as the acute physiology and chronic health evaluation scores which was unfortunately unavailable for analysis in our study. In addition, because of inadequate sample size of ICU-admitted recipients, we did not determine the predictors of mortality.

CONCLUSIONS

Admission to ICU, which is needed in about 5% of all posttransplant hospitalizations of kidney allograft recipients, increases nearly 2-fold the length of hospital stay, nearly 3-fold the hospitalization cost, up to 11-fold the inpatient mortality. Further studies to determine other risk factors other than age, cerebrovascular accident, and malignancies, which were introduced in this study, are needed to expand our knowledge regarding this neglected but important topic of the posttransplant care economy. More research to address this issue seems essential.

FINANCIAL SUPPORT

This study was fully supported and funded by Baqiyatallah Medical Sciences University.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ghoddousi K, Ramezani MK, Assari S, et al. Primary kidney disease and post-renal transplantation hospitalization costs. Transplant Proc. 2007;39:962-5.
2. Nemati E, Pourfarziani V, Jafari AM, et al. Prediction of inpatient survival and graft loss in rehospitalized kidney recipients. Transplant Proc. 2007;39:974-7.
3. Pourfarziani V, Rafati-Shaldehi H, Assari S, et al. Hospitalization databases: a tool for transplantation monitoring. Transplant Proc. 2007;39:981-3.
4. Johnson CP, Kuhn EM, Hariharan S, Hartz AJ, Roza AM, Adams MB. Pre-transplant identification of risk factors that adversely affect length of stay and charges for renal transplantation. Clin Transplant. 1999;13:168-75.
5. Henderson R, Carlin D, Kohlhase K, Leader S. Multicenter US study of hospital resource utilization associated with cytomegalovirus-related readmission of renal and heart transplant patients. Transpl Infect Dis. 2001;3 Suppl 2:57-9.
6. Neylan JF, Sullivan EM, Steinwald B, Goss TF. Assessment of the frequency and costs of posttransplantation hospitalizations in patients receiving tacrolimus versus cyclosporine. Am J Kidney Dis. 1998;32:770-7.
7. Pour-Reza-Gholi F, Labibi A, Farrokhi F, Nafar M, Firouzan A, Einollahi B. Signs and symptoms of cytomegalovirus disease in kidney transplant recipients. Transplant Proc. 2005;37:3056-8.
8. Naderi M, Aslani J, Hashemi M, Assari S, Amini M, Pourfarziani V. Prolonged rehospitalizations following renal transplantation: causes, risk factors, and outcomes. Transplant Proc. 2007;39:978-80.
9. Sadaghdar H, Chelluri L, Bowles SA, Shapiro R. Outcome of renal transplant recipients in the ICU. Chest. 1995;107:1402-5.
10. Kaplan LJ, Bailey H, Formosa V. Airway pressure release ventilation increases cardiac performance in patients with acute lung injury/adult respiratory distress syndrome. Crit Care. 2001;5:221-6.
11. Roshandel D, Rezailashkajani M, Shafaee S, Zali MR. A cost analysis of functional bowel disorders in Iran. Int J Colorectal Dis. 2007;22:791-9.
12. Kirilov D, Cohen J, Shapiro M, Grozovski E, Singer P. The course and outcome of renal transplant recipients admitted to a general intensive care unit. Transplant Proc. 2003;35:606.
13. Vincent JL. European attitudes towards ethical problems in intensive care medicine: results of an ethical questionnaire. Intensive Care Med. 1990;16:256-64.
14. Ponticelli C, Campise MR. Neurological complications in kidney transplant recipients. J Nephrol. 2005;18:521-8.
15. Candan S, Pirat A, Varol G, Torgay A, Zeyneloglu P, Arslan G. Respiratory problems in renal transplant recipients admitted to intensive care during long-term follow-up. Transplant Proc. 2006;38:1354-6.
16. Mohammadi H, Haghighi M. Survey relationship of mortality rate of hospitalized patients in ICU with different degrees of APACHE II. J Med Fac Guilan Univ Med Sci. 2006;59:85-90.
17. Mahoori AR, Heshmati F, Noroozinia H, Abbasivash R, Noroozinia S, Salmani M. The role of resident anesthesiologist in the reduction of mortality and morbidity

in intensive care units. J Iran Soc Anesthesiol Intensive Care. 2003;41:17-22.

18. Abrisham Kar S, Abedin Zadeh MR, Arti HR, Hooshmand F. Analysis of the etiology and mortality in the ICU of Kashani general hospital of Shahrekord between 1998 until 2001. Shahrekord Univ Med Sci J. 2004;3:73-8.
19. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000;342:605-12.
20. Oostenbrink JB, Kok ET, Verheul RM. A comparative study of resource use and costs of renal, liver and heart transplantation. Transpl Int. 2005;18:437-43.
21. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol. 2006;154:498-504.
22. Kiberd BA, Keough-Ryan T, Clase CM. Screening for prostate, breast and colorectal cancer in renal transplant recipients. Am J Transplant. 2003;3:619-25.
23. Kasiske BL, Ramos EL, Gaston RS. The evaluation of renal transplant candidates: clinical practice guidelines. Patient Care and Education Committee of the American Society of Transplant Physicians. J Am Soc Nephrol. 1995;6:1-34.
24. Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: what is the evidence? Clin J Am Soc Nephrol. 2008;3 Suppl 2:S87-S100.
25. Firooz A, Amin-Nejad R, Bouzari N, Nafar M, Firoozan A, Mahdavi-Mazdeh M. Sun protection in Iranian kidney transplant recipients: knowledge, attitude and practice. J Eur Acad Dermatol Venereol. 2007;21:754-7.
26. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82:603-11.
27. Townsend RR. Stroke in chronic kidney disease: prevention and management. Clin J Am Soc Nephrol. 2008;3 Suppl 1:S11-6.
28. Aull-Watschinger S, Konstantin H, Demetriou D, et al. Pre-transplant predictors of cerebrovascular events after kidney transplantation. Nephrol Dial Transplant. 2008;23:1429-35.
29. Marks R, Finke J. Biologics in the prevention and treatment of graft rejection. Springer Semin Immunopathol. 2006;27:457-76.
30. Knight SR, Morris PJ. The clinical benefits of cyclosporine C2-level monitoring: a systematic review. Transplantation. 2007;83:1525-35.

Correspondence to:
Marzieh Lak, MD
Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Mollasadra Ave, Vanak Sq, Tehran, Iran
Tel: +98 21 8126 4150
Fax: +98 21 8803 7561
E-mail: cru_common@yahoo.com

Received April 2008
Revised June 2008
Accepted July 2008