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# The impact of cancer on the risk of death with a functioning graft of Italian kidney transplant recipients

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This study assessed the impact of cancer on the risk of death with a functioning graft of kidney transplant (KT) recipients, as compared to corresponding recipients without cancer. A matched cohort study was conducted using data from a cohort of 13 245 individuals who had undergone KT in 17 Italian centers (1997–2017). Cases were

**Abbreviations:** CIs, confidence intervals; HRs, hazard ratios; IQR, interquartile range; KT, kidney transplant; mTORi, mTOR inhibitors; NHL, non-Hodgkin's lymphoma; NMSC, nonmelanoma skin cancer; PTLD, posttransplant lymphoproliferative diseases.

The members of the Italian Transplant, Cancer Cohort Study are listed in Appendix A.

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defined as subjects diagnosed with any cancer after KT. For each case, two controls matched by gender, age, and year at KT were randomly selected from cohort members who were cancer-free at the time of diagnosis of the index case. Overall, 292 (20.5%) deaths with a functioning graft were recorded among 1425 cases and 238 (8.4%) among 2850 controls. KT recipients with cancer had a greater risk of death with a functioning graft (hazard ratio, HR = 3.31) than their respective controls. This pattern was consistent over a broad range of cancer types, including non-Hodgkin lymphoma (HR = 33.09), lung (HR = 20.51), breast (HR = 8.80), colon-rectum (HR = 3.51), and kidney (HR = 2.38). The survival gap was observed throughout the entire follow-up period, though the effect was more marked within 1 year from cancer diagnosis. These results call for close posttransplant surveillance to detect cancers at earlier stages when treatments are more effective in improving survival.

**KEYWORDS**
malignancy, neoplasia, epidemiology, nephrology, cancer, science, kidney transplantation, translational research

## 1 | INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for most patients with end-stage renal disease since it is associated with overall improved quality of life and patient survival.[1] Despite the indisputable survival benefits of KT, death with a functioning graft has been reported to occur in up to 40% of patients[2,3] possibly due to posttransplant complications that negatively affect long-term graft and patient outcomes.

Cancer represents a major obstacle to long-term survival after KT. The prognostic impact of cancer has been investigated, in KT recipients, to a lesser extent than their risk of cancer, which is increased up to fourfold for all cancers and up to 100-fold for virus-associated malignancies such as non-Hodgkin's lymphoma (NHL) or Kaposi's sarcoma.[4–7] Some studies on cancer outcomes in KT recipients highlighted a consistently worse prognosis than that observed among non-transplant patients with the same cancer.[8–12] Nevertheless, the outcomes of posttransplant cancers in KT recipients may differ from those occurring in the general population due to the high burden of comorbid medical conditions, as well as to factors exclusively related to organ transplantation, including immunosuppression and other drug side effects.[13]

It has been shown that KT recipients—even in the absence of cancer—had a greater risk of death than the general population.[9,14] They thus represent an exceptional comparison group to assess the impact of cancer on survival in KT recipients who developed a malignancy. However, only few studies have carried out internal comparisons, that is, comparing the survival of KT recipients who developed cancer with that of corresponding KT recipients without cancer.[15–17] Furthermore, none of these investigations have quantified the gap in the risks of death with a functioning graft for a broad range of cancer types.

The present investigation was intended to quantify the prognostic role of a wide range of cancers on the risk of death with a functioning graft in a retrospective cohort of Italian KT recipients. To this end, we compared survival in KT recipients who developed cancer with that of matched KT recipients who did not.

## 2 | METHODS

### 2.1 | Study design and population

A matched cohort study was conducted using data from a retrospective cohort of 13245 individuals who underwent KT in 17 centers located all over Italy, between 1997 and 2017. For the purpose of this study, patients with (i) age at KT below 18 years ($n = 60$), (ii) a history of previous transplant ($n = 1172$), (iii) a cancer diagnosis within the 5 years preceding transplant or within 30 days after KT ($n = 103$), or (iv) a follow-up shorter than 30 days after KT ($n = 492$) were excluded from the analyses. Thus, the cohort of individuals eligible for the selection of cases and controls consisted of 11 418 KT recipients (86% of all KT recipients).

At each of the participating centers, trained staff gathered appropriate information from medical records, and checked data for accuracy and completeness. Information on patients' characteristics (e.g., gender, age at transplant, area of residence) and transplant details (e.g., transplant center, date of KT, underlying disease, donor status, use of immunosuppressive therapy) were retrieved by means of standard data collection forms. Follow-up data, including vital status, were actively sought. Information on cancer and vital status was actively elicited either from clinical records or cancer registries (when available) up to December 31, 2020. The whole process has been previously described in detail elsewhere.[7]

## 2.2 | Case ascertainment and control selection

Cases were defined as persons who had been diagnosed with *de novo* malignancies after KT. Cancer diagnoses were ascertained at scheduled clinical follow-up and -in areas covered by cancer registries- with a de-identifying record linkage procedure with population-based cancer registries. All cancer diagnoses were histologically confirmed and coded according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Multiple primary tumors were included in the site-specific survival analyses, while for KT recipients diagnosed with more than one cancer within the same ICD-10 group (e.g., head and neck: C00-14, C30-32; solid tumors: C00-C80 [excl. C44-C46]; all: C00-97, D09.0, D30.3, D41.4), only the first one was considered. For each cancer case, two control subjects were randomly selected by using incidence density sampling from cohort members free of cancer at the time of diagnosis of the index patient case. Each control could be selected as a control for only one case. Matching criteria included gender, age at KT (in 10-year groups), and year at KT (±1 year). When no controls were found in the exact matching category (for 45 cases), less stringent matching criteria were used, which allowed the extraction from the nearest categories of age or year at transplant. The index date for controls was defined as the date after the same length of follow-up as that for the matched case at cancer diagnosis. Since incidence density sampling matches cases to controls based on the dynamic risk set at the time of case occurrence, 314 controls became cases before the end of the sampling period, the majority of whom ($n$ = 148, 47%) were nonmelanoma skin cancers (NMSC).

## 2.3 | Statistical analyses

Cases and controls characteristics were presented as counts and percentages. Chi-square tests were used to assess differences between groups.

Death with a functioning graft was defined as mortality without prior graft loss (or need for kidney replacement therapy, i.e., dialysis). For the purpose of this study, person-time at risk was computed from the date of cancer diagnosis (or, for controls, the index date) to the date of death, to the date of irreversible graft failure denoted by the return to dialysis (or retransplantation), or to end of follow-up, whichever came first. Follow-up was truncated at 5 years after cancer diagnosis. The Kaplan–Meier method was used to generate 5-year survival curves for death with a functioning graft for all cancers combined, or separately for selected cancer types. The log-rank test was used to compare survival rates. Hazard ratios (HRs) of death with a functioning graft from cancer diagnosis in cases compared with controls, and corresponding 95% confidence intervals (CIs), were estimated using Cox proportional hazard models stratified on the matched sets.[18] The proportional hazards assumption was assessed through the Schoenfeld residuals and by including interactions with follow-up time. The HRs were also examined within strata of selected variables using multivariable Cox proportional hazard models adjusted for matching factors, and the Wald test was used to assess heterogeneity across strata. To evaluate differences in short-term and long-term survivals, the HRs for 1-year survival and 5-year survival, conditioned on being alive at 1 year since cancer diagnosis were estimated.

# 3 | RESULTS

A total of 1425 KT recipients who developed one or more cancer types were identified as cases (Table 1). Among cases, the most common cancer types other than NMSC ($N$ = 619) were kidney cancer ($N$ = 103), Kaposi's sarcoma ($N$ = 100), prostate cancer ($N$ = 98), NHL ($N$ = 97), and lung cancer ($N$ = 95).

Table 2 shows the distribution of cases and controls according to cancer type and selected characteristics. Overall, the majority of cases were males (72%), aged 50 years or older (70%), and had undergone KT after 2002 (69%). The distribution of matching variables did not differ between cases and controls. Compared to controls, cases were more likely to be residents in northern Italy ($p$ for chi-square < .01), except those with Kaposi's sarcoma who resided more frequently in southern Italy ($p$ < .01).[19] No differences were observed according to the status of the donor and the primary cause of kidney failure. Cases and controls were followed up for a median period of 5 years (interquartile range, IQR: 2–8) before cancer diagnosis (or index date), and the median length of follow-up after cancer diagnosis (or index date) were 3 years (IQR: 1–6) and 4 years (IQR: 2–7) respectively.

Figure 1 displays the Kaplan–Meier estimates of death with a functioning graft for cases of selected cancer types and their matched controls. Cases of all cancer types showed a lower 5-year survival probability than their respective controls (74% vs. 88%). After excluding NMSC, the survival rate for cases was 63% against 89% of their corresponding controls. Except for NMSC and Kaposi's sarcoma, cases of all most common cancer types had a worse prognosis compared to their matched control groups, with a 5-year survival probability ranging from 78% for kidney cancer to 20% for lung cancer. NMSC was associated with a better 5-year survival (89% in cases vs. 84% in controls, $p$ = .03), whereas no statistically significant differences emerged for Kaposi's sarcoma.

Overall, 292 deaths with a functioning graft were recorded among the 1425 cases of any cancer type (20.5%) and 238 among 2850 controls (8.4%). The proportions of cases and controls who were censored for graft failure were 9.2% and 9.6%, respectively, while 70.3% of cases and 82.0% of controls were alive (or censored for loss to follow-up) at the end of the follow-up. HRs of death with a functioning graft, according to selected cancer types and time since cancer diagnosis, are displayed in Table 3. As compared to controls, a 3.3-fold higher death risk (95% CI: 2.70–4.06) emerged among cases, a risk that substantially increased after the exclusion from the analysis of patients with NMSC (HR = 7.16, 95% CI: 5.44–9.43). Cases with NHL showed the highest HR (HR = 33.09, 95% CI: 7.96–137.62), followed by those with cancers of lung (HR = 20.51,

**TABLE 1** Distribution of cases according to cancer type

| Cancer type | ICD–10 code | Cases *N* |
|---|---|---|
| All[a] | C00-C97, D09.0, D30.3, D41.4 | 1425 |
| All but NMSC[a] | C00-C97 (excl. C44), D09.0, D30.3, D41.4 | 882 |
| NMSC | C44 | 619 |
| Solid tumors[a] | C00-C80 (excl. C44, C46) | 663 |
| Kidney | C64 | 103 |
| Prostate | C61 | 98 |
| Lung | C34 | 95 |
| Breast | C50 | 59 |
| Colon-rectum | C18-C20 | 55 |
| Colon | C18 | 46 |
| Rectosigmoid junction | C19 | 2 |
| Rectum | C20 | 7 |
| Bladder | C67, D09.0, D30.3, D41.4 | 55 |
| Head and neck | C00-C14, C30-C32 | 42 |
| Lip | C00 | 19 |
| Tongue | C02 | 1 |
| Palate | C05 | 1 |
| Mouth | C06 | 1 |
| Parotid Gland | C07 | 4 |
| Tonsil | C09 | 2 |
| Oropharynx | C10 | 1 |
| Piriform sinus | C12 | 2 |
| Accessory sinus | C31 | 1 |
| Larynx | C32 | 10 |
| Melanoma | C43 | 30 |
| Stomach | C16 | 26 |
| Soft and connective tissues | C49 | 21 |
| Thyroid and other endocrine glands | C73-C75 | 21 |
| Pancreas | C25 | 13 |
| Corpus Uteri | C54 | 12 |
| Site NOS | C76-C80 | 11 |
| Testis | C62 | 8 |
| Liver | C22 | 7 |
| Mesothelioma | C45 | 6 |
| Oesophagus | C15 | 4 |
| Ovary | C56 | 4 |
| Brain | C71 | 4 |
| Small Intestine | C17 | 3 |
| Anus | C21 | 3 |
| Heart | C38 | 3 |
| Ureter | C66 | 3 |
| Eye | C69 | 3 |
| Gallbladder and biliary tract | C24 | 2 |
| Vulva | C51 | 2 |
| Cervix Uteri | C53 | 2 |
| Trachea | C33 | 1 |
| Other respiratory tract | C39 | 1 |
| Uterus NOS | C55 | 1 |
| Other female genital organs | C57 | 1 |
| Penis | C60 | 1 |
| Other male genital organs | C63 | 1 |
| Renal pelvis | C65 | 1 |
| PTLD | C81-C96 | 130 |
| Non-Hodgkin's lymphoma | C82-C85, C88, C96 | 97 |
| Leukemias | C91-C95 | 18 |
| Multiple myeloma | C90 | 11 |
| Hodgkin lymphoma | C81 | 4 |
| Kaposi's sarcoma | C46 | 100 |

Abbreviations: NMSC, nonmelanoma skin cancer; PTLD, posttransplant lymphoproliferative diseases.

[a]The sums can exceed the total because some patients were diagnosed with more than one malignancy. For kidney transplant recipients diagnosed with more than one malignancy within the same ICD-10 group (e.g., colon-rectum ICD-10 codes: C18-C20; head and neck ICD-10 codes: C00-C14, C30-C32), only the first one was considered.

95% CI: 8.21–51.26), breast (HR = 8.80, 95% CI: 2.54–30.57), colon-rectum (HR = 3.51, 95% CI: 1.49–8.26), and kidney (HR = 2.38, 95% CI: 1.05–5.40).

When separately analyzing short-term (i.e., 1-year survival) or long-term survival (i.e., 5-year survival, conditioned to be alive at 1 year) (Table 3), the HR of death with a functioning graft for all cancer cases remained significantly higher throughout the entire follow-up period. However, the effect was more marked in the early period (HR = 7.60, 95% CI: 5.42–10.67). A similar risk pattern was noted for all but NMSC, for NHL, and for all solid cancers, including lung cancer. For cases with kidney (HR = 8.00, 95% CI: 1.70–37.67), colorectal (HR = 7.71, 95% CI: 2.17–27.36), or bladder cancer (HR = 10.00, 95% CI: 1.17–85.59) the differences in death risks emerged only within 1 year after diagnosis. On the other hand, among breast cancer cases, the survival was significantly lower only in the long term (HR = 17.06, 95% CI: 2.16–134.96). NMSC cases showed lower HR than their respective controls after the first year from diagnosis, whereas no statistically significant difference in risks emerged among cases with Kaposi's sarcoma, prostate, or head and neck cancers.

For all cancers and posttransplant lymphoproliferative diseases (PTLD), the female gender was associated with significantly greater HR of death with a functioning graft in cases versus controls

**TABLE 2** Demographic and clinical characteristics of cases of selected cancer sites and corresponding controls

| | All | | NMSC | | Solid tumors | | PTLD | | Kaposi's sarcoma | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cases *N* (%) | Controls *N* (%) | Cases *N* (%) | Controls *N* (%) | Cases *N* (%) | Controls *N* (%) | Cases *N* (%) | Controls *N* (%) | Cases *N* (%) | Controls *N* (%) |
| Total | 1425 | 2850 | 619 | 1238 | 663 | 1326 | 130 | 260 | 100 | 200 |
| Gender | | | | | | | | | | |
| Male | 1029 (72.2) | 2058 (72.2) | 469 (75.8) | 938 (75.8) | 470 (70.9) | 940 (70.9) | 91 (70.0) | 182 (70.0) | 69 (69.0) | 138 (69.0) |
| Female | 396 (27.8) | 792 (27.8) | 150 (24.2) | 300 (24.2) | 193 (29.1) | 386 (29.1) | 39 (30.0) | 78 (30.0) | 31 (31.0) | 62 (31.0) |
| Age at transplant (years) | | | | | | | | | | |
| 18–49 | 427 (30.2) | 865 (30.4) | 142 (23.0) | 288 (23.3) | 206 (31.1) | 421 (31.7) | 64 (49.2) | 128 (49.2) | 29 (29.0) | 58 (29.0) |
| 50–59 | 536 (37.3) | 1075 (37.7) | 246 (39.7) | 493 (39.8) | 253 (38.1) | 510 (38.5) | 39 (30.0) | 78 (30.0) | 39 (39.0) | 78 (39.0) |
| ≥60 | 462 (32.5) | 910 (31.9) | 231 (37.3) | 457 (36.9) | 204 (30.8) | 395 (29.8) | 27 (20.8) | 54 (20.8) | 32 (32.0) | 64 (32.0) |
| Calendar year at transplant | | | | | | | | | | |
| 1997–2001 | 440 (30.9) | 898 (31.5) | 195 (31.5) | 395 (31.9) | 202 (30.5) | 410 (30.9) | 48 (36.9) | 106 (40.8) | 36 (36.0) | 68 (34.0) |
| 2002–2006 | 618 (43.4) | 1200 (42.1) | 270 (43.6) | 513 (41.4) | 285 (43.0) | 571 (43.1) | 57 (43.9) | 105 (40.4) | 42 (42.0) | 85 (42.5) |
| 2007–2017 | 367 (25.8) | 752 (26.4) | 154 (24.9) | 330 (26.7) | 176 (26.5) | 345 (26.0) | 25 (19.2) | 49 (18.8) | 22 (22.0) | 47 (23.5) |
| Area of residence | | | | | | | | | | |
| Northern Italy | 923 (64.8) | 1662 (58.3) | 414 (66.9) | 736 (59.5) | 444 (67.0) | 763 (57.5) | 85 (65.4) | 153 (58.9) | 47 (47.0) | 129 (64.5) |
| Central Italy | 172 (12.1) | 312 (10.9) | 77 (12.4) | 139 (11.2) | 88 (13.3) | 150 (11.3) | 11 (8.5) | 24 (9.2) | 5 (5.0) | 15 (7.5) |
| Southern Italy | 329 (23.1) | 868 (30.5) | 128 (20.7) | 362 (29.2) | 131 (19.7) | 407 (30.7) | 33 (25.4) | 83 (31.9) | 48 (48.0) | 54 (27.0) |
| Abroad | 1 (0.1) | 8 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 6 (0.5) | 1 (0.8) | 0 (0.0) | 0 (0.0) | 2 (1.0) |
| Status of the donor | | | | | | | | | | |
| Deceased | 1347 (94.5) | 2649 (93.0) | 586 (94.7) | 1166 (94.2) | 629 (94.9) | 1228 (92.6) | 120 (92.3) | 233 (89.6) | 97 (97.0) | 186 (93.0) |
| Living | 78 (5.5) | 201 (7.0) | 33 (5.3) | 72 (5.8) | 34 (5.1) | 98 (7.4) | 10 (7.7) | 27 (10.4) | 3 (3.0) | 14 (7.0) |
| Primary cause of kidney failure | | | | | | | | | | |
| Diabetes | 33 (2.3) | 116 (4.1) | 11 (1.8) | 52 (4.2) | 19 (2.9) | 58 (4.4) | 1 (0.8) | 9 (3.5) | 2 (2.0) | 6 (3.0) |
| Hypertension/vascular disease | 144 (10.1) | 269 (9.4) | 69 (11.1) | 134 (10.8) | 66 (10.0) | 110 (8.3) | 12 (9.2) | 16 (6.2) | 5 (5.0) | 24 (12.0) |
| Glomerulonephritis | 508 (35.7) | 1053 (37.0) | 214 (34.6) | 432 (34.9) | 242 (36.5) | 503 (37.9) | 47 (36.2) | 111 (42.7) | 41 (41.0) | 70 (35.0) |
| Pyelonephritis/interstitial nephritis | 121 (8.5) | 222 (7,8) | 42 (6.8) | 93 (7.5) | 64 (9.7) | 98 (7.4) | 10 (7.7) | 29 (11.1) | 13 (13.0) | 18 (9.0) |
| Polycystic kidney | 248 (17.4) | 515 (18.1) | 120 (19.4) | 232 (18.8) | 101 (15.2) | 246 (18.5) | 21 (16.1) | 32 (12.3) | 15 (15.0) | 36 (18.0) |
| Uncertain | 243 (17.0) | 429 (15.0) | 104 (16.8) | 192 (15.5) | 115 (17.3) | 200 (15.1) | 18 (13.9) | 37 (14.2) | 22 (22.0) | 28 (14.0) |
| Other | 128 (9.0) | 241 (8.6) | 59 (9.5) | 103 (8.3) | 56 (8.4) | 111 (8.4) | 21 (16.1) | 26 (10.0) | 2 (2.0) | 18 (9.0) |

Abbreviations: NMSC, nonmelanoma skin cancer; PTLD, posttransplant lymphoproliferative diseases.

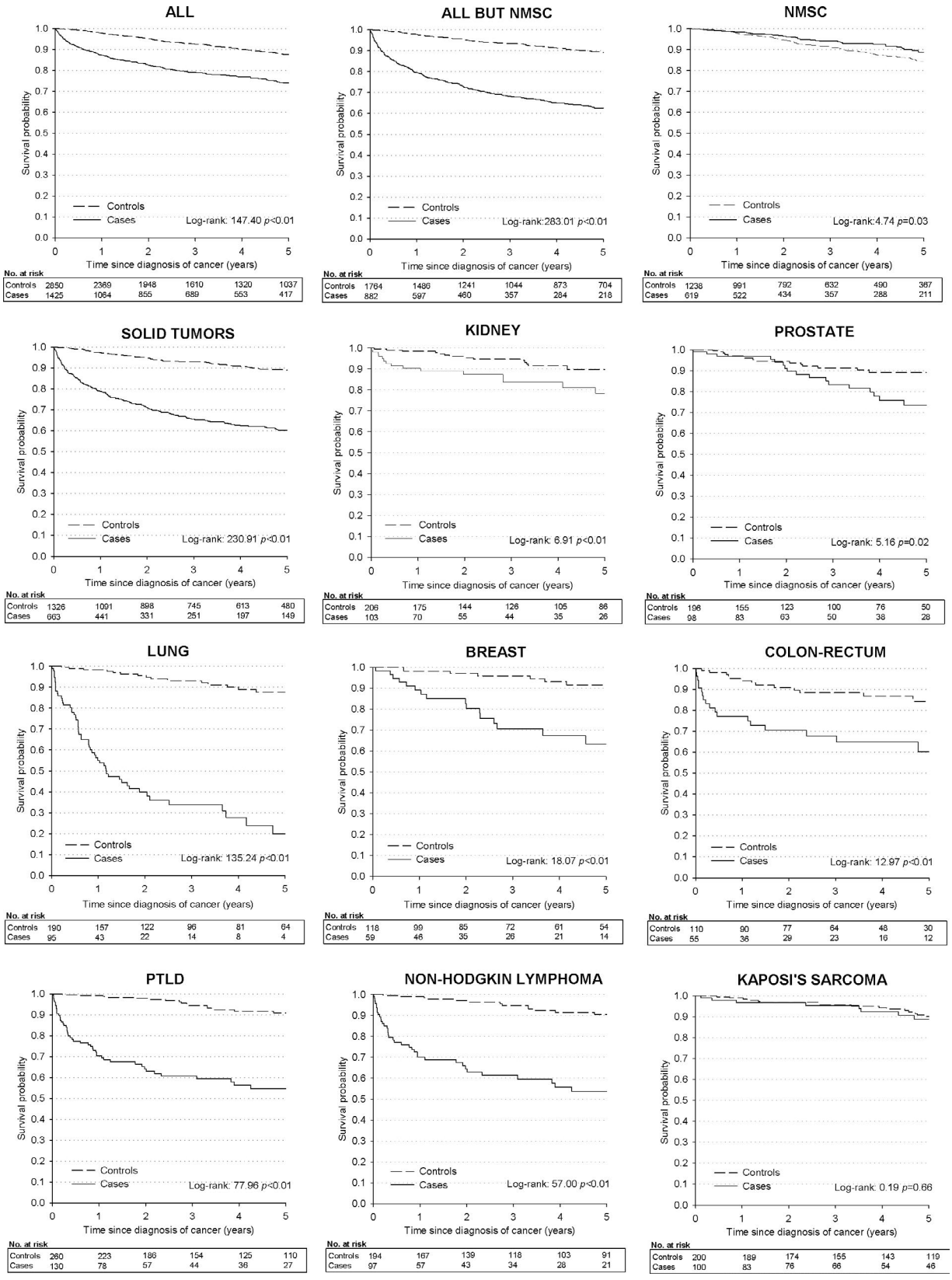


**FIGURE 1** Kaplan–Meier estimates of survival probabilities for cases of selected cancer types and corresponding controls. NMSC, nonmelanoma skin cancer; PTLD, posttransplant lymphoproliferative diseases

(Table 4). For all cancers and solid tumors, the survival gap was greater at younger ages and decreased with increasing age, and it was stronger among patients never treated with mTOR inhibitors (mTORi) after cancer diagnosis (vs. those treated with mTORi). No heterogeneity in HRs for all cancers combined or type-specific cancers was detected across strata of year at transplant, residence area,

**TABLE 3** Hazard ratios[a] (HRs) of death with functioning graft and corresponding 95% confidence intervals (CIs) in cases versus controls, according to selected cancer types and time since cancer diagnosis

| | 5-year survival | | | | | 1-year survival | 5-year survival, conditioned to be alive at 1 year |
|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | | | |
| Cancer type | *N* deaths | % death | *N* deaths | % death | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| All | 292 | 20.5 | 238 | 8.4 | 3.31 (2.70–4.06) | 7.60 (5.42–10.67) | 1.62 (1.23–2.14) |
| All but NMSC | 266 | 30.2 | 134 | 7.6 | 7.16 (5.44–9.43) | 12.69 (8.33–19.33) | 3.70 (2.52–5.41) |
| NMSC | 44 | 7.1 | 118 | 9.5 | 0.60 (0.41–0.90) | 0.77 (0.35–1.70) | 0.56 (0.35–0.89) |
| Solid tumors | 211 | 31.8 | 102 | 7.7 | 6.80 (5.02–9.22) | 10.67 (6.84–16.63) | 3.90 (2.54–5.99) |
| Kidney | 15 | 14.6 | 15 | 7.3 | 2.38 (1.05–5.40) | 8.00 (1.70–37.67) | 1.11 (0.38–3.24) |
| Lung | 57 | 60.0 | 15 | 7.9 | 20.51 (8.21–51.26) | 24.40 (7.53–79.05) | 14.72 (3.40–63.82) |
| Prostate | 17 | 17.4 | 15 | 7.7 | 1.78 (0.79–4.02) | 1.00 (0.24–4.25) | 2.39 (0.86–6.68) |
| Breast | 16 | 27.1 | 7 | 5.9 | 8.80 (2.54–30.57) | 4.76 (0.95–23.95) | 17.06 (2.16–134.96) |
| Colon-rectum | 18 | 32.7 | 13 | 11.8 | 3.51 (1.49–8.26) | 7.71 (2.17–27.36) | 1.17 (0.31–4.44) |
| Bladder | 13 | 23.6 | 11 | 10.0 | 2.21 (0.92–5.29) | 10.00 (1.17–85.59) | 1.32 (0.47–3.70) |
| Head and neck | 7 | 16.7 | 8 | 9.5 | 3.31 (0.96–11.35) | 4.00 (0.73–21.84) | 2.64 (0.43–16.02) |
| PTLD | 49 | 37.7 | 16 | 6.2 | 29.42 (9.15–94.56) | 71.01 (9.74–518.01) | 8.86 (1.96–39.99) |
| NHL | 37 | 38.1 | 13 | 6.7 | 33.09 (7.96–137.62) | 53.02 (7.20–390.29) | 13.35 (1.67–106.49) |
| Kaposi's sarcoma | 8 | 8.0 | 16 | 8.0 | 1.76 (0.66–4.73) | 5.16 (0.53–50.41) | 1.27 (0.40–4.04) |

Abbreviations: NHL, non-Hodgkin's lymphoma; NMSC, nonmelanoma skin cancers; PTLD, posttransplant lymphoproliferative diseases.
[a]Estimated using Cox proportional hazard models stratified on the matched sets.

or use of calcineurin inhibitors. The results of the most frequent solid tumors and non-Hodgkin's lymphoma are shown in Table S1. For lung cancer, treatment with mTORi after diagnosis was associated with a better prognosis than non-treatment.

## 4 | DISCUSSION

The present investigation highlighted that KT recipients diagnosed with cancer experienced a higher risk of death with a functioning graft as compared to cancer-free recipients matched for gender, age, and year at transplantation. Survival time was particularly reduced in KT recipients with NHL, lung, colon-rectum, breast, and kidney, whereas there was no difference in the death risk for cases with Kaposi's sarcoma, prostate, or head and neck cancers. Although the survival gap was observed throughout the entire follow-up period, the effect was more marked within one year from cancer diagnosis.

With improvements in recipients' long-term survival following KT, cancer has become an increasingly important contributor to mortality with a functioning graft.[12,20] An Australian study[15] has shown that only 41% of KT recipients who developed cancer survived with a functioning graft 10 years after diagnosis. Moreover, a recent study from the United States evidenced that the absolute risk of death with a functioning graft after cancer was 38% for the most recent KT recipients transplanted in 2007–2016.[12] Although the prognosis of KT recipients with cancer varies according to the type and severity of cancer at presentation, available epidemiologic evidence has suggested that it is much worse than in non-transplanted patients with the same cancer.[8–11] On the other hand, limited data have been accumulated to assess whether the onset of cancer after KT carries a poor prognosis even when compared with other cancer-free KT recipients.[15–17]

The enduring exposure to immunosuppressive treatment and transplant-specific risk factors among KT recipients may have their influence on patient survival, even in the absence of cancer.[9,14] As a result, the evaluation of the prognostic effect of cancers among KT recipients by using an internal comparison approach is crucial to fully quantify the cancer burden in this population, and to develop strategies for improving long-term outcomes. The current study not only gives a unique insight into the negative prognostic impact of several common cancers arising among KT recipients, but it also highlights the significant survival gap that currently exists when compared to corresponding KT recipients without cancer. Only a previous study has shown—in accordance with our findings—that KT recipients who developed cancer had a higher risk of death with a functioning graft compared to those without cancer, though no matching between patients with and without cancer was carried out.[15]

Our results showed that the increased risk of death with a functioning graft among KT recipients with cancer, as compared to cancer-free patients, considerably varied according to cancer type, and it seemed to be driven primarily by death within one year after cancer diagnosis, which includes 58% (170/292) of deaths observed among cancer cases. The poor outcomes experienced by KT recipients for certain cancer types may be attributed to a range of factors, such as the influence of the quality and quantity of immunosuppression on the aggressiveness of cancer development and the

**TABLE 4** Hazard ratios[a] (HRs) of death with functioning graft and corresponding 95% confidence intervals (CIs) in cases of selected cancer types versus controls across strata of selected characteristics

| | All | | NMSC | | Solid tumors | | PTLD | | Kaposi's sarcoma | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* deaths | HR (95% CI) | *N* deaths | HR (95% CI) | *N* deaths | HR (95% CI) | *N* deaths | HR (95% CI) | *N* deaths | HR (95% CI) |
| Gender | | | | | | | | | | |
| Male | 216 | 2.26 (1.87–2.74) | 37 | 0.59 (0.41–0.86) | 154 | 4.54 (3.47–5.92) | 35 | 6.57 (3.58–12.06) | 5 | 1.08 (0.38–3.09) |
| Female | 76 | 5.03 (3.37–7.51) | 7 | 0.88 (0.35–2.19) | 57 | 7.78 (4.57–13.24) | 14 | 54.69 (6.99–427.89) | 3 | 2.38 (0.52–10.91) |
| $\chi^2$ for heterogeneity | | $p < .01$ | | $p = .43$ | | $p = .07$ | | $p = .04$ | | $p = .40$ |
| Age at transplant (years) | | | | | | | | | | |
| 18–49 | 59 | 7.57 (4.46–12.83) | 0 | — | 44 | 17.86 (7.60–41.93) | 14 | 13.13 (3.74–49.07) | 1 | 2.03 (0.13–32.63) |
| 50–59 | 116 | 3.11 (2.35–4.13) | 18 | 0.83 (0.47–1.46) | 79 | 5.38 (3.64–7.97) | 23 | 9.22 (4.18–20.33) | 3 | 1.64 (0.37–7.32) |
| ≥60 | 117 | 1.75 (1.38–2.26) | 26 | 0.56 (0.36–0.86) | 88 | 3. 65 (2.62–5.08) | 12 | 8.91 (2.58–30.78) | 4 | 1.14 (0.36–3.61) |
| $\chi^2$ for heterogeneity | | $p < .01$ | | $p = .58$ | | $p < .01$ | | $p = .95$ | | $p = .97$ |
| Calendar year at transplant | | | | | | | | | | |
| 1997–2001 | 98 | 3.24 (2.38–4.40) | 17 | 0.81 (0.46–1.45) | 72 | 7.57 (4.76–12.03) | 17 | 9.25 (3.58–23.90) | 2 | 0.84 (0.17–4.21) |
| 2002–2006 | 127 | 2.25 (1.74–2.90) | 18 | 0.46 (0.27–0.78) | 93 | 4.61 (3.26–6.52) | 22 | 7.04 (3.16–15.71) | 2 | 0.72 (0.15–3.62) |
| 2007–2017 | 67 | 2.87 (2.01–4.10) | 9 | 0.73 (0.34–1.59) | 46 | 4.18 (2.60–6.72) | 10 | 32.30 (4.00–260.63) | 4 | 8.59 (1.35–54.51) |
| $\chi^2$ for heterogeneity | | $p = .18$ | | $p = .31$ | | $p = .15$ | | $p = .61$ | | $p = .19$ |
| Area of residence[b] | | | | | | | | | | |
| Northern Italy | 180 | 2.43 (1.95–3.02) | 25 | 0.47 (0.30–0.73) | 136 | 5.15 (3.78–7.02) | 28 | 7.88 (3.69–16.83) | 3 | 0.99 (0.27–3.60) |
| Central Italy | 38 | 3.07 (1.81–5.18) | 8 | 1.35 (0.51–3.58) | 29 | 3.99 (2.11–7.57) | 5 | 80.31 (2.81–2299.15) | 1 | 0.10 (0.00–39.62) |
| Southern Italy | 73 | 3.20 (2.29–4.46) | 11 | 0.89 (0.44–1.81) | 46 | 6.19 (3.90–9.83) | 15 | 9.45 (3.49–25.57) | 4 | 4.78 (0.62–37.11) |
| $\chi^2$ for heterogeneity | | $p = .35$ | | $p = .08$ | | $p = .54$ | | $p = .62$ | | $p = .49$ |
| Ever use of CNI[c,d] | | | | | | | | | | |
| No | 21 | 2.31 (1.24–4.33) | 1 | 0.22 (0.03–1.93) | 21 | 5.46 (2.59–11.48) | 6 | 8.52 (1.33–54.62) | 0 | — |
| Yes | 261 | 2.70 (2.25–3.24) | 41 | 0.65 (0.45–0.93) | 184 | 5.26 (4.06–6.80) | 42 | 9.48 (5.07–17.73) | 7 | 1.20 (0.49–2.96) |
| $\chi^2$ for heterogeneity | | $p = .65$ | | $p = .33$ | | $p = .88$ | | $p = .91$ | | $p = .83$ |
| Ever use of mTORi[d] | | | | | | | | | | |
| No | 179 | 3.32 (2.69–4.11) | 24 | 0.66 (0.42–1.04) | 128 | 6.99 (5.21–9.38) | 35 | 8.52 (1.33–54.62) | 3 | 1.13 (0.31–4.13) |
| Yes | 113 | 1.81 (1.35–2.43) | 20 | 0.54 (0.31–0.94) | 83 | 3.03 (2.01–4.56) | 14 | 11.63 (3.25–41.62) | 5 | 1.43 (0.33–6.22) |
| $\chi^2$ for heterogeneity | | $p < .01$ | | $p = .57$ | | $p < .01$ | | $p = .51$ | | $p = .80$ |

Abbreviations: CNI, calcineurin inhibitors; mTORi, mTOR inhibitors; NMSC, nonmelanoma skin cancer; PTLD, posttransplant lymphoproliferative diseases.

[a]Adjusted for gender, age at transplant, and year at transplantation.

[b]Residence abroad excluded.

[c]The sum does not add up to the total because of missing values.

[d]Ever use after cancer diagnosis.

limited available treatment options, particularly among recipients with considerable coexisting comorbidities.[8] In this regard, some authors have observed that malignancies in the KT population were more aggressive and diagnosed at a much later stage than those in patients without transplant.[21]Although in our analyses the year of transplantation did not impact the risk of death with a functioning graft in cases versus controls, the effect of the period could be significant in larger cohorts with a greater number of events. Thus, the observed difference in the two groups could be partially explained by other changes in KT care during the study periods.

The association between immunosuppression and increased risk of cancers related to oncogenic viruses is well established.[22] In this study, the risk of death with a functioning graft was particularly elevated in cases with PTLD, including NHL, as compared to cancer-free recipients. In agreement with our study, a prior report using data from the Australia and New Zealand Dialysis and Transplant Registry showed a poor survival of recipients after the development of PTLD, reporting a high mortality rate within the first year after cancer diagnosis.[23] Although Kaposi's sarcoma represented the second most common cancer in our cohort, we found no differences in survival rates between KT recipients with and without this cancer over the entire period. Similarly, a previous study showed that patients who developed Kaposi's sarcoma after KT had similar long-term survival when compared with patients without cancer.[24] Either the level of immunosuppression and the extent of the disease seem to play an important role in determining the course of Kaposi's sarcoma. The predominance of the cutaneous form, which is associated with a more favorable outcome than visceral forms, probably explains these findings.[25]

Our results showed that survival outcomes were also worse for KT recipients with solid organ tumors such as lung, kidney, breast, bladder, and colorectal cancers. The poor survival of lung cancer is not unexpected, due to its high malignant potential. Accordingly, the Scientific Registry of Transplant Recipients analysis highlighted that lung cancer was more likely to be diagnosed at an advanced stage in KT recipients than in the general population.[26] Previous studies have observed that the prognosis of KT recipients diagnosed with colorectal cancer and breast cancer is much worse than in patients with transplant or just cancer,[8,17,27–29] whereas mixed results emerged for bladder and kidney cancers.[8,17] Data from the Israel Penn International Transplant Tumor Registry have shown that transplant recipients with cancer were diagnosed early for kidney cancer, but at advanced stages for colorectal, breast, and bladder cancers. However, survival in these patients was worse for all cancer types than in the general population, regardless of the stage of diagnosis.[8] A recent study reported that the survival of KT recipients with prostate cancer was similar to that of non-transplanted counterparts with the same malignancy.[30] The present study highlighted that it did not differ also when compared to other transplant recipients. This is one of the few studies that have looked at survival after the diagnosis of NMSC. The observed reduction in the risk of death for NMSC cases as compared to their cancer-free controls was surprising. However, it is likely that NMSC were diagnosed at an earlier stage as a result of preventive skin care practices in patients who are prone to perform regular medical checkups and cancer screening. The personal willingness to engage in prevention of these patients can result in better general health status and more favorable survival outcomes. Another possible explanation is that improved survival may be associated with tapered immunosuppression after NMSC appearance.

Understanding factors associated with reduced long-term survival after cancer in the KT setting is important for predicting, and potentially improving outcomes. This study showed that the onset of cancer, particularly PTLD, tended to carry a worse prognosis among females than among males, an observation that deserves further investigation with detailed clinical information not presently available. We also found that the survival gap was stronger among younger KT recipients than in older recipients. This pattern may be attributable to the potential competing risk of death from cardiovascular disease that dampens the effect of cancer on patient survival among older transplant recipients.[31] Cancer survival tended to be better among KT recipients who were treated with mTORi after cancer diagnosis compared to never users, a not surprising finding since mTORi sirolimus and everolimus show potential anti-proliferative properties, including inhibition of cellular growth, proliferation, metabolism, and angiogenesis.[32] Nonetheless, previous reports have not been able to demonstrate improved survival in KT recipients taking mTORi.[33]

This study has strengths and drawbacks. Although a longer follow-up period and a larger number of patients would be required to draw firm conclusions, to the best of our knowledge, it is the largest and most comprehensive examination of the prognostic effect of several cancer types on survival among KT recipients in comparison with other KT recipients without cancer. Moreover, all study participants were selected from a defined cohort over a defined time frame, and controls were matched to cases by age, gender, and year of KT. The multicenter nature of the study represents another important strength.

Among potential limitations, it is worth noting that we were not able to fully explore factors that contributed to the observed increased risk of death with a functioning graft of KT recipients with cancer -such as the presence of comorbidities, cancer stage, and intensity of immunosuppression. Moreover, the lack of information on some variables associated with the risk of specific cancers (i.e., smoking habits, alcohol abuse, and obesity), which are not routinely collected in Italian KT centers, needs also to be borne in mind.

A partial lack of completeness of cancer case ascertainment cannot be excluded as cancer diagnoses were mostly clinically based. Although we could not perform a linkage with population-based cancer registries for all KT recipients, the close clinical follow-up of the KT recipients is likely to limit the lack of completeness of cancer reporting. Finally, a larger number of controls would have increased precision in estimates. However, the 2:1 ratio of controls to cases was chosen on the basis of the available number of controls who fitted matching criteria (i.e., same gender, same age, same year at transplantation, and at least the same length of follow-up as the case).

In conclusion, although posttransplant monitoring and cancer management so far have been based on patterns of increased cancer incidence, the knowledge of the prognostic impact of cancers on

survival of KT recipients compared to matched recipients without cancers may provide an additional basis for improving survival in this population. The survival gap herein quantified for a wide range of cancer types prompts for close posttransplant surveillance to detect tumors, hopefully, at the earliest stages, not only for a better chance of cancer treatment, but also for effectively modulating immunosuppressive therapy. Although in our cohort we are not aware of how many cancers were identified by cancer screening, specific strategies aimed at emphasizing screening and surveillance efforts would be advisable to optimize long-term outcomes after KT. Further investigations should be conducted to develop tailored cancer screening programs in this population.

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## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

## DATA AVAILABILITY STATEMENT

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

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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## APPENDIX A

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