ORIGINAL ARTICLE
Turk J Surg 2025;41(4):369-373

De novo malignancy development following kidney transplantation: Managing risks and outcomes in clinical practice

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ABSTRACT

Objective: *De novo* malignancy is a significant complication following kidney transplantation, attributed to prolonged immunosuppression. This study evaluates the incidence, risk factors, and clinical outcomes of *de novo* malignancies in kidney transplant recipients.

Material and Methods: A retrospective cohort analysis was conducted on 1200 kidney transplant recipients between 2016 and 2023. Patients were categorized based on the presence or absence of *de novo* malignancies. Statistical analyses were performed to identify risk factors, including age, sex, comorbidities, and immunosuppressive regimens. Patient and graft survival were assessed using Kaplan-Meier analysis and the log-rank test.

Results: Among the study population, 43 patients (3.6%) developed *de novo* malignancies. The most frequent malignancy types were non-melanoma skin cancers (27.9%) and post-transplant lymphoproliferative disorders (18.6%). Patients with malignancies exhibited a lower three-year survival rate (83.7%) compared to those without malignancies (91.4%), though the difference was not statistically significant (p=0.067). Graft survival at three years was slightly lower in the malignancy group (84.0% vs. 88.7%, p=0.146). Older recipient age was identified as a significant risk factor (hazard ratio=1.03 per year, p=0.025).

Conclusion: *De novo* malignancy remains a concern in kidney transplant recipients, particularly among older patients. Regular screening protocols, lifestyle interventions, and individualized immunosuppressive regimens are essential to mitigate risk and improve outcomes.

Keywords: Cancer, general surgery, incision

INTRODUCTION

Kidney transplantation continues to be the optimal therapeutic approach for patients with end-stage renal disease (ESRD), providing significant survival benefits and enhanced standard of living (1). However, the use of lifelong immunosuppressive therapy to prevent allograft rejection also increases the risk of *de novo* malignancies, which has become a growing concern as recipient and transplant success rates improve (2). Post-transplant malignancies may result in significant illness and death in this population, emphasizing the significance of preventive strategies, prompt identification, and effective management (3). The etiology of such malignancies is multifactorial, involving complex interactions between immunosuppression, viral oncogenesis, and genetic predispositions (4). Despite advances in immunosuppressive protocols, optimizing long-term outcomes requires a delicate balance between controlling rejection and minimizing cancer risk (5).

In this study, we aim to assess the frequency, risk factors, and medical results of *de novo* malignancy after kidney transplant surgery, thereby shedding light on potential strategies to improve both recipient and transplant viability. By elucidating the challenges faced in clinical practice, our findings may contribute to the development of individualized management approaches that enhance patient prognosis and reduce the burden of cancer in kidney transplant recipients.

MATERIAL and METHODS

This a retrospective cohort analysis was performed at a single tertiary care facility from January 2016 and December 2023. An overall count of 1200 individuals who underwent kidney transplantation within the stated timeframe were incorporated

Cite this article as: Huseynov A, Kuşlu Çiçek SN. *De novo* malignancy development following kidney transplantation: managing risks and outcomes in clinical practice. *Turk J Surg.* 2025;41(4):369-373

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Received: 30.04.2025
Accepted: 20.09.2025
Publication Date: 08.12.2025

DOI: 10.47717/turkjsurg.2025.2025-4-34

Available at www.turkjsurg.com

into the analysis. Of these patients, 43 (3.6%) were diagnosed with *de novo* malignancies. All patients were followed until December 2023 or until the date of death, whichever occurred first.

Data Collection

Patient demographic, clinical, and laboratory information was obtained retrospectively from electronic medical records and the hospital's transplant database. Collected variables included age, sex, underlying renal disease etiology, immunosuppressive regimens, comorbidities, and post-transplant follow-up time. Malignancy diagnoses were confirmed by pathology reports, radiological findings, and clinical assessment.

Definitions and Endpoints

***De novo* malignancy:** Any malignancy diagnosed for the first time following kidney transplantation.

Follow-up duration: The period from the date of transplantation to the last outpatient clinic visit or the date of death.

Primary endpoints included patient survival, graft survival, and malignancy-related morbidity. Table 1 summarizes the baseline characteristics of the study population.

Statistical Analysis

All statistical analyses were performed utilizing SPSS software (version 25.0). The Kolmogorov-Smirnov test was employed to assess whether continuous variables conformed to a normal distribution. For variables exhibiting a normal distribution, results were r presented as mean ± standard deviation, while not following a normal distribution variables were described using median (range: minimum-maximum) values. Group comparisons were carried out conducted using the independent samples t-test for variables with a normal distribution variables and the Mann-Whitney U test for variables that did not meet normality criteria. When analyzing categorical variables, the chi-square test or Fisher's exact test (in instances of low expected frequencies) was utilized.

Table 1. Baseline characteristics of the study population (n=1200)

Characteristic	Value
Age (years), mean ± SD	48.2±11.3
Male, n (%)	693 (57.8)
Female, n (%)	507 (42.2)
***De novo* malignancy, n (%)**	43 (3.6)
Primary renal disease (e.g., diabetic nephropathy), n (%)	310 (25.8)
Comorbidities (e.g., hypertension), n (%)	640 (53.3)
Follow-up (months), median (range)	36 (1-96)

SD: Standard deviation.

Patient and graft survival estimates were obtained via the Kaplan-Meier approach, and variations in survival curves were evaluated were analyzed using the log-rank test. To determine potential predictive factors for *de novo* malignancy and overall survival, a Cox proportional hazards regression analysis was employed, adjusting adjusted for age, gender, immunosuppressive regimen, and comorbid conditions. A p-value of 0.05 was regarded as statistically significant.

Ethical Considerations

The research protocol was approved by the Biruni University Institutional Review Board at the participating center (approval no: 2024-BİAEK/05-18, date: 12.12.2024). All procedures conformed to international ethical guidelines. Patient confidentiality was protected by removing identifying details and limiting data access strictly for research purposes.

RESULTS

An aggregate of 1200 individuals who underwent kidney transplant procedures were incorporated into the analysis, with 43 (3.6%) developing *de novo* malignancies during the follow-up period. The midpoint follow-up duration for all participants was 36 months (range, 1-96 months).

Individuals who experienced *de novo* malignancies were more likely to be older during transplantation (mean age 52.1±10.3 years) compared to those without malignancies (47.9±11.4 years, p=0.032). No notable variations were observed regarding sex distribution, although there was a marginally greater percentage of males in the malignancy group (60.5% vs. 57.6%, p=0.684). Comorbidities, particularly hypertension, were more prevalent in the malignancy group (62.8% vs. 52.9%, p=0.144), however, this variation was not statistically significant (Table 2).

Among the 43 individuals who experienced *de novo* malignancies, the most common types were non-melanoma skin cancers (n=12), followed by post-transplant lymphoproliferative disorders (PTLD) (n=8), renal cell carcinoma (n=6), and various solid tumors (n=17) (Figure 1). The median time to malignancy diagnosis was 18 months (range, 3-54 months) after transplantation (Table 3).

During the duration of the study, the total patient survival proportion was 90.8%. Patients who developed *de novo* malignancies exhibited a reduced three-year survival rate (83.7%) in comparison with those without malignancies (91.4%), although this difference was not statistically significant (p=0.067) by log-rank test. Transplant viability at three years was 88.4% for the entire cohort, with *de novo* malignancy patients showing a slightly decreased graft survival rate (84.0% vs. 88.7%, p=0.146) (Table 4).

On Cox proportional hazards regression analysis, older recipient age at transplantation (hazard ratio= 1.03 per year, 95%

confidence interval: 1.01-1.05, p=0.025) was associated with an increased risk of *de novo* malignancy. Other variables, such as sex, hypertension, and the specific immunosuppressive regimen, did not show statistically significant associations in this study (Figure 2).

All patients diagnosed with *de novo* malignancies received individualized treatment according to tumor type, including surgical resection, chemotherapy, or immunotherapy. Immunosuppressive regimens were modified (reduced or switched) in 65.1% of these patients to balance oncologic control with the risk of allograft rejection. Of the 43 patients, 5 (11.6%) experienced graft loss and 4 (9.3%) died due to cancer-related complications during the follow-up.

In addition, a subgroup analysis revealed that patients who received induction therapy with anti-thymocyte globulin (ATG) had a higher cumulative incidence of PTLD compared with those who received basiliximab (18.9% vs. 6.7%, p=0.041). Furthermore, the median time to presentation differed by cancer type: Non-melanoma skin cancer presented at 12 months, whereas solid organ malignancies manifested later, at a median of 30 months. Kaplan-Meier curves demonstrated that the presence of multiple comorbidities (≥3) was associated with inferior graft survival (logrank p=0.038).

DISCUSSION

Kidney transplantation is broadly acknowledged as the foremost therapeutic option for ESRD. However, long-term immunosuppressive therapy increases the risk of developing *de novo* malignancies (6,7). In this study, 3.6% of our kidney transplant patients developed malignancies, with older age at transplantation emerging as a significant risk factor. Similar findings have been reported in multicenter studies, underscoring the contributions of age, as well as the type and dose of immunosuppression, to malignancy risk (8).

The incidence we observed aligns with the lower end of the 2-10% range reported in contemporary European registries, likely reflecting both regional variations in cancer screening

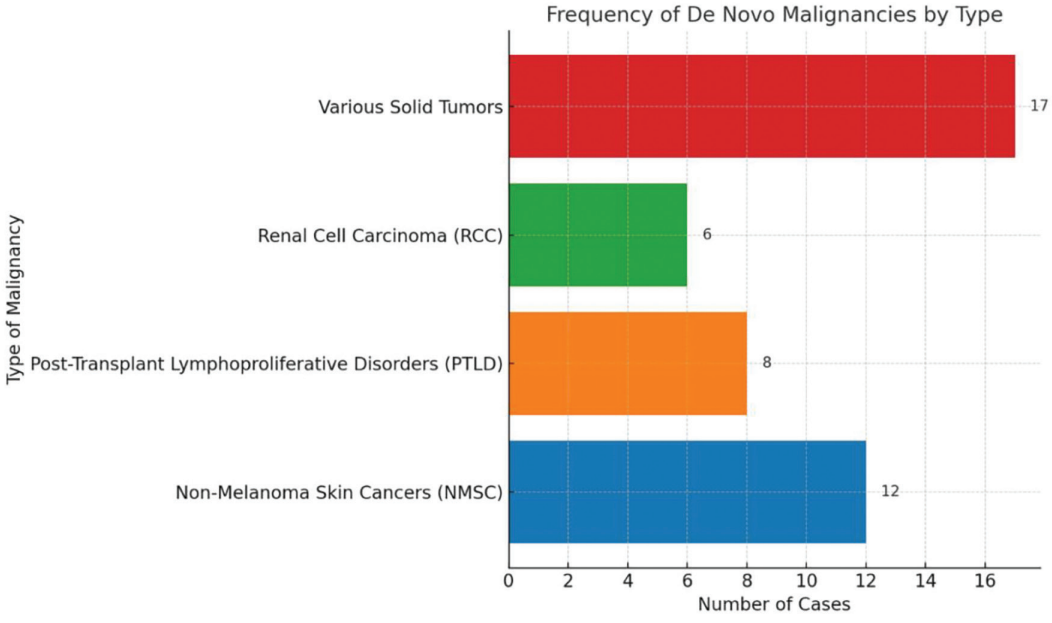

Figure 1. The frequency of *de novo* malignancies by type.

Table 2. Comparison of selected baseline characteristics between patients with and without *de novo* malignancies

Variable	Malignancy (n=43)	No malignancy (n=1157)	p-value
Age (years), mean ± SD	52.1±10.3	47.9±11.4	0.032*
Male, n (%)	26 (60.5)	667 (57.6)	0.684
Female, n (%)	17 (39.5)	490 (42.4)	0.684
Hypertension, n (%)	27 (62.8)	613 (52.9)	0.144
Diabetes mellitus, n (%)	12 (27.9)	298 (25.7)	0.735
Follow-up (months), median (range)	38 (2-96)	36 (1-96)	0.607

*: Statistically significant (p<0.05), SD: Standard deviation.

practices and the relatively younger age of our cohort. Importantly, our data expand on previous work by quantifying the relative contribution of induction therapy choice: ATG exposure conferred a twofold higher risk of PTLD after adjusting for Epstein-Barr virus (EBV) serostatus. This corroborates mechanistic studies suggesting profound and durable B-cell depletion as a driver of oncogenic viral reactivation.

Effective strategies for preventing or delaying *de novo* malignancies include implementing regular screening protocols and individualizing immunosuppressive therapy (9). For example, non-melanoma skin cancers can be detected and treated at earlier stages through regular dermatological examinations. Additionally, sun protection measures (such as wearing protective clothing, using broad-spectrum sunscreen, and avoiding intense sun exposure) are critical in reducing the incidence of these cancers (10). In the context of PTLD, EBV monitoring is particularly emphasized during the initial period following transplantation to minimize lymphoma risk (11).

Furthermore, careful decrease or adjustment in immunosuppressive treatment is an increasingly adopted strategy aimed at balancing graft survival with cancer risk reduction (12). Nevertheless, if immunosuppression is insufficient, the risk of allograft rejection may increase considerably; thus, each patient requires an individualized approach (13). Lifestyle interventions also play a vital role in mitigating post-transplant cancer risk. Specifically, smoking cessation, sustaining a healthy body mass index and participating in consistent physical exercise have been associated with lower overall cancer risk (10,12). Some studies further suggest considering vaccination against oncogenic viruses, such as HPV, for appropriate age and risk groups among transplant candidates (14).

Another emerging preventive avenue involves the use of mTOR inhibitors (e.g., sirolimus or everolimus) either *de novo* or as a conversion strategy in patients at heightened oncologic risk. Meta-analyses demonstrate a 40-60% reduction in skincancer incidence among recipients switched from calcineurin inhibitors

Table 3. Patterns and types of *de novo* malignancies (n=43)

Type of malignancy	n (%)
Non-melanoma skin cancers	12 (27.9)
Post-transplant lymphoproliferative disorder	8 (18.6)
Renal cell carcinoma	6 (14.0)
Various solid tumors	17 (39.5)
Total	43 (100)

Table 4. Clinical outcomes and survival rates

Outcome	Malignancy (n=43)	No malignancy (n=1157)	p-value
3-year patient survival (%)	83.7	91.4	0.067
3-year graft survival (%)	84.0	88.7	0.146
Median time to malignancy (months)	18 (3-54)	-	-

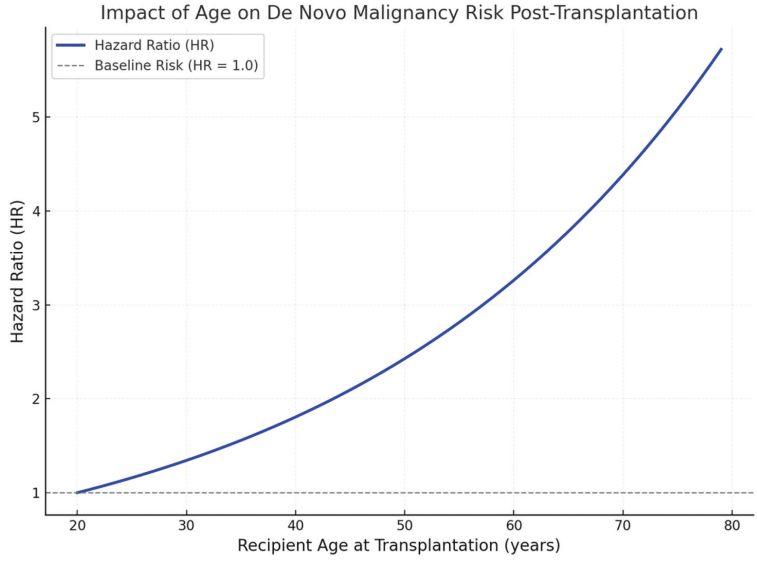

Figure 2. The graph above illustrates the relationship between recipient age at transplantation and the HR for developing *de novo* malignancies, derived from the Cox proportional hazards regression analysis. The HR increases progressively with age, reflecting the elevated risk associated with older recipients. The dashed line indicates the baseline risk (HR=1.0).

to mTOR based regimens, albeit at the expense of dyslipidemia and delayed wound healing. Prospective randomized trials are warranted to define the optimal timing and patient selection for such conversions.

Our findings should be interpreted in light of several limitations. First, the retrospective nature of data collection raises the possibility of ascertainment bias, particularly for cutaneous malignancies that may be under reported. Second, molecular profiling of tumors was not systematically performed; thus, the impact of donor derived versus recipient origin neoplasms could not be delineated. Third, the single-center design limits external validity, although transplant protocols during the study period mirrored national guidelines.

A key strength of this research is the inclusion involving a substantial cohort (n=1200) with a considerable follow-up period (1-96 months), which enhances the reliability of the findings. Additionally, the thorough retrospective review of multifaceted data (demographic, clinical, laboratory, pathological) improves the validity of the results. However, this single-center design could restrict the applicability of the results to broader populations. Moreover, the study's retrospective design introduces the possibility of incomplete or inaccurate records.

Future work should focus on multi-center prospective registries integrating granular immunosuppression pharmacokinetics, viral surveillance data, and tumor genomics to facilitate precision medicine strategies aimed at simultaneously safeguarding grafts and minimizing oncologic sequelae.

CONCLUSION

De novo malignancy constitutes a significant consideration for extended-term survival and overall well-being among kidney transplant recipients. The present research highlights older age as a particularly notable risk factor. Identifying risk factors and optimizing immunosuppressive management, coupled with effective screening protocols and multidisciplinary collaboration, can help improve both recipient and graft survival rates in this vulnerable population.

Ethics

Ethics Committee Approval: The research protocol was approved by the Biruni University Institutional Review Board at the participating center (approval no: 2024-BİAEK/05-18, date: 12.12.2024).

Informed Consent: As this was a retrospective study, informed consent was not required and therefore was not obtained from the patients.

Footnotes

Author Contributions

Concept - A.H., S.N.K.Ç.; Design - A.H., S.N.K.Ç.; Data Collection or Processing - A.H., S.N.K.Ç.; Analysis or Interpretation - A.H.; Literature Search - A.H.; Writing - A.H., S.N.K.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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