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Abstract	The aim of this study was to relate in-hospital mortality (IHM), cardiovascular events (CVEs) and non-immunologic comorbidity evaluated on the basis of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codification, in Italian kidney transplant recipients (KTRs). We evaluated IHM and admissions due to CVEs between 2000 and 2013 recorded in the database of the region Emilia Romagna. The Elixhauser score was calculated for evaluation of non-immunologic comorbidity. Three main outcomes (i.e. IHM, admission due to major CVEs and combined outcome) were the dependent variables of the multivariate models, while age, gender and Elixhauser score were the independent ones. During the examined period, a total of 9063 admissions in 3648 KTRs were recorded; 1945 patients were males (53.3 %) and 1703 females (46.7 %) and the mean age was 52.9 ± 13.1 years. The non-immunological impaired status of the KTRs, examined by the Elixhauser score, was 3.88 ± 4.29. During the 14-year follow-up period, IHM for any cause was 3.2 % (n = 117), and admissions due to CVEs were 527 (5.8 %). Age and comorbidity were independently associated with CVEs, IHM and the combined outcome. Male gender was independently associated with IHM and combined outcome, but not with CVEs. Evaluation of non-immunological comorbidity is important in KTRs and identification of high-risk patients for major clinical events could improve outcome. Moreover, comorbidity could be even more important in chronic kidney disease patients who are waiting for a kidney transplant.

Keywords (separated by '-')	Renal transplantation - In-hospital mortality - Cardiovascular events - Elixhauser score - Comorbidity - ICD-9-CM
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Impact of comorbidity on outcome in kidney transplant recipients: a retrospective study in Italy

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Abstract The aim of this study was to relate in-hospital mortality (IHM), cardiovascular events (CVEs) and non-immunologic comorbidity evaluated on the basis of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codification, in Italian kidney transplant recipients (KTRs). We evaluated IHM and admissions due to CVEs between 2000 and 2013 recorded in the database of the region Emilia Romagna. The Elixhauser score was calculated for evaluation of non-immunologic comorbidity. Three main outcomes (i.e. IHM, admission due to major CVEs and combined outcome) were the dependent variables of the multivariate models, while age, gender and Elixhauser score were the independent ones. During the examined period, a total of 9063 admissions in 3648 KTRs were recorded; 1945 patients were males (53.3 %) and 1703 females (46.7 %) and the mean age was 52.9 ± 13.1 years. The non-immunological impaired status of the KTRs, examined by the Elixhauser score, was 3.88 ± 4.29. During the 14-year follow-up period, IHM for any cause was 3.2 % ($n = 117$), and admissions due to CVEs were 527 (5.8 %). Age and comorbidity were independently associated with CVEs, IHM and the combined outcome. Male gender was independently associated with IHM and combined outcome, but not with CVEs. Evaluation of non-immunological comorbidity is important in KTRs and identification of high-risk patients for major clinical events could improve outcome. Moreover, comorbidity could be even more important in chronic kidney disease patients who are waiting for a kidney transplant.

Keywords Renal transplantation · In-hospital mortality · Cardiovascular events · Elixhauser score · Comorbidity · ICD-9-CM

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Introduction

In spite of improvements in immunosuppressive therapy in the last 20 years, cardiovascular disease (CVD) mortality remains the first cause of death in kidney transplant recipients (KTRs) [1]. Decreased renal function, traditional and nontraditional risk factors, and immunosuppressive therapy act synergistically in increasing CVD risk in KTRs [2], between 35 and 50 % of all-cause mortality has been ascribed to CVD [3–6]. Nevertheless, CVD mortality is lower in KTRs than in dialysis patients, but higher than in the general population [5]. The unadjusted annual death rates per 100 patient-years at risk for patients on dialysis, patients on the waiting list and KTRs, have been calculated as 16.1, 6.3, and 3.8, respectively [7]. The explanation for a higher CVD morbidity in KTRs than in the general

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population has been explained by a high prevalence of coronary artery disease [8] and left ventricular hypertrophy [9–13]. KTRs are exposed to traditional, non-modifiable and modifiable, CVD risk factors such as age, gender, family history, diabetes mellitus (DM) and tobacco intake [14]. Moreover, other CVD risk factors specifically related to uremia and transplantation need also to be considered [15], such as immunosuppressive drugs. Among these drugs, calcineurin inhibitors and steroids [16] can influence the development of hypertension [17], hyperlipidemia, [18] and hyperglycemia [19].

Previous studies from our group observe that in-hospital mortality (IHM) for myocardial infarction and stroke is higher in patients with renal dysfunction than in subjects with normal renal function [20, 21], but not for pulmonary embolism [22]. On the other hand, in KTRs, morbidity and mortality may be related to non-immunologic factors; therefore, co-morbid conditions have to be evaluated in these patients. Terasaki, using the United Network of Organ Sharing (UNOS) registry graft survival records, reports that 43 % of graft failures are attributable to non-immunological factors [23]. The relationship between renal transplantation and comorbidity is still a matter of debate, especially when considering IHM. Thus, the aim of this retrospective study was to investigate the risk factors for IHM and hospitalization attributable to CVD, taking into consideration non-immunologic comorbidity evaluated on the basis of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codification, in a large sample of KTRs in Italy.

Methods

Patient selection and eligibility

This study, conducted with the approval of the local institutional committee for human research, included all hospital KTR admissions between January 1, 2000, and December 31, 2013, recorded in the database of the region Emilia Romagna (RER) of Italy, maintained by the Center for Health Statistics. The RER is situated in north-eastern Italy, and has a total population of 4,400,000 people (7 % of the entire population of Italy). Since 1999, this region began to use an electronic database to track all Discharge Hospital Sheets (DHS) of patients admitted to all the regional hospitals. The DHS lists the 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 in terms of privacy, the RER Health authorities removed patient names, exact addresses, and other potential identifiers from the database provided for this study. A consecutive identification number for each patient was the only identification data allowed, to categorize admissions by age group and to identify multiple admissions of a single patient. Thus, the study included all KTRs, considering all cases of admission because of any complications recorded from 2001 to 2013. The inclusion criterion was the presence, as a main discharge diagnosis, of any cardiovascular event (CVE) cerebral, cardiac and peripheral such as myocardial infarction, stroke, congestive heart failure, and any intervention for aortic abdominal aneurysm and for peripheral re-vascularization, according to ICD-9-CM. The Elixhauser index was calculated taking into account ICD-9-CM codes, and IHM was also recorded. Finally, 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). The ICD-9-CM codes used to define KTRs was V420. The ICD-9-CM classifies chronic kidney disease (CKD) based on severity. The severity of CKD is designated by stages I-V. The code V420 defines the diagnosis of kidney transplant status or kidney replaced by transplant.

Data collection

As the administrative regional database does not provide clinical information, we considered as main outcomes: (a) IHM, considering fatal cases (death during hospitalization) and non-fatal cases (patient discharged alive); (b) admission due to major cardiovascular events (ICD-9-CM 014, 015, 016, 078, 121, 122, 123, 124, 125, 127, 129, 130, 140, 524, 559); (c) both a + b. The Elixhauser index was calculated for evaluation of non-immunologic comorbidity [24]. The Elixhauser score is able to identify the following most important limitations to individual wellness, such as 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. For ICD-9-CM codes for calculating the Elixhauser score we referred to Quan et al. [25].

Statistical analysis

All admissions of different KTRs were analyzed as a single record, so that one patient could have had different admissions. Readmissions are a frequent event in solid organ transplant patients [26]. The data are expressed as absolute numbers, percentages, and mean ± SD. The analysis of the variables was conducted using Chi squared, Student *t* tests or Mann–Whitney *U* test, as appropriate. To

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evaluate the risk of IHM, major CVEs and the combined outcome, logistic analysis regression was carried out determining the odds ratios with their 95 % confidence interval (CI). The three outcomes i.e. IHM, admission due to major cardiovascular events and the combined outcome were the dependent variables of the multivariate models, while age, gender and Elixhauser score were the independent ones.

Receiver operating characteristic (ROC) curves were generated to determine the discriminative ability of different cut-off, such as age >50 years and Elixhauser index equal or greater than 10 in predicting outcomes. The two cut-off levels were arbitrarily selected. However, non-immunological factors, such as age and comorbidity impact survival of CKD patients before kidney transplantation, and age older than 50 years and the Charlson comorbidity index were independently associated with mortality [27].

Statistical analysis was performed using SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, 2004, for statistical analysis of the demographic data.

Results

During the examined period, a total of 9063 admissions in 3648 KTRs were recorded, i.e. about 2.5 admissions per patient. Table 1 shows the characteristics of the analyzed population: 1945 patients were males (53.3 %) and 1703 females (46.7 %), and the mean age was 52.9 ± 13.1 years. The non-immunological impaired status of the KTRs, examined by the Elixhauser score, was 3.88 ± 4.29 (median value 5). Elixhauser index ≥10 was calculated in 926 subjects (10.2 %). During the 14-year follow-up period, IHM for any cause was 3.2 % ($n = 117$), and admissions due to CVEs were 527 (5.8 %). IHM and CVEs were recorded in 626 of the admissions analyzed (6.9 %), and were ascribed to older patients with higher comorbidity. Age, gender and Elixhauser score in subjects with and without CVEs, in survivors and deceased patients, and in those with or without combined outcome, are reported in Table 2. Duration of hospitalization was longer in deceased patients than in survivors (20.8 ± 20.1 vs 9.5 ± 11.9 days, $p < 0.001$). Thirty-three out of 117 deceased KTRs underwent major surgical procedures (8 gastrointestinal, 8 orthopedic, 6 cardiovascular, 6 other interventions), and 35 out of 117 deceased KTRs underwent dialysis treatment, the latter being performed in a higher percentage of patients in the deceased grout than in survivors (29.9 vs. 9 %, $p < 0.001$).

Results of logistic regression analysis are shown in Table 3. Age and comorbidity are independently associated with CVEs, IHM and the combined outcome. Moreover, male gender is independently associated with IHM and combined outcome, but not with CVEs.

ROC analysis showing areas under the curve (AUC) considering the cut-off of 50 years for age and 10 for Elixhauser score related to the 3 outcomes as shown in Figs. 1, 2 and 3.

Table 1 Data regarding the kidney transplant recipient admissions evaluated from January 1, 1999, and December 31, 2013, recorded in the database of the region Emilia Romagna of Italy, and maintained by the Center for Health Statistics (n = number)

Total admissions	9063
Total patients	3648
Age (years)	52.9 ± 13.1
Elixhauser score	3.88 ± 4.29
Deceased [n (%)][a]	117 (3.2)
Cardiovascular events [n (%)][b]	527 (5.8)
Total events [n (%)]	626 (6.9)

[a] Related to total number of patients

[b] Related to total number of admissions

Discussion

This was a retrospective cohort study considering a large number of KTRs, even though the number of events over a 14 years of follow-up was limited. However, in this study we investigated the impact of clinical non-immunologic factors on KTRs outcome, without considering the very complicated relationship between graft, recipient and immunosuppressive therapy. Results show that non-immunological comorbidity and age >50 years are related to the development of major CVEs and IHM, especially in male patients. Although we could not exclude the influence of immunologic factors, including immunosuppression, on development of different risk factors, comorbidity appeared to impact the outcome of KTRs. These results are in agreement with previous data on >1000 KTRs in Washington State, USA, showing that risk for hospitalization and fatal hospitalization are higher in KTRs than in the reference population; circulatory diseases are the top primary diagnostic category [28].

The impact of comorbidity on outcomes after kidney transplantation is still a matter of debate, since the progressive aging of the transplant recipient population might increase comorbidity [29]. Wu et al. studied the Charlson comorbidity index in patients who underwent kidney transplantation between January 1998 and January 2003. They find that high comorbidity i is associated with an increased risk for patient death, both in the perioperative period and >3 months after transplantation. They conclude that the Charlson comorbidity index is a practical tool for the evaluation of comorbidity in the transplant population,

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Table 2 Univariate analysis comparing age, sex and Elixhauser score in subjects with and without CVEs, in survivors and deceased patients and in those with or without combined outcome

	No-CVEs	CVEs	*p*	Survivors	Deceased	*p*	No outcome	With outcome	*p*
Number of admissions	8536	527		8946	117		8437	626	
Age	52.6 ± 13.2	58.8 ± 11.3	<0.001	52.8 ± 13.1	61.6 ± 10.2	<0.001	52.5 ± 13.2	59.2 ± 11.2	<0.001
Male sex	5345	358	0.014	5615	88	0.005	5270	433	0.001
Female sex	3191	169		3331	29		3167	193	
Elixhauser score	3.76 ± 4.18	5.85 ± 5.40	<0.001	3.81 ± 4.2	9.27 ± 6.93	<0.001	3.69 ± 4.09	6.44 ± 5.81	<0.001

CVEs cardiovascular events

Table 3 Logistic analysis regression results expressed as odds and 95 % confidence interval (CI) for determining the risk of CVEs (cardiovascular events), IHM (in-hospital mortality) and combined outcome

	CVEs		IHM		Total outcome	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Age	1.034 (1.026–1.042)	<0.001	1.045 (1.027–1.064)	<0.001	1.036 (1.028–1.043)	<0.001
Male sex	_	NS	1.544 (1.005–2.371)	0.047	1.218 (1.018–1.456)	<0.001
Elixhauser score	1.075 (1.056–1.093)	<0.001	1.1.65 (1.132–1.198)	<0.001	1.101 (1.084–1.119)	0.031

The three outcomes were the dependent variables of the multivariate models whilst age, gender, and Elixhauser score the independent ones

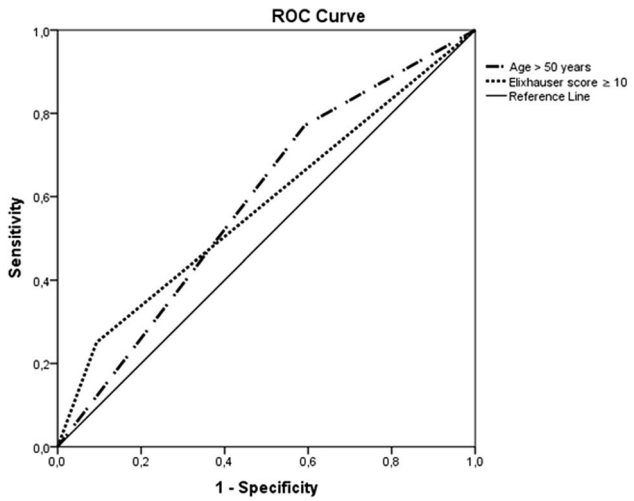

Fig. 1 ROC analysis showing areas under the curve (AUC) considering the cut-off of 50 years for age (0.590, 95 % CI 0.566–0.613; $p < 0.001$) and the cut-off of 10 for Elixhauser score (0.579, 95 % CI 0.551–0.606; $p < 0.001$) related to cardiovascular events

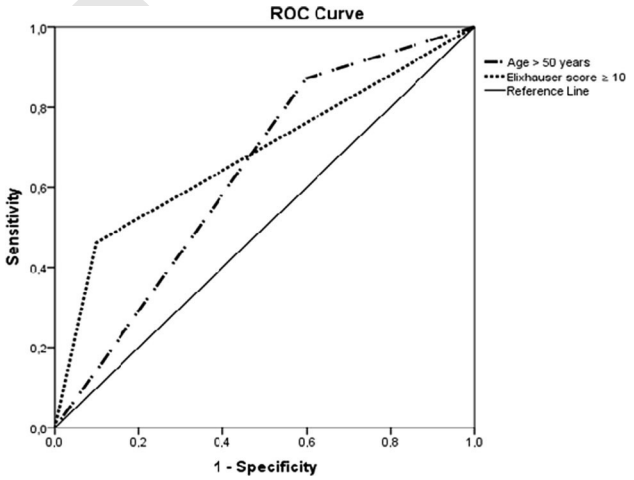

Fig. 2 ROC analysis showing areas under the curve (AUC) considering the cut-off of 50 years for age (0.637, 95 % CI 0.594–0.680; $p < 0.001$) and the cut-off of 10 for Elixhauser score (0.682, 95 % CI 0.625–0.739; $p < 0.001$) related to in-hospital mortality

which has an increasing burden of comorbid disease [30]. Baskin-Bey et al. studied a recipient risk score, retrospectively reviewing 47,535 adult recipients of deceased donor renal transplants between 1995 and 2002. They find that the strongest predictors of recipient survival after transplantation used in the recipient risk score are recipient age, history of DM, history of angina and time on dialysis therapy [31]. Karim et al. analyzed data of more than 19,103 KTRs, with 2085 deaths (10.9 %) during a median follow-up of 4.4 years [32]. Cardiac death is the most frequent event in subjects aged ≥70 years, together with infection and malignancy deaths; increasing age is a strong independent risk factor for death in KTRs.

Comorbidity should be taken into consideration independently from immunological parameters in KTRs, increasing Charlson comorbidity index scores are significantly related to graft and patient survival, especially when the Charlson comorbidity index is >1 [33].

Congestive heart failure, hypertension, venous thromboembolism, atrial fibrillation, cerebrovascular accidents and myocardial infarction are the main primary diagnoses

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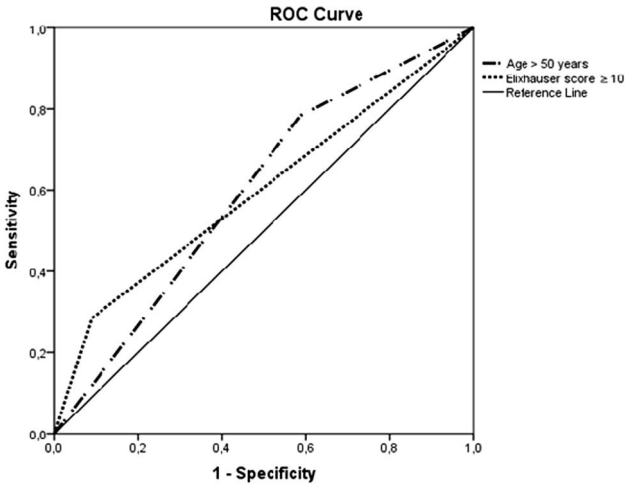

Fig. 3 ROC analysis showing areas under the curve (AUC) considering the cut-off of 50 years for age (0.598, 95 % CI 0.577–0.620; $p < 0.001$) and the cut-off of 10 for Elixhauser score (0.598, 95 % CI 0.572–0.623; $p < 0.001$) related to combined outcome

of cardiac hospitalization in the first and second years post-transplant according to USRDS data [34]. The same data was cited to report that causes of death with functioning graft are ascribed to cardiovascular diseases in 29.7 %, infection in 20.9 %, malignancy in 9.3 %, different and unknown in 22.3 and 17.8 %, respectively [34].

CKD being a risk factor for cardiovascular death, Meier-Kriesche et al. investigated the relationship between renal function and cardiovascular death in KTRs in nearly 60,000 adult patients registered in the United States Renal Data System, who received a primary renal transplant between 1988 and 1998, and had at least 1 year of graft survival. The authors find that high serum creatinine values at 1 year after transplantation are strongly associated with the risk for cardiovascular death and death from infections, but not for malignancy-related death [35].

Israni et al. [36] developed KTR risk-calculation equations to predict coronary artery disease in everyday clinical practice. They retrospectively assessed risk factors for coronary artery disease (acute myocardial infarction, coronary artery revascularization or sudden death) in >23,000 adult KTRs from 14 transplant centers worldwide. Risk factors included pre-transplant DM, new onset post-transplant DM, prior pre- and post-transplant CVD events, estimated glomerular filtration rate (eGFR), delayed graft function, acute rejection, age, gender, race and duration of pre-transplant end-stage kidney disease. Contrary to our results, traditional risk factors, such as hypertension, dyslipidemia, and cigarette smoking added only little additional predictive value [36]. Based on the same data, Kasiske et al. show that decreasing renal function of the graft is associated with mortality [8].

Weiner et al. performed a post hoc analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial to assess risk factors for CVD and mortality in KTRs. All-cause mortality and cardiovascular events that included cardiovascular death, myocardial infarction, resuscitated sudden death, stroke, coronary revascularization or peripheral, carotid, aortic or renal procedures, were evaluated in about 4000 participants, aged 52 years of whom 20 % had prior CVD and with mean eGFR of 49 ± 18 ml/min/1.73 m^2 after a follow-up of 3.8 ± 1.6 years. They recorded nearly 600 cardiovascular events and nearly 500 deaths; decreasing eGFR, age, previous CVD, DM, blood pressure and body mass index are independently associated with cardiovascular events, while decreasing eGFR, age, previous CVD, DM, blood pressure, smoking and being transplanted by a living donor are independently associated with all-cause mortality [37].

Jardine et al. analyzed the data in the placebo arm of Assessment of Lescol in Renal Transplantation (ALERT) to evaluate the relationship between cardiovascular risk factors and outcomes in 1052 KTRs aged 30–75 years, with stable graft function and receiving cyclosporine-based immunosuppression. They analyzed myocardial infarction, cardiac death, and non-cardiac death, and in multivariate analysis, preexisting coronary heart disease, total cholesterol level, and prior acute rejection are independent risk factors. On the other hand, independent risk factors for cardiac death are age, diabetes, ST-T changes on the ECG and serum creatinine level [38].

Machnicki et al. investigated the predictive ability of multiple pre-transplant comorbidity, including Elixhauser ones, for graft and patient survival. They evaluated 25,270 first-kidney transplant deceased donor recipients between 1995 and 2002, and conclude that pre-transplant comorbidity derived from administrative claims could not identify factors that have a significant impact on graft outcome predictions [39]. All these data suggest that several factors are involved in KTR prognosis including graft function, immunosuppressive therapy, and renal disease history associated with different non-immunologic parameters, suggesting that the studies had different study design and patient selection. In our study design we did not take into consideration immunologic factors, we wanted to evaluate the impact of comorbidity on major clinical events through the calculation of a well validated index. Moreover, we found that male KTRs are exposed to a higher risk of negative outcome, a result that could be defined as quite new. Nevertheless, we could not exclude the influence of environmental factors such as diet or lifestyle.

In our population, more than 10 % of patients had an Elixhauser index ≥10. This represents a significant finding since in a large population of more than 120,000 patients, a score ≥10 is associated with the highest mortality [40]. In

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another important study conducted in the United States (1992–2005), nearly 102,000 adult kidney-only transplant cases were analyzed. Among deceased-donor recipients, 10 out of 31 comorbid conditions were predictors of graft failure. Among these, the prevalence of some conditions, such as congestive heart, failure, cardiac dysrhythmias, hypertension, diabetes, renal failure, liver disease, fluid and electrolyte disorders, and deficiency anemia exceed 10 %. Moreover, the prevalence of most conditions increased significantly from 1992 to 2005, with increases in cardiovascular comorbidity, hypertension, chronic pulmonary disease, diabetes, and iron deficiency anemia [41]. Rehospitalization is a frequent event in RTRs, and may also predict future adverse outcomes. In a single-center study conducted on 753 adults aged 51 years, a total of 237 (32 %) experienced rehospitalization within 30 days, and, more specifically, 180 (24 %) KTRs experienced one early rehospitalization, 43 (5.7 %) had two rehospitalizations, and 14 (1.9 %) had three rehospitalizations [42]. In our study we calculated a mean number of about 2.5 hospitalization per patient. Unfortunately, due to our study design, it was not possible to relate different records to patients. Therefore, we could not relate the number of hospitalizations to Elixhauser index. Possible strategies for reducing comorbidities, rehospitalizations, and especially IHM in KTRs are still a matter of debate. Physicians should consider how to perform follow-up, factors modification, optimization of immunosuppressive therapy, as well as to give greater attention to in-hospital management, by means of even more careful patients evaluation and utilization of invasive procedures, always performed by highly trained experts.

Limitations

This study has several limitations. It is a retrospective study analyzing an administrative dataset. Potentially important parameters such as disease severity, including the degree of renal dysfunction, were not available. We did not analyze single patients but all records, and the number of patients was lower than the number of admissions. On the other hand, our aim was to investigate the impact of comorbidity on in-hospital death. Moreover, we cannot exclude that diagnoses might be biased by hospital codifying procedures, however the number of cases considered was high, and the large size could mitigate this error. Furthermore, details for specific clinical outcome were lacking in administrative data, and deaths outside of the hospital were not considered. Several variables could impact on IHM, and they include hospital status (teaching, location and profit status), staff (i.e. percentage of board-certified physicians, number of nurses), volume of cases, technical resource availability and operating expenses [43]. Moreover, the severity of illness also affects the mortality rate of the hospitalizations [44]. We also analyzed data from a single Italian region, where inhabitants were mainly Caucasian, therefore our results may not be generalizable.

Finally, we did not take into account variables describing recipient, donor and transplant factors, including, race, body mass index (BMI), cause of uremia, dialysis duration, peak panel reactive antibodies, donor type, donor age, race, human leukocyte antigen mismatches, donor-recipient cyto-megalovirus sero-pairing, cold ischemia time, immunosuppressant therapy, induction therapy, year of transplant, and clinical factors such as delayed graft function or rejection episodes. Due to the study design we were not able to measure these characteristics, but our aim was merely to evaluate the impact of a clinical score of non-immunologic parameters on in-hospital outcomes. As a final consideration, however, there is convincing evidence that use of administrative data enables a prediction of hospital admissions and complications [45].

Conclusions

Evaluation of non-immunological comorbidity is important in KTRs, and the identification of high-risk patients for major clinical events might improve outcome. Moreover, comorbidity could be even more important in CKD patients who are waiting for a kidney transplant. Current evidence suggests the need to correct CVD risk factors such as dyslipidemia in patients with CKD, before worsening in kidney function occurs. This may prevent CVD and delay progression of renal dysfunction [46].

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Compliance with ethical standards

Conflict of interest F. Fabbian, A. De Giorgi, F. Manfredini, N. Lamberti, S. Forcellini, A. Storari, P. Todeschini, M. Gallerani, G. La Manna, R. Manfredini, had no conflict of interest; D. P. Mikhailidis has given talks, attended conferences and participated in advisory boards and trials sponsored by Merck, Sharp & Dohme, AstraZeneca and Libytec. 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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