

Neoplasms and renal transplantation: impact of gender, comorbidity and age on in-hospital mortality. A retrospective study in the region Emilia-Romagna of Italy

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Abstract. – OBJECTIVE: The aim of this retrospective study was to investigate the relationship between cancer, non-immunologic comorbidity, estimated by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codification, gender and in-hospital mortality (IHM) in a large sample of renal transplant recipients (RTRs) living in the region Emilia-Romagna (RER) of Italy.

PATIENTS AND METHODS: We evaluated IHM in RTRs admitted between 2000 and 2013 recorded in the RER database. By using ICD-9-CM codes, the Elixhauser index (EI) was calculated, and cancers were identified and classified as skin cancers (SC), solid organ cancers (SOC) and post-transplant lymphoproliferative disorders (PTLD). IHM was the dependent variable of the multivariate models, while age, gender, EI corrected removing the effect of malignancies (cEI), and different types of cancer were the independent ones.

RESULTS: During the examined period, a total of 9,063 admissions in 3,648 RTRs were recorded, of whom 117 died (3.2%). The mean age was 52.9±13.1 years. Cancers were reported in 580 admissions (6.4%), and mean cEI was 3.5±3.4. Deceased RTRs were older, had a higher prevalence of PTLD and SOC, and had a higher cEI than survivors. IHM was independently associated with (in decreasing order) PTLD (OR 12.431, 95%CI 5.834-26.489, $p<0.001$), SOC (OR 6.804, 95%CI 4.323-10.707, $p<0.001$), female gender

(OR 1.633, 95%CI 1.057-2.523, $p=0.006$), cEI (OR 1.106, 95%CI 1.068-1.145, $p<0.001$), and age (OR 1.049, 95%CI 1.031-1.068, $p<0.001$)

CONCLUSIONS: Cancer, in particular SOC and PTLD, is strongly associated with IHM in RTRs. On the other hand, rather surprisingly, female gender exhibited a stronger association with IHM than other more expected factors, such as comorbidity and age.

Key Words:

Neoplasms, Kidney transplantation, Sex, Comorbidity, Gender, In-hospital mortality.

Introduction

Cancer represents one of the leading causes of mortality in renal transplant recipients (RTRs)¹. RTRs population is rapidly growing due either to the increasing number of patients and longer graft survival, reaching up to 20 years with a functioning graft. Recently, McCaughan and Courtney identified factors associated with prolonged survival and described the clinical course of RTRs after two decades of transplant function. They reported that cancer was the commonest cause of death and de novo malignancy developed in

37% of RTRs², in spite of the several therapeutic options currently employed³. Moreover, renal function should be considered in patients with advanced cancer⁴.

Although hemodialysis is a life-saving renal replacement modality for end-stage renal disease (ESRD), it also represents a major challenge to the intravascular innate immune system, and chronic inflammation is strongly associated with cardiovascular (CV) disease in these patients⁵. Moreover, patients undergoing maintenance hemodialysis develop both structural and functional cardiovascular abnormalities, and show a high cardiovascular mortality^{6,7}. Previous studies from our group showed an independent association between renal dysfunction and in-hospital mortality (IHM), in particular with myocardial infarction⁸, stroke⁹, and severe chronic obstructive pulmonary disease¹⁰. On the other hand, morbidity and mortality in RTRs could also be related to non-traditional CV factors¹¹. In fact, data from the United Network of Organ Sharing (UNOS) registry graft survival showed that 43% of graft failures could be ascribed to non-immunological factors¹². In a previous study, we investigated the relationship between IHM, cardiovascular events and non-immunologic comorbidity using codes of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). We found that age and comorbidity were independently associated with IHM, admission due to major CV events, and the combined outcome¹³.

The relationship between cancer, comorbidity, and mortality in RTRs is still a matter of debate, especially when considering IHM, and no data are available for subgroups by gender. Thus, the aim of this study was to investigate the relationship between cancer, non-immunologic comorbidity, estimated on the basis of ICD-9-CM codification, gender, and IHM in a large sample of RTRs in living in the region Emilia-Romagna (RER) of Italy.

Patients and Methods

Patient Selection and Eligibility

This retrospective study, conducted in agreement with the declaration of Helsinki, included all hospital admissions of RTRs between January 1, 2000, and December 31, 2013, recorded in the RER database, maintained by the Center for Health Statistics. RER is situated in the North-East of Italy and the total population is around

4,400,000 people (~7% of Italy as a whole). Since 1999, the RER has been storing all Discharge Hospital Sheets (DHS) of patients admitted to all the regional hospitals in an electronic database. The DHS lists name, gender, date of birth, date and department of hospital admission and discharge, vital status at discharge, length of stay, charge details, main and up to 15 accessory discharge diagnoses, and the most important diagnostic procedures, based on the ICD-9-CM. In agreement with national dispositions by law regarding privacy, all potential identifiers from the database provided for this study have been removed, and only a consecutive identification number has been given to every record, corresponding to a single admission. Thus, this work included only RTRs, considering all cases of admission because of any complications recorded from 2001 to 2013. The inclusion criterion was the identification of the ICD-9-CM code V420. ICD-9-CM codes were used to identify all different types of cancers, and to calculate the Elixhauser index (EI)¹⁴. Finally, IHM was also recorded. In the case of patients admitted to one hospital and then transferred to another, one only admission was considered (with date of hospitalization referring to the admission hospital and final diagnosis made by the discharging hospital). Neoplasms were grouped in skin cancers (SC, including melanoma), solid organ cancers (SOC), and post-transplant lymphoproliferative disorders (PTLD).

Data Collection

Since the administrative regional database does not provide clinical information, we considered as main outcome IHM, considering fatal cases (death during hospitalization) and non-fatal cases (patient discharged alive). EI was calculated for evaluation of non-immunologic comorbidity¹⁴, based on presence of paralysis, drug abuse, metastatic cancer, peptic ulcer disease excluding bleeding, obesity, alcohol abuse, peripheral vascular disorders, valvular disease, other neurological disorders and rheumatoid arthritis/collagen disorders. Finally, to avoid overestimation, EI was corrected with the exclusion of the diagnosis of cancer from the index calculation, so obtaining a corrected index (cEI). Moreover, according to codification algorithms for defining comorbidities, SC were identified by codes 172.x-173.x, SOC by codes 140-172.x, 174.x-195.x, 196.x-199.x, and PTLD by codes 200.x-202.x, 203.0, 238.6¹⁵.

Table I. Characteristics of the population investigated. RTRs: renal transplant recipients; PTLD: posttransplant lymphoproliferative disorders; *Elixhauser index corrected with the exclusion of the diagnosis of cancer from the index calculation.

Number of admissions	9063
Number of RTRs	3648
Admissions in male (n (%))	5703 (62.9%)
Admissions in female (n (%))	3360 (37.1%)
Age (years)	52.9±13.1
Corrected Elixhauser index*	3.5±3.4
Deceased (n (%))	117 (3.2%)
Total cancers (n (%))	580 (6.4%)
Solid organ cancers (n (%))	370 (4.1%)
PTLD (n (%))	107 (1.1%)
Skin cancers (n (%))	103 (1.1%)

Statistical Analysis

Readmissions are a frequent event in solid organ transplant patients¹⁶. Thus, since one patient could have had multiple admissions, admissions of different RTRs were considered as a single record. The data have been expressed as absolute numbers, percentages, and means ± SD. We compared survivors and deceased during admission, and the analysis of the variables was conducted using Chi-Squared, Student *t*-tests or Mann Whitney U test, as appropriate. To estimate the risk of IHM, a logistic multivariate analysis regression was carried out determining the odds ratios with their 95% confidence interval (CI), in which IHM represented the dependent variable, and age, gender, cEI, and diagnosis of SC, SOC and PTLD were the independent ones. A two-sided *p* < 0.05 was considered significant. For statistical analy-

sis, SPSS 13.0 for Windows 2004 was used (SPSS Inc., Chicago, IL, USA).

Results

The total sample consisted of 9,063 admissions related to 3,648 patients, with 117 deaths (3.2%). All clinical characteristics of the population studied are reported in Table I. The mean age was 52.9±13.1 years, and the number of mean admissions per patient was 2.5. Admissions in male patients were 5,703 (62.9%). Cancers were reported in 580 admissions (6.4%), and mean cEI was 3.5±3.4. SC were recorded in 103 admissions (1.1%), PTLD in 107 admissions (1.1%) and SOC in 370 admissions (4.1%). Comparison between deceased and discharged RTRs is reported in Table II. Deceased RTRs were more likely to be male (75.2 vs. 62.8%, *p*=0.006), to be older (61.6±10.2 vs. 52.8±13.1 years, *p*<0.001), to show higher cEI (6.1±5.9 vs. 3.4±3.9, *p*<0.001), to have higher prevalence of cancer (35 vs. 6%, *p*<0.001), PTLD (7.7 vs. 1.1%, *p*<0.001), and SOC (20 vs. 3.9%, *p*<0.001) than survivors. On the contrary, prevalence of SC was not different in the two groups of RTRs (2.6 vs. 1.1%, *p*=ns). In-hospital mortality was independently associated (in decreasing order) with PTLD (OR 12.431, 95%CI 5.834-26.489, *p*<0.001), SOC (OR 6.804, 95%CI 4.323-10.707, *p*<0.001), female gender (OR 1.633, 95%CI 1.057-2.523, *p*=0.006), cEI (OR 1.106, 95%CI 1.068-1.145, *p*<0.001), and age (OR 1.049, 95%CI 1.031-1.068, *p*<0.001) (Table III and Figure 1).

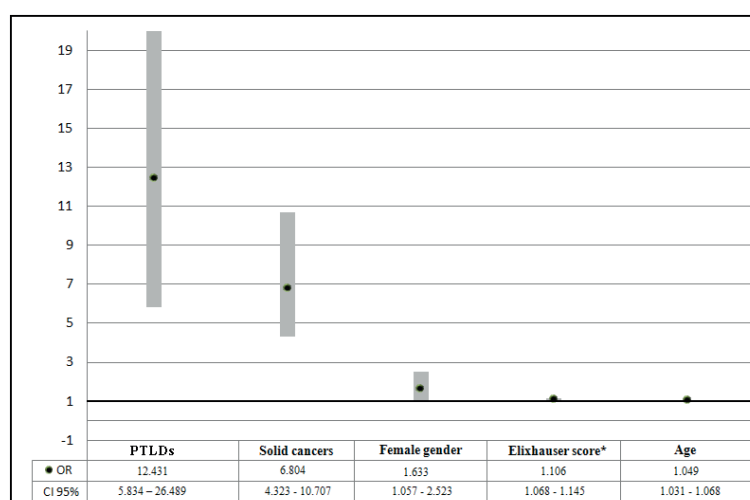


Figure 1. Strength of association between factors investigated and in-hospital mortality: odds ratio: OR, with 95% Confidence Intervals: CI). PTLD: posttransplant lymphoproliferative disorders. *Elixhauser index corrected with the exclusion of the diagnosis of cancer from the index calculation.

Table II. Comparison between deceased and discharged renal transplant recipients. PTLD: posttransplant lymphoproliferative disorders; *Elixhauser index corrected with the exclusion of the diagnosis of cancer from the index calculation.

	Discharged (n=8946)	Deceased (n=117)	p
Male (n (%))	5615 (62.8%)	88 (75.2%)	0.006
Female (n (%))	3331 (37.2%)	29 (24.8)	
Age (years)	52.8±13.1	61.6±10.2	<0.001
Corrected Elixhauser index*	3.4±3.9	6.1±5.9	<0.001
Total cancers (n (%))	539 (6%)	41 (35%)	<0.001
Solid organ cancers (n (%))	346 (3.9%)	24 (20%)	<0.001
PTLD (n (%))	98 (1.1%)	9 (7.7%)	<0.001
Skin cancers (n (%))	100 (1.1%)	3 (2.6%)	NS

Discussion

On one hand, this study shows that cancer, in particular SOC and PTLD, is strongly associated with IHM in RTRs, suggesting that RTRs are admitted to hospitals even if cancer disease is very advanced. It could be that in Italy palliative care is not adapted to solid organ transplantation recipients. On the other, rather surprisingly, female gender exhibits a stronger association with IHM than other more expected factors, such as comorbidity and age.

ESRD per se could be considered a risk factor for cancer. A large study evaluating a cohort of 831,804 patients on dialysis treatment in the USA, Europe, Australia, or New Zealand (years 1980-1994), showed that 3% (25,044 subjects) developed cancer (compared with an expected number of 21,185)¹⁷. The higher risk was observed in patients younger than 35 years, gradually decreasing with increasing age. High risks were observed for cancer of the kidney, bladder, and thyroid and other endocrine organs. The authors concluded that in uremia the excess of risk could be ascribed to effects of underlying renal or urinary tract disease, or of loss of renal function, on the kidney and bladder, and probably to increased susceptibility to viral carcinogenesis¹⁷. A further evaluation of the same population confirmed that

the risk for kidney and bladder cancer was increased, relatively more in younger than older patients and in females than male¹⁸.

In RTR subjects, cancer could develop in three different ways, i.e., *de novo* occurrence in the recipient, recurrent malignancy in the recipient or transmission of malignancy from the donor. In this special population, the main risk factors for cancer include immunosuppression, conventional risk factors, such as age and smoking, chronic viral infection, genetic risk factors, and history of treatment with cytotoxic agents¹⁹. Farrugia et al²⁰, in the United Kingdom, reported that among 19,103 RTRs, 2,085 died and 376 deaths (18%) were cancer-related, with a crude mortality rate of 361 per 100,000 person-years. The median age of the cohort was 45 years, and the risk for malignancy-related death raised with increasing age being 0.8, 2.5, 4.8, 6.5, and 9.1%, respectively, in subjects aged <50, 50-59, 60-69, 70-79, and over 80 years. A relative excess of risk, although with borderline statistical significance, was shown for females. Cox regression analysis showed that cancer mortality risk was independently associated with increased age, receipt of a deceased donor kidney, pre-transplant malignancy history, and cerebral vascular accident²⁰. Data from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) registry

Table III. Factors independently associated with in-hospital mortality in renal transplant recipients. PTLD: posttransplant lymphoproliferative disorders; *Elixhauser index corrected with the exclusion of the diagnosis of cancer from the index calculation.

	OR	95% C.I.	p
Age	1.049	1.031 - 1.068	<0.001
Female	1.633	1.057 - 2.523	0.006
Corrected Elixhauser index*	1.106	1.068 - 1.145	<0.001
Solid organ cancers	6.804	4.323 - 10.707	<0.001
PTLD	12.431	5.834 - 26.489	<0.001

(168,156 patients who started renal replacement therapy between 1993 and 2007), reported 4.6 cancer-related deaths per 1,000 person-years²¹. Again, data from Ontario, Canada, on 85,557 person-years of follow-up collected between 1991 and 2010, reported that out of 3,068 deaths, 603 (20%) were cancer-related¹. Different results were reported in the United States Renal Data System²². The authors calculated 1,937 cancer deaths and 36,619 non-cancer deaths among 164,078 first kidney-only RTRs. The observed cancer death rate was 206 per 100 000 patient-years compared to an expected rate of 215 per 100,000 patient-years in the general population²².

In 2008, a Spanish group observed that risk factors associated with development of any malignancy were age, number of grafts, tacrolimus treatment, and time post-transplantation²³. In 2015, the same authors analyzed prognosis and survival of SOC, PTLT, and non-melanoma skin cancer (NMSC) in 1,450 kidney transplants recipients, with a mean follow-up of 10 years²⁴. SOC, PTLT, and NMSC incidences were 6.2%, 1.2%, and 6%, respectively, and risk factors associated with developing SOC and PTLT were patient age and time post-transplant, whereas for NMSC were male gender, assumption of calcineurin inhibitors, patient age, and time post-transplant²⁴. Data from a single-center Greek experience (1983-2013) in 2,054 RTRs, showed visceral malignancies developed in 74 patients (3.6%)²⁵. Mean age at transplant was 43.9 years, and mean age at death was 61.9 years. Sixty-eight patients (91.9%) died with a functioning graft, and fifty-four (73%) died during follow-up. The mean time from transplant to malignancy was 96.4 months, and from malignancy to death was 27.5 months²⁵. An interesting paper from the Transplant Cancer Match Study, which links the U.S. transplant registry with 15 cancer registries, analyzed cancer occurrence in re-transplanted RTRs (n=245) and primary RTRs (n=5757)²⁶. Overall cancer risk was similar in re-transplants compared with primary recipients (incidence rate ratio [IRR] 1.06, 95% CI 0.93-1.20, adjusted for age, gender, race/ethnicity). However, renal cell carcinoma (RCC) occurred in excess among re-transplants (adjusted IRR 2.03, 95% CI 1.45-2.77), based on 514 cases in primary recipients and 43 cases in re-transplants²⁶. As for age and risk of mortality, Karim et al [27] analyzed data for 19,103 kidney transplant procedures, with a median follow-up of 4.4 years, and reported 2,085 deaths. The mortality risk increased with age, being 5.8, 14.2, 22.0, 31.9 and

45.5%, respectively, below 50 years, 50 to 59, 60 to 69, 70 to 79, and 80 years and above. The three most common causes of deaths for recipients 70 and over were cardiac (21.2%), infection (21.2%), and malignancy (20.2%), respectively²⁷. As for gender, data from the Bureau of National Health Insurance of Taiwan (1999-2007), enrolling 2,245 RTRs who developed urologic malignancy and matched with 8,980 incident ESRD, showed that female gender (hazards ratio, 2.10; 95% CI, 1.52-2.95) but not male gender (hazards ratio, 1.47; 95% CI, 0.93-2.32) was determined to be an independent factor for the development of urologic malignancy after kidney transplantation²⁸.

The present study has several limitations, mainly due to its retrospective design and utilization of administrative data, based on ICD-9-CM codes. The main limit is the lack of clinical data, necessary to stratify the risk of all types of cancers and the lack of information about treatment. Furthermore, it is likely that administrative comorbidity data underestimate the true prevalence of comorbid conditions. Again, mortality assessment was limited to all-cause IHM with inability to determine whether deaths were related to malignancy or to other hospital-acquired events. With this respect, there was no “present on admission” flag for diagnoses of cancer in the analyzed dataset, so that it is also possible that subjects were affected by cancer before admission or malignancy could have been diagnosed during admission. On the other hand, however, there is convincing evidence that use of administrative data makes possible to predict hospital admissions and complications²⁹. This study also has the significant strength of its large sample size, we analyzed the regional hospital database, allowing a representative picture of Italian clinical management of RTRs. Moreover, at least to the best of our knowledge, this is the first study in Italy considering the relationship between malignancy and IHM in RTRs.

Conclusions

RTRs are exposed to the risk of IHM related to occurrence of malignancies. However, this risk involves not only RTRs but also for other organ transplants. Recent data from the Taiwan National Health Insurance Research Database, analyzed 5,396 cases, comprising 801 heart, 2,847 kidney, and 1,748 liver transplant recipients between 2001 and 2012³⁰. Compared with the general population, the risk of cancer increased 3.8-fold

after heart transplantation, 4.1-fold after kidney transplantation and 4.6-fold after liver transplantation. Interestingly, differences by gender were found in types of cancer: male recipients had an increased risk of cancers of the head and neck and liver, and female kidney recipients had a significant risk of bladder and kidney cancer³⁰. Again, data from the United States (229,300 U.S. solid organ transplant recipients linked with 15 stage/regional cancer registries (1987-2012), showed that among recipients of different organs, kidney recipients had the highest occurrence of thyroid cancer (RR = 1.26, 95% CI 1.03-1.53), even if post-transplantation diagnosis of thyroid cancer was associated with modestly increased risk of death (HR = 1.33, 95% CI 1.02-1.73)³¹.

Despite our previous studies showed that age and comorbidity were independently associated with cardiovascular events and IHM in RTRs¹³, in this study focused on cancer-related deaths, female gender exhibited an even stronger association with IHM (OR 1.66) than comorbidities and age. Interesting data, although regarding a small population, come from a Korean study on 248 kidney transplant patients who underwent a colonoscopy (1996 to 2008)³². Advanced colonic neoplasms were found in 8.1% of patients after kidney transplant, and the risk was 2.3 times greater in RTRs than in the matched subjects, increasing to 5.4 times in those aged ≥ 50 years³². Looking at the sub-analysis by gender, even if the results did not reach statistical significance, female gender was a risk factor both at univariate (HR 1.289, 95% CI 0.494-3.365) and at multivariate analysis (HR 1.124, 95% CI 0.380-3.322)³². On one hand, further researches are certainly needed to confirm these data and explore possible favoring causes. On the other, a particular attention should be devoted to gender differences, in terms of follow-up, careful physical examination, attempt of early diagnosis and treatment of cancer, especially evaluating impact of RNA^{33,34}.

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Conflict of Interest

The authors declare that there are not any potential conflicts of interests that are directly or indirectly related to the data presented in the paper.

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