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Cancer mortality after kidney transplantation: A multicenter cohort study in Italy

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Abstract

Kidney transplant (KT) recipients are known to be at risk of developing several cancer types; however, cancer mortality in this population is underinvestigated. Our study aimed to assess the risk of cancer death among Italian KT recipients compared to the corresponding general population. A cohort study was conducted among 7373 individuals who underwent KT between 2003 and 2020 in 17 Italian centers. Date and cause of death were retrieved until 31 December 2020. Indirect standardization was used to estimate standardized mortality ratios (SMRs) and corresponding 95% confidence intervals (CIs). Cancer was the most common cause of death among the 7373 KT recipients, constituting 32.4% of all deaths. A 1.8-fold excess mortality (95% CI: 1.59-2.09) was observed for all cancers combined. Lymphomas (SMR = 6.17, 95% CI: 3.81-9.25), kidney cancer (SMR = 5.44, 95% CI: 2.97-8.88) and skin melanoma (SMR = 3.19, 95% CI: 1.03-6.98) showed the highest excess death risks. In addition, SMRs were increased about 1.6 to 3.0 times for cancers of lung, breast, bladder and other hematopoietic and lymphoid tissues. As compared to the general population, relative cancer mortality risk remained significantly elevated in all age groups though it decreased with increasing age. A linear temporal increase in SMR over time was documented for all cancers combined ($P < .01$). Our study documented significantly higher risks of cancer death in KT recipients than in the corresponding general population. Such results support further investigation into the prevention and early detection of cancer in KT recipients.

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; KT, kidney transplant; NHL, non-Hodgkin lymphoma; PTLD, post-transplant lymphoproliferative diseases; PY, person-year; SMR, standardized mortality ratio.

For affiliations refer to page 849

KEYWORDS
cancer mortality, cohort study, immunosuppression, kidney transplant, virus-related malignancy

What's new?

Kidney transplant recipients have increased risk of developing certain cancers, but their cancer mortality is not well documented. Here, the authors conducted a cohort study of 7373 individuals who had received a transplanted kidney. Cancer was the most common cause of death, accounting for 32% of all deaths. For all cancers combined, the transplant recipients had a 1.8-fold excess mortality; the highest excess death risks were seen with lymphomas, kidney cancers and skin melanoma. These results suggest a need for increased cancer surveillance among transplant recipients.

1 | INTRODUCTION

Cancers represent a major adverse outcome of organ transplantation, as they are often diagnosed at advanced stages and exhibit more aggressive behaviors than those occurring in the general population.[1,2] While trends in mortality from cardiovascular disease and infections in the transplant population shows declines due to a combination of improved therapies and preventive strategies,[3,4] cancer is expected to become the leading cause of death. Transplant recipients who have developed post-transplant cancer have been shown to have a higher risk of death with a functioning graft than recipients without cancer,[5,6] with most deaths attributed to cancer.[7] However, cancer as a cause of death in transplant recipients have not yet been fully elucidated in comparison with the general population.

Several studies have shown that a wide range of cancers occur with excess rates in the post-transplant scenario.[8-12] Nevertheless, an increase in cancer incidence relative to the general population may not necessarily lead to an increase in cancer mortality in this population. Cancer patterns and outcomes among transplant recipients may differ from those in the general population, due to the high burden of comorbid medical conditions, the influence of transplant-related factors and immunosuppression.

Although the burden of cancer death is increasing in this high-risk population, the literature on cancer mortality after kidney transplantation is sparse,[9,13-15] and little evidence has emerged in southern European countries, including Italy.[16] Further evidence of cancer mortality patterns among transplant recipients will help to identify high-risk patients, and facilitate appropriate interventions (eg, targeted cancer screening and cancer-specific treatments) which could lead to further improvements in long-term survival of organ transplant recipients.

In our study, we aimed to assess whether cancer mortality among Italian kidney transplant (KT) recipients was higher than in the corresponding general population.

2 | MATERIALS AND METHODS

2.1 | Study population

We conducted a cohort study using data collected among individuals undergoing a first KT in 17 centers throughout Italy between 2003 and 2020. The permanently open recruitment started in 1997, that is, this is a dynamic cohort where KT recipients enter the cohort at different times when they meet eligibility criteria.

From 8503 potentially eligible KT recipients, we excluded those who met any of the following criteria: a history of transplantation received before 2003 (n = 783); age at the time of KT <18 years (n = 20); follow-up <30 days after KT (n = 245); or a cancer diagnosis within 30 days after KT (n = 82). Therefore, 7373 KT recipients were included in the present analysis.

2.2 | Data collection and death ascertainment

At each participating center, a trained study coordinator retrieved the appropriate information from medical records and quality-checked the data for completeness and accuracy. Data collected included demographic characteristics of KT recipients (eg, sex, age at KT, area of residence), transplant information (eg, transplant center, date of KT, underlying renal disease and donor status), plus follow-up data. Histologically confirmed post-transplant cancer diagnoses were ascertained as a result of clinical follow-up. The vital status and cause of death were actively collected from medical records until 31 December 2020. Deaths caused by cancer were classified according to the "European shortlist of causes of death", based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

2.3 | Statistical analyses

For each KT recipient, person-years (PYs) at risk of death were calculated as the time elapsed from 30 days after KT to the date of death, to the date of return to dialysis, to the date of loss of follow-up or to 31 December 2020, whichever occurred first. The proportion of individuals who were censored for return to dialysis was 18%, while 16% of participants were censored for loss to follow-up. For each participating center, we counted as lost to follow-up those who did not show up for scheduled follow-up, and those for whom follow-up was incomplete because participating centers had not yet updated their data.

Demographic and clinical characteristics of cohort members were summarized using absolute counts and proportions.

To determine absolute mortality risk estimates, all-cause and cause-specific cumulative incidence function was estimated. For cancer mortality and non-cancer mortality, the analysis was performed treating all other causes of death as a competing risk.[17]

The risk of cancer death of KT recipients, compared to that of the general population, was estimated using sex-, age-, area of residence- and period-standardized mortality ratios (SMRs). SMRs were computed by dividing the observed number of cancer deaths by the expected one.[18] The latter number was estimated by multiplying the amount of PYs among KT recipients by the corresponding cancer mortality rates in the Italian general population (data provided by the Italian Institute of Statistics).[19] The 95% confidence intervals (CIs) for SMRs were calculated using the exact Poisson method.

Time trend analyses for cancer mortality and non-cancer mortality were performed through "rolling average" SMRs by 10-year overlapping calendar periods (10-year periods from 2003-2012 to 2011-2020).[14,20]

To evaluate factors associated with cancer death, hazard ratios (HRs) of death and corresponding 95% CIs were estimated using Cox proportional hazard models, adjusted for sex and age at transplantation.

All tests were two-sided, and a *P*-value <.05 was considered statistically significant. All statistical analyses were performed using SAS (SAS Institute, Cary, NC, version 9.4).

3 | RESULTS

The 7373 KT recipients were followed for a total of 43 163 PYs, with a median follow-up time of 5.8 years (interquartile range, IQR: 3.0-8.3 years) (Table 1). A total of 664 KT recipients (9.0%) died during the observation period (median follow-up time 4.4 years; IQR: 1.8-7.0 years). The proportion of deaths among KT recipients increased with age at the time of KT, while it decreased with increasing transplantation calendar period; moreover, it was higher among males, among residents of central Italy, among those who received a kidney from a deceased donor, and among those who had hypertensive nephropathy/vascular disease as the primary cause of renal failure (Table 1).

Cancer accounted about one-third of all deaths (n = 215, 32.4%). It was the most common cause of death in our cohort, followed by cardiovascular disease (23.0%) and genitourinary disease (14.3%) (Table 2). The cumulative incidence of all-cause and cause-specific mortality is presented in Figure 1. The risk of all-cause death was 5.9% at 5 years after KT and 16.0% after 10 years (Figure 1A). As with non-cancer deaths, the cumulative incidence of cancer deaths increased over the follow-up period, but at a lower rate. The risk of cancer death reached 1.6% at 5 years after KT and 5.8% at 10 years (Figure 1B).

Among cancer deaths, lung cancer (n = 47) was the most common cause, accounting for 7.1% of all deaths, followed by post-transplant lymphoproliferative diseases (PTLD) (n = 34, 5.1%; mostly due to non-Hodgkin lymphomas [NHL]), and kidney cancer (n = 14, 2.1%). The observed and expected numbers of cancer deaths, with corresponding SMRs, by cancer types/sites are presented in Figure 2. Considering all cancer deaths combined, a 1.8-fold excess mortality was found among KT recipients as compared to the corresponding general population (95% CI: 1.59-2.09). Elevated SMRs were found in several cancer types/sites (Figure 2). Lymphomas (SMR = 6.17, 95% CI: 3.81-9.25), kidney cancer (SMR = 5.44, 95% CI: 2.97-8.88) and skin melanoma (SMR = 3.19, 95% CI: 1.03-6.98) showed the highest excess death risks. In addition, the SMR was increased about 1.6 to 3.0 times for cancers of the trachea, bronchus and lung (SMR = 1.57, 95% CI: 1.15-2.07), breast (SMR = 2.12, 95% CI: 1.13-3.52), bladder (SMR = 2.56, 95% CI: 1.10-4.82) and other hematopoietic and lymphoid tissues (SMR = 2.95, 95% CI: 1.08-6.09). For a composite group of other malignant neoplasms, a 2.8-fold excess mortality was observed (95% CI: 1.95-3.73); this group includes relevant malignancies such as nonmelanoma skin cancer (n = 12), mesothelioma (n = 6) and Kaposi's sarcoma (n = 3) for which cause-specific mortality data were not available, thus not allowing calculation of specific SMRs.

SMRs for all cancers deaths were also estimated according to sex, attained age and follow-up time (Figure S1). All-site relative cancer mortality risk decreased with increasing attained age, but it remained significantly elevated as compared to the general population in all age groups: it was increased 6-fold (95% CI: 2.22-13.17) for the ≤40-year-old group and 1.7-fold (95% CI: 1.44-2.00) in the ≥60-year-old group. In addition, SMRs were 2.38 (95% CI: 1.85-3.01) among female recipients and 1.65 (95% CI: 1.39-1.94) among males. In the analysis by follow-up time, the risk increased with increasing follow-up and it was particularly high after 7 years since KT (SMR = 4.96, 95% CI: 3.86-6.26; Figure S1).

A linear temporal increase in SMR for cancer mortality (all cancers combined) was documented in the unadjusted analysis and after adjustment for sex, age and follow-up time ($P < .01$; Figure 3A,B, respectively). In the adjusted analysis, all-site cancer mortality was 2.3 times higher than that of the corresponding general population between 2003 and 2012 (95% CI 1.88-2.83) and was 3.2 times higher between 2011 and 2020 (95% CI: 2.65-3.75). For non-cancer deaths, relative mortality risk did not change over time in the unadjusted analysis ($P = .33$; Figure 3C), whereas there was evidence of a slight decrease after adjustments ($P < .01$; Figure 3D).

Table 3 shows the HRs of cancer death according to selected characteristics of KT recipients. The HRs increased with age (HR = 10.65, 95% CI: 6.20-18.32 in those aged ≥60 years) and were higher among subjects who underwent transplantation in the most recent period (HR = 1.56, 95% CI: 1.04-2.35 among KT recipients transplanted in 2010-2020) and in those who received a kidney from a deceased donor (HR = 2.99, 95% CI: 1.23-7.29). No statistically significant associations emerged for area of residence and primary cause of kidney failure.

4 | DISCUSSION

This multicenter cohort study provided estimates of excess cancer mortality among Italian KT recipients compared to the general

TABLE 1 Distribution of 7373 kidney transplant (KT) recipients and of 664 KT recipients deceased, by selected characteristics.

	Total	Deaths	
	(N = 7373)	(N = 664)	
Characteristics	No. (%)	No.	%
Sex			
Male	4692 (63.6)	459	9.8
Female	2681 (36.4)	205	7.6
Age at transplantation			
<40	1663 (22.6)	39	2.3
40-49	1663 (22.6)	83	5.0
50-59	2164 (29.3)	213	9.8
≥60	1883 (25.5)	329	17.5
Calendar year at transplantation			
2003-2005	2540 (34.4)	311	12.2
2006-2009	2563 (34.8)	246	9.6
2010-2020	2270 (30.8)	107	4.7
Area of residence			
Northern Italy	4149 (56.3)	354	8.5
Central Italy	959 (13.0)	97	10.1
Southern Italy	2233 (30.3)	210	9.4
Abroad	32 (0.4)	3	9.4
Status of the donor			
Alive	795 (10.8)	23	2.9
Deceased	6578 (89.2)	641	9.7
Primary cause of kidney failure			
Glomerulonephritis	2602 (35.3)	217	8.3
Polycystic kidney disease	1315 (17.8)	109	8.3
Pyelonephritis/Interstitial nephritis	657 (8.9)	56	8.5
Hypertensive nephropathy/vascular disease	464 (6.3)	56	12.1
Diabetes	473 (6.4)	55	11.6
Other/uncertain	1862 (25.3)	171	9.2
Follow-up (years)			
Median (IQR)	5.8 (3.0-8.3)	4.4 (1.8-7.0)	
Total person-years	43 162.7	3100.0	

Abbreviation: IQR, interquartile range.

population of the same sex, age, period and area. The magnitude of increased risks varied by cancer site, with particularly elevated increases observed for cancers frequently diagnosed among KT recipients, such as lymphomas, kidney cancer, cutaneous melanoma and lung cancer.

Despite the large number of studies that have explored cancer incidence in the context of KT, cancer mortality in this population has been poorly investigated. Nevertheless, available epidemiological evidence has suggested that the prognosis of KT recipients diagnosed with cancer is much worse than that of cancer-free transplanted patients or subjects with cancer in the general population.[9,13-15] In our study, cancer was found to be the most common cause of death among KT recipients, representing 32.4% of all deaths after 30 days post-transplantation. This finding suggests that cancer may have overtaken cardiovascular diseases as the leading cause of death among Italian individuals undergoing KT.

We found that, in comparison with the general population, cancer mortality risk was increased almost 2-fold among KT recipients. In contrast, a large investigation that examined cancer mortality among 164 078 US KT recipients reported no excess risk of cancer mortality compared to the general population, a finding attributed to the competing risk of non-cancer death.[21] Our results are consistent with those from studies carried out in Canada,[13] Northern Europe,[9,22] Australia and New Zealand,[14,15] where excess cancer mortality risks ranging from 1.9 to 2.9 times have been reported. According to other cohort studies,[13-15] we also found that the excess risk of cancer

TABLE 2 Causes of death among kidney transplant (KT) recipients.

Causes of death (ICD-10 codes)	Deaths of KT recipients (N = 664) N (%)
Malignant neoplasms (C00-C97)	215 (32.4)
Circulatory system (I00-I99)	153 (23.0)
Genitourinary system (N00-N99)	95 (14.3)
Infectious and parasitic diseases (A00-B99)	48 (7.2)
Digestive system (K00-K93)	45 (6.8)
Respiratory system (J00-J99)	26 (3.9)
Endocrine, nutritional and metabolic diseases (E00-E90)	25 (3.8)
External causes (S00-Y99)	14 (2.1)
Other	29 (4.4)
Missing	14 (2.1)

mortality for all cancers combined was highest in the younger attained age group, though the risk remained elevated across all age groups. This pattern may be attributed to the low cancer mortality rates in the young general population, and to increased competing causes of death (ie, cardiovascular and infectious diseases) in the older transplant population.

The risk of site-specific cancer mortality for KT recipients was significantly elevated for several individual cancer sites, reflecting the pattern of site-specific cancer incidence in this population.[8-10,12,23] The greatest relative cancer mortality risks (ie, SMR > 3) occurred for virus-related neoplasms such as PTLD (associated with infection of Epstein Barr virus infection), cancers associated with impaired immune surveillance such as melanoma skin cancers, and those related to underlying end-stage renal disease, such as kidney cancers.[2] These results were consistent with previous studies.[13-15] Regarding cancers with high mortality burden in the general population, elevated excess risks were found for lung and breast cancers, while the relative risk of death for colorectal and prostate cancers was not increased in our cohort. Notably, lung cancer was the most common cause of cancer death in our cohort. Although the risk of developing lung cancer is only slightly increased in KT recipients compared to the general population,[8] the risk of death is significantly higher.[14,24,25] There is consistent evidence from observational studies indicating that the risk of breast cancer in transplant recipients is either reduced or comparable to that of the general population.[8,23] However, in line with our results, previous registry-based studies have shown that the risk of breast cancer death is increased at least 2-fold in female KT recipients compared to women with breast cancer in the matched general population.[26,27] The reasons for this increased risk of death are unclear, but it could be attributed to increased biological aggressiveness and invasiveness of the tumor under the influence of immunosuppression.[28]

While cancer mortality has improved in recent decades in the general population,[29] this trend has not been confirmed in our transplant population. Indeed, we observed an increase in overall cancer mortality in the most recent calendar years. One could argue that this could be the result of an increase in cancer incidence, but recent studies have shown that cancer incidence has not changed significantly over time in the past three decades.[8,30] It is more likely that this upward trend is the result of long-term immunosuppression in long-term survivors. It cannot be ruled out that a partial lack of completeness in the follow-up data, particularly regarding subjects lost to follow-up among those transplanted in the early years of the study, may have impacted the upward trend observed in the overall cancer mortality, though no significant difference was detected in survival distributions according to transplantation period (data not shown). In contrast to our results, using the same approach a study from the Australian and New Zealand Dialysis and Transplantation Registry found that the relative cancer mortality risk did not change between 1980 and 2013, with the exception of colorectal cancer (for which a linear temporal increase in SMR was shown).[14] However, SMRs in that investigation were constantly higher than those found herein, and the different observation periods did not allow for an adequate comparison. A recent investigation conducted in the United States[30] which, conversely, used an internal comparison approach, showed that KT recipients with cancer had a persistently elevated risk of death compared to those without cancer over three decades (1987-1996/1997-2006/2007-2016), with no significant change over time. Only among KT recipients with NHL, the authors found a significant decrease in the relative risks of death over the three periods.

Prolonged immunosuppression may result in increased tumor proliferation and spread, leading to more advanced stages of disease at the occurrence, which may preclude surgical or chemo-radiotherapeutic options.[31] Given the potential role of immunosuppression in reducing immune surveillance and promoting cancer growth, treatment modulation in high-risk patients may have an impact on cancer mortality in transplant recipients, particularly for those cancers with a presumed viral or immunosuppression-related etiology.[32,33] However, this approach must be carefully balanced against the risk of causing graft rejection.[12] In our study, we could not further explore the contribution of immunosuppression to the observed cancer mortality, since we did not collect information on immunosuppressive drugs with the same details and completeness. Nevertheless, it is worth noting that in a setting where KT recipients are generally treated with multidrug maintenance therapy, it is difficult to isolate the single effect of a particular drug from the effect of the overall immunosuppressive regimen.

Prevention and screening play an important role in reducing the cancer burden in this at-risk population. Although routine cancer screening is recommended for all individuals undergoing KT, current surveillance strategies are largely based on data from the general population.[34] Recommendations for cancer screening should also be targeted to cancers for which transplant recipients are at high risk and, therefore, individualized based on the risk factors specific to the transplant population.[11,12]

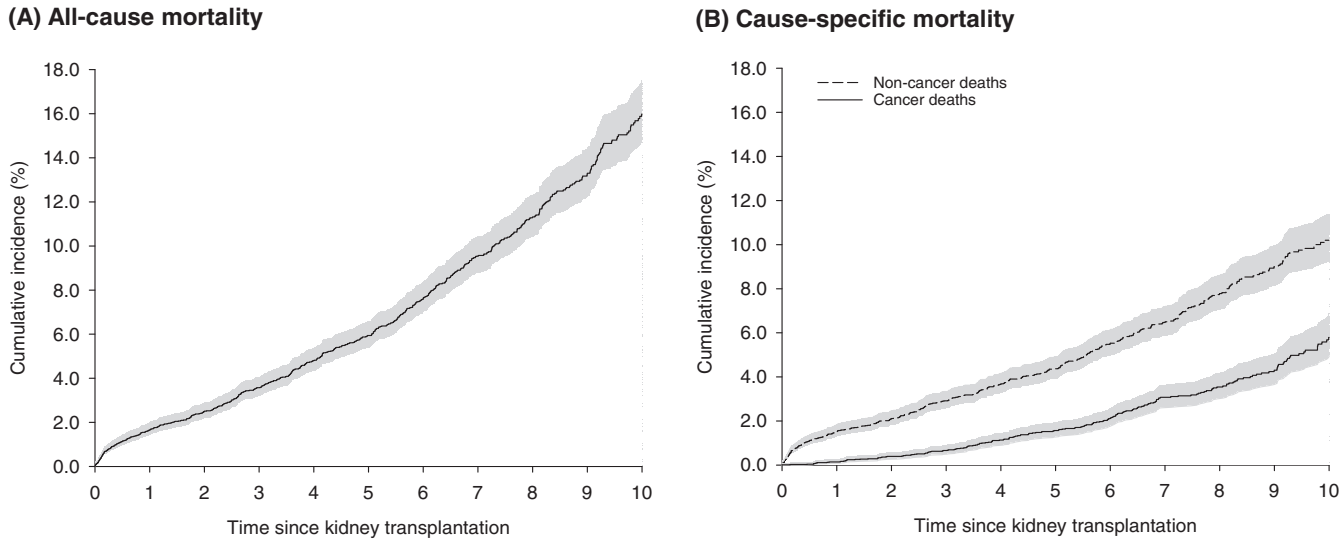

FIGURE 1 Cumulative incidence of all-cause (A) and cause-specific mortality (B) in kidney transplant recipients by time since transplantation. The gray filled area represents the 95% confidence interval.

Cancer site (ICD-10 codes)	Deaths of KT recipients (N = 664)		
	Observed deaths (%)	Expected deaths	SMR (95% CI)
All malignant neoplasms (C00-C97)	215 (32.4)	117.4	1.83 (1.59-2.09)
Lip, oral cavity, pharynx (C00-C14)	4 (0.6)	3.0	1.32 (0.36-3.14)
Oesophagus (C15)	2 (0.3)	1.9	1.04 (0.13-3.34)
Stomach (C16)	11 (1.7)	6.6	1.66 (0.83-2.88)
Colon, rectum and anus (C18-C21)	11 (1.7)	11.8	0.93 (0.47-1.62)
Liver (C22)	5 (0.8)	7.8	0.64 (0.21-1.41)
Pancreas (C25)	8 (1.2)	7.8	1.03 (0.44-1.94)
Larynx (C32)	2 (0.3)	1.7	1.20 (0.15-3.88)
Trachea, bronchus, lung (C33-C34)	47 (7.1)	29.9	1.57 (1.15-2.07)
Skin melanoma (C43)	5 (0.8)	1.6	3.19 (1.03-6.98)
Breast (C50)	13 (2.0)	6.1	2.12 (1.13-3.52)
Other and unspecified parts of uterus (C54-C55)	3 (0.5)	1.1	2.65 (0.55-7.09)
Ovary (C56)	1 (0.2)	1.8	0.57 (0.01-2.66)
Prostate (C61)	4 (0.6)	3.5	1.13 (0.31-2.69)
Kidney (C64)	14 (2.1)	2.6	5.44 (2.97-8.88)
Bladder (C67)	8 (1.2)	3.1	2.56 (1.10-4.82)
Brain and central nervous system (C70-C72)	4 (0.6)	3.7	1.07 (0.29-2.55)
Thyroid (C73)	1 (0.2)	0.4	2.84 (0.07-13.27)
PTLD (C81- C96)	34 (5.1)	8.9	3.81 (2.64-5.26)
Hodgkin disease and Lymphomas (C81-C86)	21 (3.2)	3.4	6.17 (3.81-9.25)
Leukaemia (C91-C95)	7 (1.1)	3.5	2.00 (0.81-3.93)
Other of lymph./haematopoietic tissue (C88,C90,C96)	6 (0.9)	2.0	2.95 (1.08-6.09)
Other malignant neoplasms[a]	38 (5.7)	13.8	2.75 (1.95-3.73)

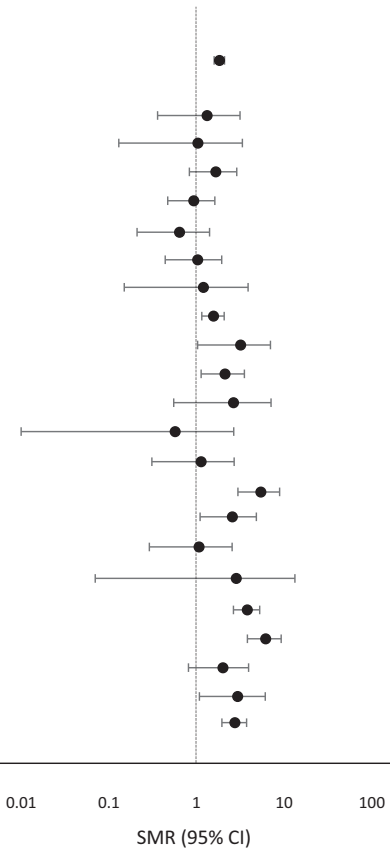

FIGURE 2 Site-specific cancer observed deaths vs expected deaths and standardized mortality ratios (SMR) among kidney transplant (KT) recipients. [a]It includes cancer sites (ICD-10 codes: C17, C23-C24, C26-C31, C37-C41, C44-C49, C51-C52, C57-C60, C62-C63, C65-C66, C68-C69, C74-C80, C97) for which cause-specific mortality data were not available, among these (n ≥ 3 cases): 12 nonmelanoma skin cancers (C44), 6 mesotheliomas (C45), 3 Kaposi's sarcomas (C46) and 6 unspecified malignant cancers (C80). CI, confidence interval; PTLD, post-transplant lymphoproliferative diseases.

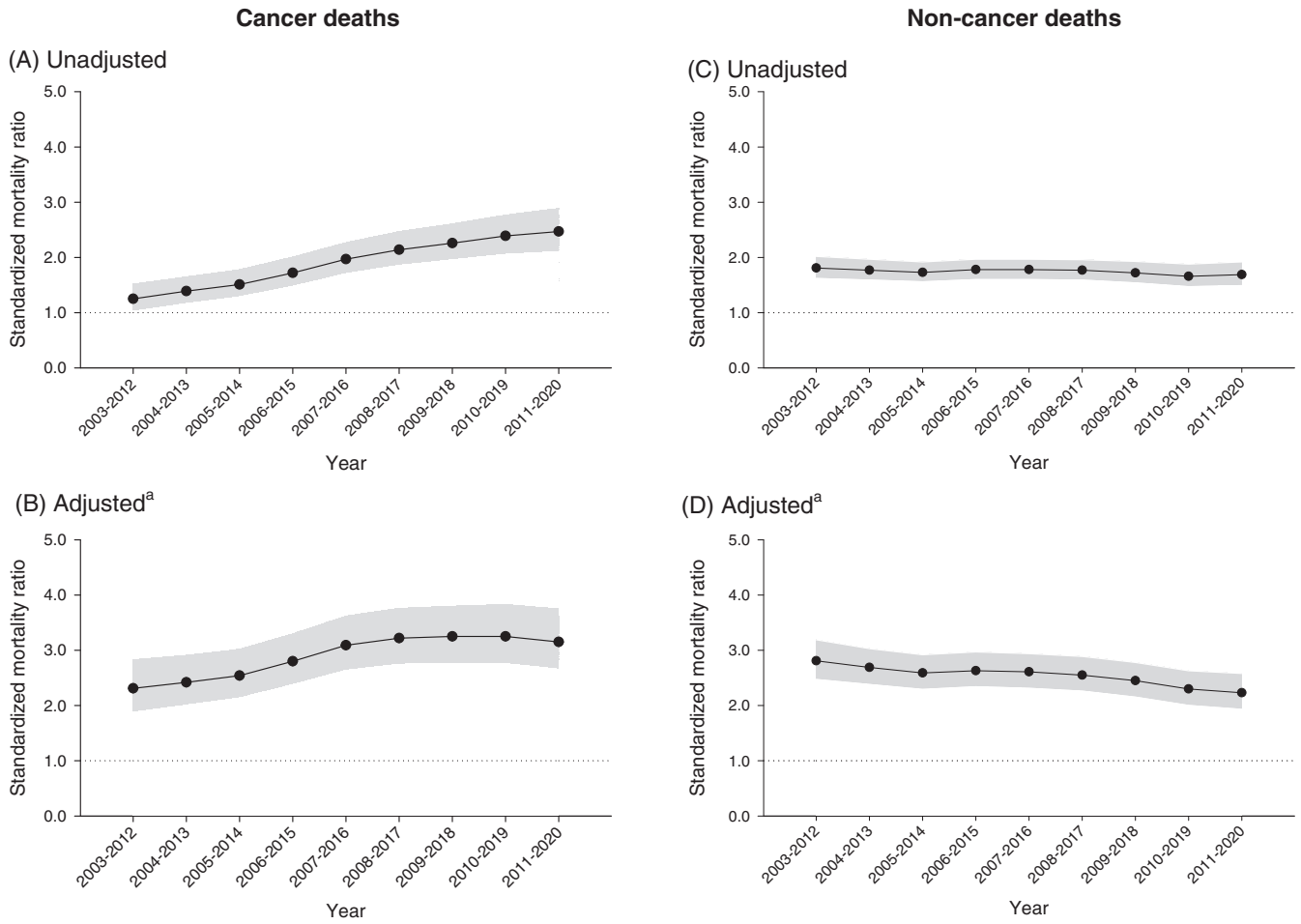

FIGURE 3 Rolling standardized mortality ratios for cancer deaths (A,B) and non-cancer deaths (C,D) by 10-year overlapping calendar periods. The gray filled area represents the 95% confidence interval. [a]Adjusted for sex, age and follow-up time.

Some limitations related to the nature of the data used should also be taken into account. Data on causes of death were collected from medical records, and the quality of reported information may vary across participating centers. Despite the close clinical follow-up of the KT recipients, a partial lack of completeness of follow-up data cannot be ruled out. However, the cause of death was determined in most KT recipients and only 2% in our study were classified with an unknown cause of death due to insufficient information. Furthermore, our results require careful interpretation because of the lack of information on cancer stage at diagnosis and treatment details, which are not routinely collected in Italian KT centers. Finally, SMRs of Kaposi's sarcoma and nonmelanoma skin cancers—which are common malignancies in the KT population—were not calculated because mortality rates for these cancers lack in the general population.

Nonetheless, our study contributes to the currently limited literature on the impact of cancer on the mortality of KT recipients. To our knowledge, the present study is the largest cohort to provide recent estimates of excess cancer mortality among KT recipients in a southern European population. Important strengths include the relatively large sample size that allowed analyses by cancer type, the regular follow-up of KT recipients and the multicentric nature of the study.

In conclusion, the results of our study further stress the need of monitoring the burden of cancer among KT recipients, as they are also at a higher risk of cancer death than the general population. Strategies to improve cancer prevention and surveillance, as well as a greater understanding of risk factors and treatment approaches that contribute to mortality, are crucial to further improve long-term outcomes in this population.

AUTHOR CONTRIBUTIONS

Martina Taborelli: Conceived and designed the study and draft the article; Performed statistical analyses. **Diego Serraino:** Conceived and designed the study and draft the article. **Claudia Cimaglia:** Coordinated data collection and managed the databases. **Lucrezia Furian:** Collected data and contributed to data interpretation. **Luigi Biancone:** Collected data and contributed to data interpretation. **Ghil Busnach:** Collected data and contributed to data interpretation. **Nicola Bossini:** Collected data and contributed to data interpretation. **Franco Citterio:** Collected data and contributed to data interpretation. **Massimiliano Veroux:** Collected data and contributed to data interpretation. **Maurizio Iaria:** Collected data and contributed to data interpretation. **Davide Argiolas:** Collected data and contributed to data

TABLE 3 Hazard ratios (HR) for cancer death (all cancers combined) among kidney transplant recipients according to selected variables.

	Cancer deaths (N = 215) HR (95% CI)[a]
Sex	
Male	1[b]
Female	1.13 (0.85-1.51)
Age at transplantation	
<40	1[b]
40-49	1.98 (1.05-3.71)
50-59	3.97 (2.26-6.97)
≥60	10.65 (6.20-18.32)
Calendar year at transplantation	
2003-2005	1[b]
2006-2009	1.26 (0.93-1.71)
2010-2020	1.56 (1.04-2.35)
Area of residence	
Northern Italy	1[b]
Central Italy	1.32 (0.91-1.93)
Southern Italy	0.95 (0.69-1.31)
Status of the donor	
Alive	1[b]
Deceased	2.99 (1.23-7.29)
Primary cause of kidney failure	
Glomerulonephritis	1[b]
Polycystic kidney disease	0.86 (0.58-1.28)
Pyelonephritis/Interstitial nephritis	1.32 (0.81-2.15)
Hypertensive nephropathy/vascular disease	1.20 (0.73-1.97)
Diabetes	0.91 (0.47-1.75)
Other/uncertain	1.08 (0.76-1.55)

[a]Estimated using Cox proportional hazard models adjusted for sex and age at transplantation.
[b]Reference category.
Abbreviation: CI, confidence interval.

interpretation. **Paola Todeschini:** Collected data and contributed to data interpretation. **Tommaso Maria Manzia:** Collected data and contributed to data interpretation. **Francesco Pisani:** Collected data and contributed to data interpretation. **Vincenzo Cantaluppi:** Collected data and contributed to data interpretation. **Simona Simone:** Collected data and contributed to data interpretation. **Margherita Mangino:** Collected data and contributed to data interpretation. **Mariarosaria Campise:** Collected data and contributed to data interpretation. **Andrea Ambrosini:** Collected data and contributed to data interpretation. **Flavia Caputo:** Collected data and contributed to data interpretation. **Pierluca Piselli:** Conceived and designed the study and draft the article; Coordinated data collection and managed the databases. All authors critically revised the article for important intellectual content and approved the final version. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano (Prot. IRB-15-2012), Comitato Etico Lazio 1, A.O. San Camillo Forlanini (Prot. 980/CE Lazio 1), Ethical Committee of Padua University Hospital (Prot. 4231/AO/17). Informed consent was obtained from all subjects involved in the study at time of transplant.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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