British Journal of Cancer www.nature.com/bjc

ARTICLE

Epidemiology

De novo colorectal cancer after kidney transplantation: a systematic review and meta-analysis

Bima J. Hasjim[1], Arsha Ostowari[1], Monique Gandawidjaja[1], Mohsen D. Mohammadi[2], Linda Suk-Ling Murphy[3], Matthew D. Whealon[4], Valery Vilchez[4], Hirohito Ichii[5], Robert R. Redfield III[5] and Oliver S. Eng[6]✉

BACKGROUND: Kidney transplant (KT) patients have higher risks of developing de novo colorectal cancer (CRC) compared to the general population. However, there is still a knowledge gap in their clinical characteristics, as most single- or multi-center efforts are underpowered and lack generalizability.
METHODS: PubMed, Web of Science, Cochrane CENTRAL, and Scopus databases were queried for studies published until July 22nd, 2024. Studies reporting the clinicopathologic characteristics and outcomes of de novo CRC among KT recipients were included.
RESULTS: There were 49 articles included involving 1855 KT patients who developed CRC. The mean time from transplantation to CRC diagnosis was 8·7 years (95%CI 7·2, 10·3 years; $I^2 = 98·3\%$). De novo CRC was most commonly located in the ascending colon (43·6%; 95%CI 29·5%, 58·9%; $I^2 = 55·3\%$), and 37·1% had advanced CRC at diagnosis (95%CI 22·3%, 54·8%; $I^2 = 64·1\%$). Although 68·8% underwent curative intent treatment (95%CI 45·4%, 85·4%; $I^2 = 65·4\%$), pooled 5-year survival rate was 31·8% (95%CI 10·5%, 65·1%; $I^2 = 82·5\%$).
CONCLUSIONS: De novo CRC was diagnosed in under 10 years after KT, and nearly 40% of patients already have advanced stage disease at diagnosis. The pooled rate of 5-year survival was 31.8%. However, there was wide heterogeneity between studies and further research is required. PROSPERO Registration: CRD42023415767.

British Journal of Cancer; https://doi.org/10.1038/s41416-025-02994-7

BACKGROUND

Kidney transplantation (KT) is the only definitive treatment for chronic kidney disease and is the most common type of solid organ transplant globally [1]. Unfortunately, de novo colorectal cancer (CRC), or CRC that develops after KT, is a concerning potential sequelae after solid organ transplantation with incidences as high as 2–3 times those of the general population [2]. Additionally, these tumors have been postulated to be more aggressive as KT recipients have been found to have a 5.4-fold increased risks of developing advanced stage CRC [3]. These complications are likely due to the combined effects of obligate immunosuppression, chronic inflammation, and other factors related to long-term renal disease [4].

Although there have been systematic reviews and meta-analyses dedicated to describing the increased incidence of de novo CRC in solid organ transplant patients, there is still a critical knowledge gap regarding the characteristics and outcomes of these tumors, particularly among KT patients [4–6]. Existing studies on the natural history of this disease process are currently confined to relatively small, underpowered, patient cohorts that restrict the generalizability of their findings. Furthermore, there are no specialized CRC screening or surveillance guidelines for KT patients despite their higher prevalence and various risk factors for de novo CRC [7–9]. This clinical oversight and gap in the literature highlight the need for larger-scale analyses to better understand the characteristics and clinical trajectory of de novo CRC in KT recipients.

Thus, we conducted a systematic review and meta-analysis of observational studies that synthesize the available literature on the oncologic characteristics and outcomes of patients who developed CRC after KT. We hypothesized that KT patients develop de novo CRC in a short time interval, are diagnosed at more advanced stages, and have poor survival [10]. By pooling data from multiple studies, this analysis aims to overcome the limitations of individual small-scale studies, offering a more robust estimation of the clinical presentation of CRC and outcomes among KT patients.

METHODS

Search strategy

This systematic review and meta-analysis were designed and analyzed in accordance to the Preferred Reporting Items for Systematic Reviews and

[1]Department of Surgery, University of California, Orange, CA, USA. [2]Industrial Engineering and Management Sciences, Northwestern University, Evanston, IL, USA. [3]Research Librarian for Health Sciences, University of California, Irvine, CA, USA. [4]Division of Colon and Rectal Surgery, Department of Surgery, University of California, Orange, CA, USA. [5]Division of Transplantation, Department of Surgery, University of California Irvine School of Medicine, Orange, CA, USA. [6]Division of Surgical Oncology, Department of Surgery, University of California, Orange, CA, USA. ✉email: oeng@hs.uci.edu

Received: 30 October 2024 Revised: 5 March 2025 Accepted: 21 March 2025
Published online: 05 April 2025

Meta-analyses Protocols (PRISMA-P) [11] and Meta-analyses of Observational Studies in Epidemiology (MOOSE) [12] guidelines (Supplemental Table S1, Table S2). This study was also registered in the PROSPERO database of systematic review protocols (PROSPERO ID: CRD42023415767).

We conducted an electronic literature search using PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify relevant studies with the help of a biomedical information specialist (LSM). Studies identified from database inception through, July 22nd, 2024 were included. To develop a comprehensive search strategy adaptable to each selected database, we identified relevant keywords, synonyms, and MeSH (Medical Subject Headings) terms addressing incidence and risk factors of de novo CRC in KT patients. An initial comprehensive search of the selected databases was conducted on April 15th, 2023, with no language or publication date restrictions. An updated search was conducted on July 22nd, 2024, to capture any newly published relevant studies since the initial search. See Supplementary Table S3 and S4 for the detailed search strategy of each database.

Study selection and eligibility criteria

All observational studies that describe the oncologic characteristics and outcomes of KT patients with de novo CRC were included. Based on the predefined eligibility and inclusion criteria, two independent reviewers (BJH and AO) screened each study's title/abstract and full text using Covidence, a systematic review software tool (Veritas Health Innovation, Melbourne, Australia). Discrepancies were discussed, resolved, and, if necessary, reconciled through discussion with a third reviewer (MG). Three investigators (BJH, AO, MG) independently extracted the data from each included study. Studies involving cohorts with non-colorectal cancers, patients with elevated risks of CRC (e.g., inflammatory bowel disease), transplants that occurred to treat cancer, or multi-organ transplantation were excluded. Case reports, animal studies, non-peer reviewed communications (e.g., editorials, letters), other systematic reviews or meta-analyses, or conference abstracts were also excluded from our analysis. Articles regarding patients with concomitant known cancer risks (e.g., inflammatory bowel disease), those where full texts were unavailable, or any other cases where data could not be extracted were excluded. Figure 1 shows the PRISMA flow diagram detailing the study selection process.

Study population and outcomes of interest

A standardized data extraction form was used to collect the study details, patient characteristics and outcomes. KT recipient characteristics of interest included demographic, oncologic characteristics, treatment strategies, and outcomes. Only cases of colorectal cancers (e.g., adenocarcinoma, sarcoma) were included in the study. Although adenomas and their different types (e.g., high-grade, advanced, Tubulovillous) were excluded from the analysis because their management is different from confirmed cancers, their outcomes are qualitatively described in Supplement Table S5. Curative intent treatment strategies included surgical resection of the primary tumor with or without neoadjuvant or adjuvant chemotherapy. Cancer-related death was defined as death with a functioning graft. The main outcomes of interest were time from transplant to CRC diagnosis and 5-year survival.

Quality assessment and risk of bias

The quality of evidence for each study and risk of bias were assessed using the Newcastle-Ottawa Quality Assessment for Cohort Studies tool [13]. A score was given by three investigators (BJH, AO, MG) who independently

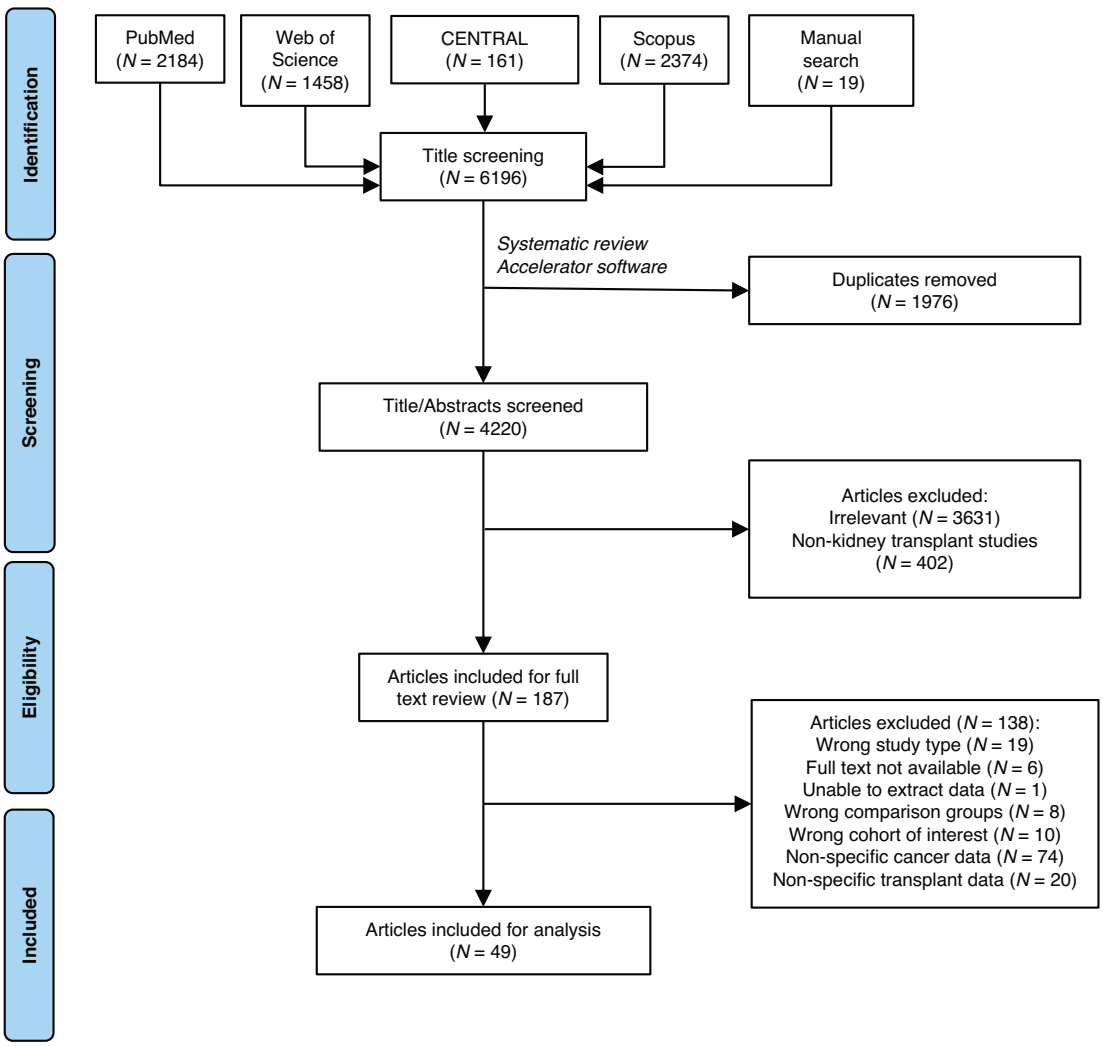

Fig. 1 Search results and application of eligibility criteria. Flow chart of included articles.

rated the quality of each study across three domains: 1) patient selection and ascertainment of the exposure; 2) comparability of cohorts based on the study design; 3) availability and assessment of outcomes. Based on the scores obtained through the quality assessment, studies were rated as "Good Quality", "Fair Quality", or "Poor Quality" (Supplemental Table S6). Disagreements in scoring were discussed and resolved to reach a consensus. A meta regression analysis was conducted to determine if the true effect size of the main outcomes of interest was associated with its risk of bias (Supplemental Fig. S1). Publication bias was assessed using funnel plots and Egger's test for asymmetry (Supplemental Fig. S2).

Statistical analysis

Pooled categorical and continuous variables were presented as percentages and means (center value), respectively, with a corresponding 95% confidence interval (95%CI). As previously published, sample sizes, medians, and interquartile ranges were used to estimate means and standard deviations in situations where these variables were missing [14, 15]. If statistical components for analyses were not available, these studies were omitted from the final analysis but were maintained in the dataset and forest plots for completeness. A common effect (or fixed-effect method) and random effect model were used for the analyses of statistically homogenous ($I^2 < 50\%$) and heterogenous data ($I^2 > 50\%$), respectively. Both common effect and random effect models were conducted for each outcome as sensitivity analyses to ensure there were no significant differences. The Mantel-Haenszel and inverse variance approaches were used to analyze categorical and continuous data, respectively. An alpha level (*P*-value) of <0.05 was considered to be statistically significant. Data processing and analysis were performed using R studio (version 4.3.1; Vienna, Austria).

RESULTS

Overview of the study selection process

A total of 6196 articles were identified. After removing duplicates ($N = 1976$ articles) and screening titles/abstracts ($N = 4220$ articles), 187 articles were included for full-text review. Of these, 138 did not meet the selection criteria, and 49 manuscripts [2, 3, 16–62] were included in the final analysis (Fig. 1).

There were 32 (65.3%) single center studies, 3 (6.1%) multi-center studies, and 14 (28.6%) nationwide database studies with the majority being a retrospective study design ($N = 44$, 89.8%). Studies from the following countries were represented in this analysis: Korea ($N = 12$, 24.5%), Italy ($N = 7$, 14.3%), USA ($N = 6$, 12.2%), Portugal ($N = 3$, 6.1%), Australia/New Zealand ($N = 3$, 6.1%), Ireland ($N = 2$, 4.1%), Poland ($N = 2$, 4.1%), Taiwan ($N = 2$, 4.1%), United Kingdom ($N = 2$, 4.1%), Japan ($N = 2$, 4.1%), Belgium, China, Finland, France, Hungary, Singapore, Spain, Thailand (all $N = 1$, 2.0%). Supplemental Table S6 provides a summary of study characteristics and findings of each study included in the analysis.

Characteristics of kidney transplant recipients with de novo CRC

Across the 49 studies, there were 1855 KT recipients who developed de novo CRC. The mean age at receipt of transplant was 47.6 years (95%CI 45.9, 49.4 years; $I^2 = 85.4\%$), while the mean age at CRC diagnosis was 58.2 years (95%CI 56.4, 59.9 years; $I^2 = 90.1\%$). The mean time from transplant to CRC diagnosis was 8.7 years (95%CI 7.2, 10.3 years; $I^2 = 98.3\%$) (Fig. 2). The majority of KT patients with de novo CRC were male (55.4%; 95%CI 51.2%, 59.6%; $I^2 = 1.1\%$), and 27.6% (95%CI 14.2%, 46.7%; $I^2 = 40.2\%$) had a history of smoking (Table 1).

De novo CRC was most commonly located in the ascending colon (43.6%; 95%CI 29.5%, 58.9%; $I^2 = 55.3\%$), followed by the descending colon (28.6%; 95%CI 21.4%, 37.1%; $I^2 = 0.0\%$), rectum (25.4%; 95%CI 18.7%, 33.6%; $I^2 = 0.0\%$), and transverse colon (5.1%; 95%CI 2.0%, 12.7%; $I^2 = 0.0\%$). Advanced stage (Stage III/IV)

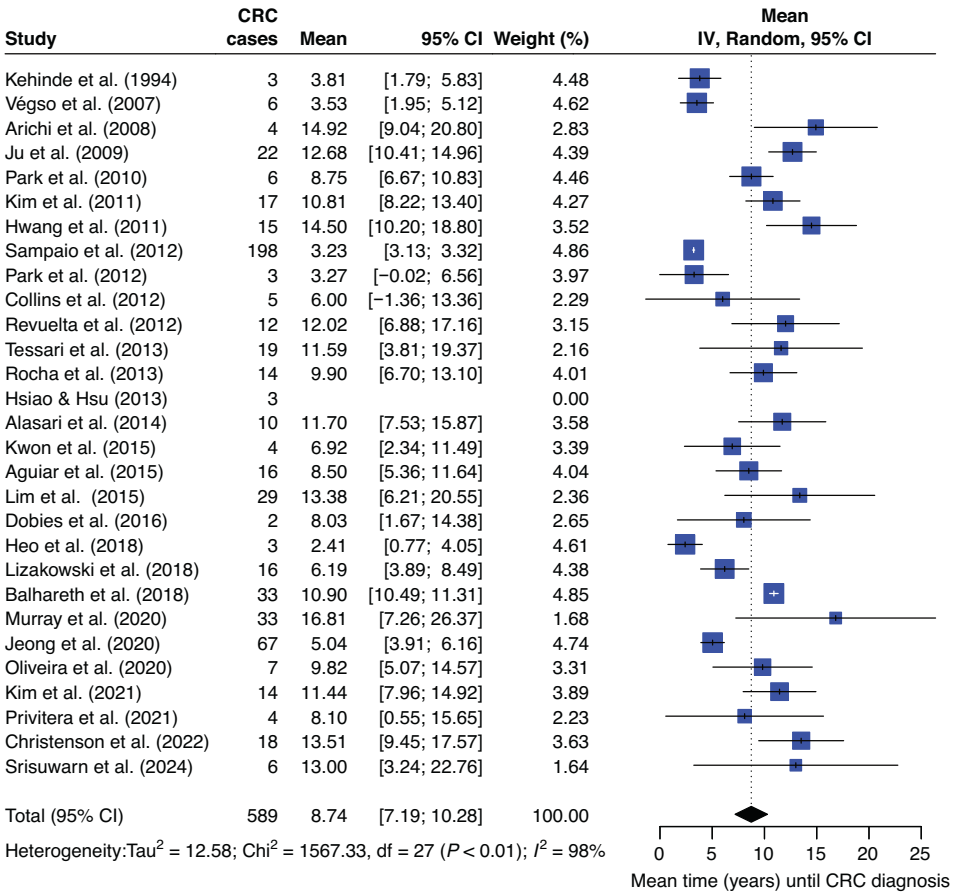

Fig. 2 Forrest plot of mean time from KT to CRC diagnosis in years. The mean time from transplant to CRC diagnosis was 8.7 years (95%CI 7.2, 10.3 years; I2 = 98.3%).

Table 1. Clinicodemographic characteristics of KT patients with de novo CRC.

Characteristics	Studies analyzed (Total $N = 49$)	KT recipients analyzed (Total $N = 1855$)		I^2
Age (years), mean (95%CI)				
At Transplantation	21	659	47.6 (45.9, 49.4)	85.4%
At CRC diagnosis	22	586	58.2 (56.4, 59.9)	90.1%
Time (years) from transplant to CRC diagnosis, mean (95% CI)	28	589	8.7 (7.2, 10.3)	98.3%
Male, % (95%CI)	23	536	55.4% (51.2%, 59.6%)	1.1%
Smoking history, % (95%CI)	3	48	27.6% (14.2%, 46.7%)	40.2%
Location, % (95%CI)				
Ascending	6	113	43.6% (29.5%, 58.9%)	55.3%
Transverse	3	79	5.1% (2.0%, 12.7%)	0.0%
Descending	8	126	28.6% (21.4%, 37.1%)	0.0%
Rectum	7	130	25.4% (18.7%, 33.6%)	0.0%
Stage at Diagnosis, % (95%CI)				
Local	11	147	45.6% (37.7%, 53.7%)	26.0%
Advance	11	158	37.1% (22.3%, 54.8%)	64.1%
CEA at diagnosis, mean (95%CI)	2	29	4.99 (2.84, 7.14)	95.8%
Treatment, % (95%CI)				
Curative	10	133	68.8% (45.4%, 85.4%)	65.4%
Palliative	6	80	26.3% (17.8%, 36.9%)	6.5%
Histology, % (95%CI)				
Well Differentiated	3	79	16.5% (9.8%, 26.3%)	36.4%
Moderately Differentiated	4	112	62.4% (46.7%, 75.9%)	67.4%
Poorly Differentiated	5	113	11.5% (6.8%, 18.8%)	0.0%
Mucin or Signet	3	79	21.9% (8.9%, 44.8%)	71.5%
CRC Recurrence, % (95%CI)	3	47	19.2% (10.3%, 32.9%)	0.0%
Cancer-related Death, % (95%CI)	8	145	41.4% (33.7%, 49.6%)	32.9%
Time to death after CRC diagnosis (years), mean (95%CI)	5	58	1.9 (0.3, 3.5)	78.7%
5-year survival, % (95%CI)	7	158	31.8% (10.5%, 65.1%)	82.5%

KT kidney transplant, *CRC* colorectal cancer, *CEA* carcinoembryonic antigen.

CRC was found at diagnosis in 37.1% (95%CI 22.3%, 54.8%; $I^2 = 64.1\%$) of patients. Most of the tumors were moderately differentiated (62.4%; 95%CI 46.7%, 75.9%; $I^2 = 67.4\%$), and 21.9% were mucinous or signet cell tumors (95%CI 4.2%, 60.8%; $I^2 = 71.5\%$) (Table 1).

Of all patients with de novo CRC, 68.8% underwent curative intent treatment (95%CI 45.4%, 85.4%; $I^2 = 65.4\%$). The pooled rate of recurrence was 19.2% (95%CI 10.3%, 32.9%; $I^2 = 0.0\%$). There were 41.4% (95%CI 33.7%, 49.6%; $I^2 = 32.9\%$) cancer-related deaths or deaths that occurred with a functioning allograft (Fig. 3a). The mean time to death after CRC diagnosis was 1.9 years (95%CI 0.3, 3.5 years; $I^2 = 78.7\%$), and the 5-year survival rate was 31.8% (95%CI 10.5%, 65.1%; $I^2 = 82.5\%$) (Fig. 3b) (Table 1).

Study quality

There was high heterogeneity and variable quality among studies. There were 32 (65.3%) studies that were graded as "Good Quality", 13 (26.5%) studies as "Poor Quality", and four (8.2%) studies as "Fair Quality". All studies did well in ascertaining the exposure and allowed adequate amount of follow-up to observe outcomes. There were a minority of studies ($N = 19$, 32.7%) that demonstrated a process to ascertain that patients did not have a prior history of CRC prior to KT (Table S5). In a meta regression analysis of the study quality and its association with mean time to de novo CRC diagnosis, 31.0% ($R^2 = 31.0\%$) of the effect sizes may be explained by the quality of data (Fig. S1). Though there is wide variability in the reported results, the Egger's test showed that there was no evidence of publication bias ($P = 0.29$) (Fig. S2).

DISCUSSION

Despite the known risk of de novo CRC among KT recipients, there is a dearth in the literature that describes the epidemiologic characteristics and outcomes of these patients. Currently, the empirical evidence on this topic is limited to small sample sizes that lack generalizability. To our knowledge, this is the first systematic review and meta-analysis that synthesizes the characteristics and outcomes of this disease process. We found that de novo CRC developed in just under 10 years after KT, with high rates of advanced stage at diagnosis (37.1%), and low 5-year survival (31.8%). As expected, there was heterogeneity among studies with differing risks of bias. Though further rigorous research is required in this population to definitively suggest changes in practice, this meta-analysis may be an essential first step to inform thoughtful screening guidelines and guide future research in this high-risk population.

The molecular pathways of de novo CRC can yield important insights towards immunosuppression management and mitigating its risk of oncogenesis, as each KT patient may also have their own unique genetic predispositions. Four main pathways have been implicated in the development of CRC: 1) chromosomal instability (e.g., adenomatous polyposis coli [APC]), 2) mutations in

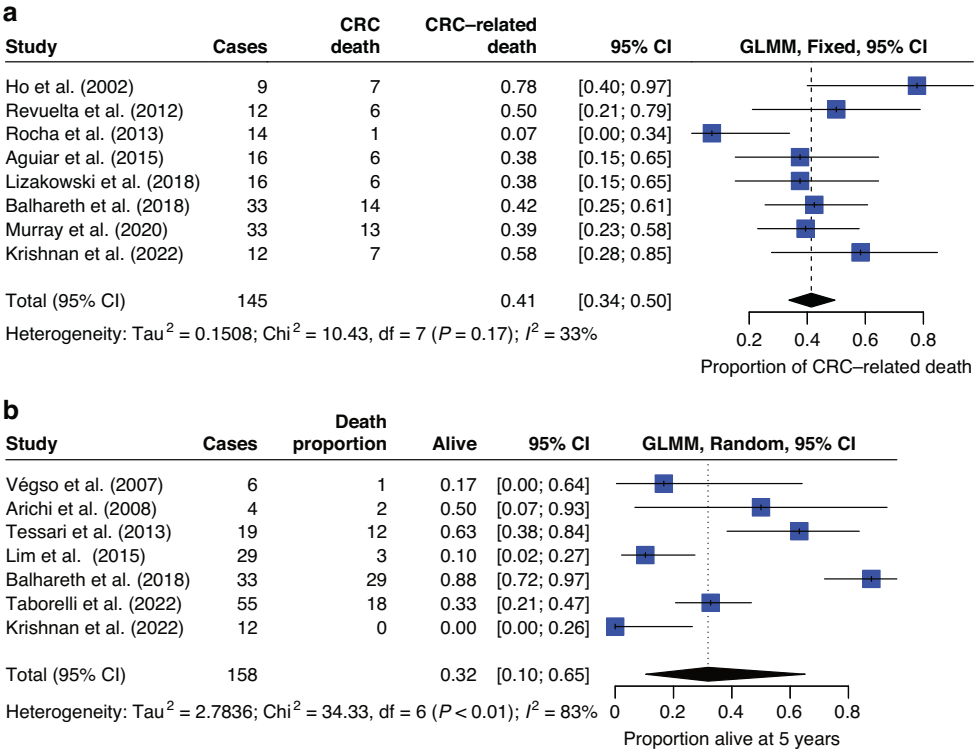

Fig. 3 Pooled overall survival rates and long-term survival of KT patients with de novo CRC. Forrest plot of (**a**) the proportion of CRC-related death and (**b**) 5-year survival among KT patients with de novo CRC. There were 41.4% (95%CI 33.7%, 49.6%; $I^2 = 32.9\%$) cancer-related deaths or deaths that occurred with a functioning allograft (**a**). The pooled 5-year survival rate was 31.8% (95%CI 10.5%, 65.1%; $I^2 = 82.5\%$) (**b**).

DNA mismatch repair (e.g., mutL homolog 1 [MLH1], MLH2), 3) inappropriate activation of proto-oncogenes (e.g., Ras), and 4) dysregulation of the phosphatidylinositol-3-kinase (PI3K) pathway (Fig. 4) [4, 63, 64]. Of the four pathways, sporadic mutations leading to chromosomal instability involving the APC gene are the most prevalent and responsible for over 70% of all CRC [4, 65]. Higher CRC incidence has been associated with longer exposure and higher doses of immunosuppression [66]. Solid organ transplant recipients do not necessarily have different pathogenic pathways towards CRC compared to the general population. Rather, it is the immunosuppression that accelerates these pathways and interferes with immune surveillance [41]. For example, Christensen et al., found that patients with de novo CRC had higher rates of mismatch repair and tumor mutation burden [41]. Additionally, KT recipients who were treated with calcineurin inhibitors were associated with higher rates of KRAS mutations [2]. Conversely, mTOR inhibitors may have anti-oncogenic properties as they were associated with decreased rates of cancer development compared to other immunosuppression regimens [67]. These findings highlight the differential effects of immunosuppression strategies on colorectal oncogenesis as they often overlap in their mechanisms of action [68–70].

Despite the higher prevalence of CRC [2], KT recipients do not receive specialized screening or surveillance schedules. Currently, these patients are still considered as "average risk" and follow screening intervals every 10 years just as the general population. In a meta-analysis by Acuna et al., the European Best Practice Guideline was the only guideline of 10 others that recommended enhanced screening recommendations for solid organ transplant recipients through fecal occult blood tests – though they did not mention a specific screening frequency [8]. Among the liver transplant community, the American Association for the Study of Liver Disease (AASLD) recommends colonoscopies annually, but only for liver transplant patients with another established risk factor for CRC such as primary sclerosing cholangitis and inflammatory bowel disease [8]. Through our meta-analysis, we found that KT recipients develop de novo CRC in about 8 years, providing evidence that suggests a specific, more frequent, screening and surveillance strategy may be beneficial. Single-center efforts, such as those from Kato et al., have found clinical benefits after implementing an annual screening protocol to screen for post-KT malignancy [40, 56, 71]. In this study, patients who did not participate in the specialized screening protocol had more than a 2.5-fold increased risk of malignancy [56]. Screening guidelines for KT recipients should reflect the increased risk for CRC incidence and aggressive tumor behavior. Further research regarding the implementation of such guidelines and their survival benefits is warranted.

Along with the timing of CRC screening and surveillance, the modality used should also be considered. Although current guidelines allow for the use of sigmoidoscopy for screening, this may lead to higher false negative results, as our meta-analysis showed that de novo CRC was most frequently found in the ascending colon (43.6%). These findings underscore the importance of visualizing the entire colon through a full colonoscopy, as a sigmoidoscopy will be inadequate to detect these tumors. In a cross-sectional study of 229 KT recipients, one case of advanced neoplasia was identified for every eight colonoscopies [40]. However, it is important to note that colonoscopies are more invasive in nature and require more care coordination with each patient's social support system compared to other screening modalities that can be performed without anesthesia, in the clinic (e.g., sigmoidoscopy, fecal occult bleed tests [FOBT]), or collected at home (e.g., Fecal immunochemical tests [FIT]). Care providers should have an individualized discussion regarding the most appropriate method for screening and surveillance. Annual FOBT could be a non-invasive alternative to colonoscopies, and there is evidence to show that its positive predictive value may increase as

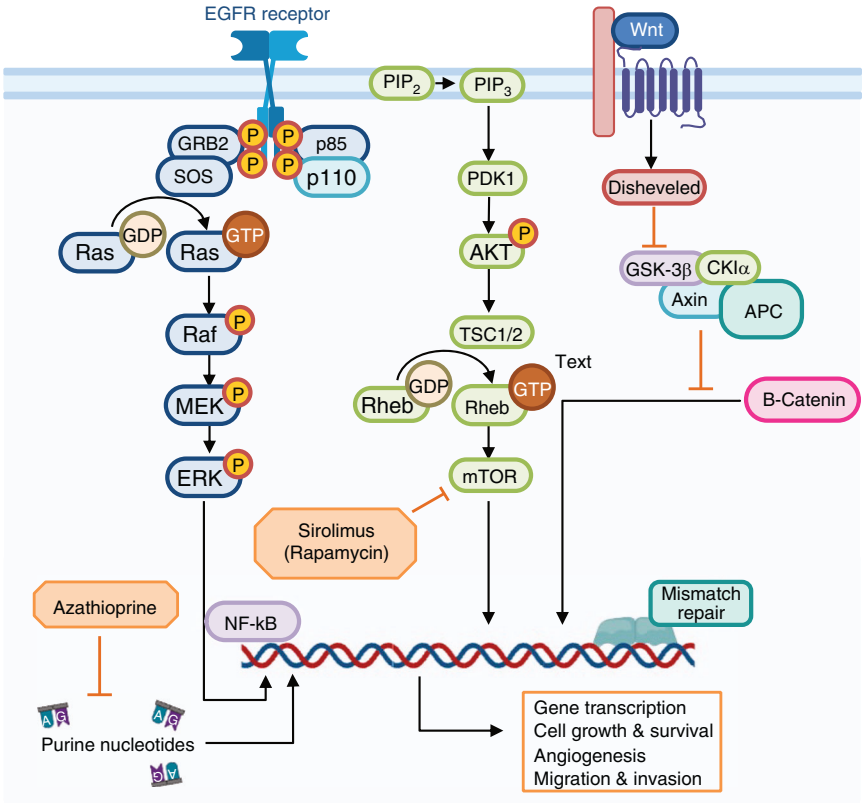

Fig. 4 Main intracellular pathways within intestinal epithelial cells that may lead to de novo CRC in KT patients. Illustration of the four main pathways within intestinal epithelial cells that can result in de novo CRC among KT patients and the interaction with common immunosuppression drugs: 1) chromosomal instability (e.g., APC), 2) mutations in DNA mismatch repair (e.g., MLH1, MLH2), 3) inappropriate activation of proto-oncogenes (e.g., Ras), and 4) deregulation of the phosphatidylinositol-3-kinase (PI3K) pathway [4]. Inhibitors of mTOR and purine nucleotide synthesis may have anti-oncogenic properties.

the severity of chronic kidney disease worsens due to the immunosuppressive effects of uremia and tendency for occult bleeding [72, 73]. FOBT efficacy among a cohort of KT patients still requires further investigation, but there are reasons to conjecture that it would perform more poorly, as KT recipients are predisposed to gastrointestinal bleeding due to infectious complications, angiodysplasia, drug toxicity, and mucosal inflammation [72]. FIT has poor sensitivity (31.0%) but can be used to supplement interval colonoscopies, as it has been shown to have similar accuracy at detecting neoplasia with reasonable specificity (90.5%) [40]. Annual FIT, followed by colonoscopy, has been reported to have an incremental cost effective ratio of $22,309 per life years saved with a 45% relative risk reduction in CRC-specific mortality [74]. The larger KT community may benefit from guideline recommendations similar to those receiving lung transplantation for cystic fibrosis. In these cases, CRC surveillance has been recommended to be performed within two years after lung transplantation and every three years after [75]. At the bare minimum, our findings suggest that KT recipients should be recognized as a "high risk" subpopulation for developing CRC – though not as high as known CRC syndromes such as inflammatory bowel disease. Given that our meta-analysis showed that CRC diagnosis occurs an average of 8.7 years after KT, the potential survival benefits of more frequent screening, while also considering its direct costs, a reasonable approach to screening may involve interval colonoscopy every five years with or without supplementation of annual screening through non-invasive methods (e.g., FOBT, FIT). This screening interval, positioned between those for the general population and high risk CRC syndromes, may offer a balanced, cost-effective, and practical strategy with survival benefits.

At the very least, our data suggest the importance of adherence to CRC screening guidelines prior to transplantation given the current recommended age for CRC surveillance in the general population is now 45 years old [76]. The prevalence of advanced neoplasia among solid organ recipients are also elevated at 9.2%, which is over 2-fold of the general population [77]. It will be important to screen for pre-malignant polyps in the pre-transplant setting—polyps that could potentially advance to malignancy once the post-transplant immunosuppression regimen begins. Kwon et al. found that KT recipients were associated with 2.3 times higher odds of developing advanced colonic neoplasms compared to matched controls [3]. Among these patients, elderly age and advanced neoplasms were independent risk factors of developing advanced neoplasms [3]. Given the various modalities of CRC screening, a personalized approach to screening can be used in addition to sweeping guideline recommendations. Length of exposure and intensity of maintenance immunosuppression medications may interact with individual genetic predispositions and family history of CRC that should be considered when counseling screening intervals and immunosuppression strategies [78]. Traditional, individual risk factors of CRC, such as smoking, comorbidities, and viral-related cancers, are also at play. Previously discussed standards for surveillance intervals may be shortened to be more frequent considering the interactions of immunosuppression, family and individual history though future prospective work is necessary.

There were several limitations to our systematic review and meta-analysis. First, the level of heterogeneity among studies that were included was fair and these findings should be interpreted cautiously. Future research should emphasize comparisons with the general population, and match for potential confounders (e.g.,

sex, age), in order to better inform screening and surveillance strategies. Prospective, multicenter collaboratives or construction of dedicated registries for patients with de novo CRC with systematic data collection may help moderate the heterogeneity and biases we encountered. Second, the studies included in our review did not have the granularity to account for differences in immunosuppression regimen, country-specific epidemiology, and screening practices for CRC. The studies that were included in our meta-analysis spanned an international cohort encompassing many countries, and it should be worth noting that the prevalence of CRC differs from country to country depending on the unique epidemiology of international cohorts. However, because de novo CRC is such a rare occurrence, our meta analysis's ability to pool samples from different, international studies has wide generalizability compared to smaller studies. Third, though we excluded studies that included patient factors with known risks of de novo CRC (e.g., inflammatory bowel disease, cystic fibrosis), these patients may be inherently included in national kidney transplant registries where these data were not specifically collected. Fourth, our analyses were restricted by lack of data from each study regarding their data missingness, time of follow-up, and cohort censoring. Lastly, our review may be susceptible to publication bias since only published, peer-reviewed articles were included. Although our Egger's test showed that the risk of publication bias was low, there was high variability in the funnel plot analysis. Yet, this ensures that the quality of studies is as high as possible. Nevertheless, our systematic review and meta-analysis describing the characteristics of de novo CRC in KT patients worldwide highlights the need for more vigilant screening in a high-risk population.

CONCLUSION

In summary, our systematic review and meta-analysis found that de novo CRC may arise in under 10 years after KT. KT patients with de novo CRC were associated with advanced stage disease at diagnosis and poor 5-year survival. However, future prospective research are warranted to more accurately inform screening or surveillance guidelines as currently available studies in the literature have wide heterogeneity and vary in quality.

DATA AVAILABILITY

Data used in the results of this systematic review and meta-analysis, its study protocol, and statistical analysis plan will be made available following publication upon request. Please contact the corresponding author via email with a study proposal (e.g., statistical plan, study protocol) and details regarding how the data will be used.

REFERENCES

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. Nephrol Dialysis Transplant. 2019;34:1803–5.
2. Revuelta I, Moya-Rull D, García-Herrera A, Rovira J, Ayala De La Peña F, Misiego A, et al. Role of oncogenic pathways and KRAS/BRAF mutations in the behavior of colon adenocarcinoma in renal transplant patients. Transplantation. 2012;93:509–17.
3. Kwon JH, Koh SJ, Kim JY, Kim JW, Lee KL, Kim BG, et al. Prevalence of advanced colorectal neoplasm after kidney transplantation: surveillance based on the results of screening colonoscopy. Dig Dis Sci. 2015;60:1761–9.
4. Prenner S, Levitsky J. Comprehensive review on colorectal cancer and transplant. Am J Transplant. 2017;17:2761–74.
5. Jin F, Vajdic CM, Poynten IM, McGee-Avila JK, Castle PE, Grulich AE. Cancer risk in people living with HIV and solid organ transplant recipients: a systematic review and meta-analysis. Lancet Oncol. 2024;25:933–44.
6. Safaeian M, Robbins HA, Berndt SI, Lynch CF, Fraumeni JF, Engels EA. Risk of colorectal cancer after solid organ transplantation in the United States. Am J Transplant. 2016;16:960–7.
7. Au E, Wong G, Chapman JR. Cancer in kidney transplant recipients. Nat Rev Nephrol. 2018;14:508–20.
8. Acuna SA, Huang JW, Scott AL, Micic S, Daly C, Brezden-Masley C, et al. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. Am J Transplant. 2017;17:103–14.
9. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, et al. Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol. 2000;11:S1.
10. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA A Cancer J Clin. 2023;73:233–54.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372. Available from: https://www.bmj.com/content/372/bmj.n71.
12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283:2008–12.
13. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2024. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
14. Shi J, Luo D, Weng H, Zeng XT, Lin L, Chu H. et al. Optimally estimating the sample standard deviation from the five-number summary. Res Synth Methods. 2020;11:641–54.
15. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27:1785–805.
16. Kim JY, Ju MK, Kim MS, Kim NK, Sohn SK, Kim SI, et al. Clinical characteristics and treatment outcomes of colorectal cancer in renal transplant recipients in Korea. Yonsei Med J. 2011;52:454.
17. Park JM, Choi M-G, Kim SW, Chung I-S, Yang CW, Kim YS, et al. Increased incidence of colorectal malignancies in renal transplant recipients: a case control study. Am J Transplant. 2010;10:2043–50.
18. Dobies A, Renke M, Wołyniec W, Palenicek L, Januszczyk J, Król E, et al. Gastrointestinal pathologies in patients after successful renal transplantation—a pilot study. Transplant Proc. 2016;48:1566–9.
19. Heo J, Noh OK, Oh YT, Chun M, Kim L. Cancer risk after renal transplantation in South Korea: a nationwide population-based study. BMC Nephrol. 2018;19:311.
20. Friman TK, Jäämaa-Holmberg S, Åberg F, Helanterä I, Halme M, Pentikäinen MO, et al. Cancer risk and mortality after solid organ transplantation: a population-based 30-year cohort study in Finland. Int J Cancer. 2022;150:1779–91.
21. Murray SL, O'Leary E, De Bhailís ÁM, Deady S, Daly FE, O'Kelly P, et al. Cancer survival in kidney transplant recipients in Ireland. Nephrol Dial Transplant. 2020;35:1802–10.
22. Blosser CD, Haber G, Engels EA. Changes in cancer incidence and outcomes among kidney transplant recipients in the United States over a thirty-year period. Kidney Int. 2021;99:1430–8.
23. Kim M, Kim CW, Hwang S, Kim YH, Lee JL, Yoon YS, et al. Characteristics and prognosis of colorectal cancer after liver or kidney transplantation. World J Surg. 2021;45:3206–13.
24. Papaconstantinou HT, Sklow B, Hanaway MJ, Gross TG, Beebe TM, Trofe J, et al. Characteristics and survival patterns of solid organ transplant patients developing de novo colon and rectal cancer. Dis Colon Rectum. 2004;47:1898–903.
25. Privitera F, Gioco R, Civit AI, Corona D, Cremona S, Puzzo L, et al. Colorectal cancer after kidney transplantation: a screening colonoscopy case-control study. Biomedicines. 2021;9:937.
26. Ho H, Russ G, Stephens J, Rieger N. Colorectal cancer in patients with chronic renal failure: the effect of dialysis or renal transplantation. Colorectal Dis. 2002;4:193–6.
27. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit. Am J Transplant. 2010;10:1889–96.
28. Wang HE, Liao YC, Hu JM, Wu WC, Chou WY, Chen YC, et al. Correlation between kidney transplantation and colorectal cancer in hemodialysis patients: a nationwide, retrospective, population-based cohort study. BMC Cancer. 2019;19:1120.
29. Mazzucotelli V, Piselli P, Verdirosi D, Cimaglia C, Cancarini G, Serraino D, et al. De novo cancer in patients on dialysis and after renal transplantation: north-western Italy, 1997–2012. J Nephrol. 2017;30:851–7.
30. Kim B, Kang M, Kim Y, Lee HS, Kim B, Lee JJ, et al. De novo cancer incidence after kidney transplantation in South Korea from 2002 to 2017. JCM. 2021;10:3530.
31. Gioco R, Corona D, Agodi A, Privitera F, Barchitta M, Giaquinta A, et al. De novo cancer incidence and prognosis after kidney transplantation: a single center analysis. Transplant Proc. 2019;51:2927–30.
32. Miao Y, Everly JJ, Gross TG, Tevar AD, First MR, Alloway RR, et al. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation. 2009;87:1347.

33. Taborelli M, Serraino D, Cimaglia C, Furian L, Biancone L, Busnach G, et al. The impact of cancer on the risk of death with a functioning graft of Italian kidney transplant recipients. Am J Transplant. 2022;22:588–98.
34. Jeong S, Lee HS, Kong SG, Kim DJ, Lee S, Park MJ, et al. Incidence of malignancy and related mortality after kidney transplantation: a nationwide, population-based cohort study in Korea. Sci Rep. 2020;10:21398.
35. Tessari G, Naldi L, Boschiero L, Minetti E, Sandrini S, Nacchia F, et al. Incidence of primary and second cancers in renal transplant recipients: a multicenter cohort study. Am J Transplant. 2013;13:214–21.
36. Teo S, Lee K, Lim G, Koo S, Ramirez M, Chow K, et al. Incidence, risk factors and outcomes of malignancies after kidney transplantation in Singapore: a 12-year experience. Singapore Med J. 2019;60:253–9.
37. Hwang JK, Moon IS, Kim JI. Malignancies after kidney transplantation: a 40-year single-center experience in Korea. Transplant Int. 2011;24:716–21.
38. Sampaio MS, Cho YW, Qazi Y, Bunnapradist S, Hutchinson IV, Shah T. Post-transplant malignancies in solid organ adult recipients: an analysis of the U.S. national transplant database. Transplant. 2012;94:990–8.
39. Park HY, Chang BJ, Lim SW, Kim J, Kim JY, Chang DK, et al. Risk of colorectal neoplasia in patients with solid organ transplantation. Clin Transplant. 2012;26:50–6.
40. Collins MG, Teo E, Cole SR, Chan CY, McDonald SP, Russ GR, et al. Screening for colorectal cancer and advanced colorectal neoplasia in kidney transplant recipients: cross sectional prevalence and diagnostic accuracy study of faecal immunochemical testing for haemoglobin and colonoscopy. BMJ. 2012;345:e4657.
41. Christenson ES, Lee V, Wang H, Yarchoan M, De Jesus-Acosta A, Azad N, et al. Solid organ transplantation is associated with an increased rate of mismatch repair deficiency and PIK3CA mutations in colorectal cancer. Curr Oncol. 2023;30:75–84.
42. Ramsey-Goldman R, Brar A, Richardson C, Salifu MO, Clarke A, Bernatsky S, et al. Standardised incidence ratios (SIRs) for cancer after renal transplant in systemic lupus erythematosus (SLE) and non-SLE recipients. Lupus Sci Med. 2016;3:e000156.
43. Ju MK, Joo DJ, Kim SJ, Huh KH, Kim MS, Jeon KO, et al. Chronologically different incidences of post-transplant malignancies in renal transplant recipients: single center experience. Transplant Int. 2009;22:644–53.
44. Braconnier P, Del Marmol V, Broeders N, Kianda M, Massart A, Lemy A, et al. Combined introduction of anti-IL2 receptor antibodies, mycophenolic acid and tacrolimus: effect on malignancies after renal transplantation in a single-centre retrospective cohort study. Nephrol Dial Transplant. 2012;27:2547–53.
45. Cheung CY, Ma MKM, Chak WL, Chau KF, Tang SCW. Conversion to mammalian target of rapamycin inhibitors in kidney transplant recipients with de novo cancers. Oncotarget. 2017;8:44833–41.
46. Oliveira RC, Tavares-Silva E, Abrantes AM, Antunes H, Teixeira P, Gomes A, et al. De novo colorectal cancer after liver and kidney transplantation–microenvironment disturbance. Transplant Rep. 2020;5:100057.
47. Adani GL, Baccarani U, Lorenzin D, Gropuzzo M, Tulissi P, Montanaro D, et al. De novo gastrointestinal tumours after renal transplantation: role of CMV and EBV viruses. Clin Transplant. 2006;20:457–60.
48. Krishnan A, Wong G, Teixeira-Pinto A, Lim WH. Incidence and outcomes of early cancers after kidney transplantation. Transplant Int. 2022;35:10024.
49. Rascente M, Pisani F, Barletta A, D'Angelo M, Giammaria A, Parzanese I, et al. Malignancies after kidney transplantation. Transplant Proc. 2005;37:2529–31.
50. Végső G, Tóth M, Hídvégi M, Toronyi É, Mlanger R, Dinya E, et al. Malignancies after renal transplantation during 33 years at a single center. Pathol Oncol Res. 2007;13:63–9.
51. Arichi N, Kishikawa H, Nishimura K, Mitsui Y, Namba Y, Tokugawa S, et al. Malignancy following kidney transplantation. Transplant Proc. 2008;40:2400–2.
52. Alasari S, Kim MS, Baik SH, Min BS, Kim NK. Minimally invasive colorectal resection in kidney transplant recipients: technical tips, short- and long-term outcomes. Int Sch Res Not. 2014;2014:1–5.
53. Rocha A, Malheiro J, Fonseca I, Martins LS, Dias L, Almeida M, et al. Noncutaneous neoplasms after kidney transplantation: analysis at single center. Transplant Proc. 2013;45:1102–5.
54. Lizakowski S, Kolonko A, Imko-Walczuk B, Komorowska-Jagielska K, Rutkowski B, Więcek A, et al. Solid organ cancer and melanoma in kidney transplant recipients: TumorTx base preliminary results. Transplant Proc. 2018;50:1881–8.
55. Balhareth A, Reynolds IS, Solon JG, Harte EG, Boland F, O'Sullivan JM, et al. Thirty-seven-year population-based study of colorectal cancer rates in renal transplant recipients in Ireland. Transplant Proc. 2018;50:3434–9.
56. Kato T, Kakuta Y, Abe T, Yamanaka K, Imamura R, Okumi M, et al. The benefits of cancer screening in kidney transplant recipients: a single-center experience. Cancer Med. 2015;5:153–8.
57. Aguiar B, Santos Amorim T, Romãozinho C, Santos L, Macário F, Alves R, et al. Malignancy in kidney transplantation: a 25-year single-center experience in Portugal. Transplant Proc. 2015;47:976–80.
58. Kehinde EO, Petermann A, Morgan JD, Butt ZA, Donnelly PK, Veitch PS, et al. Triple therapy and incidence of de novo cancer in renal transplant recipients. Br J Surg. 1994;81:985–6.
59. Lim SM, Jung M, Shin SJ, Baek SJ, Hur H, Min BS, et al. Clinical implications from a single-center study of colorectal adenocarcinoma in transplant recipients. Oncol. 2014;88:195–200.
60. Kessler M, Jay N, Molle R, Guillemin F. Excess risk of cancer in renal transplant patients. Transplant Int. 2006;19:908–14.
61. Srisuwarn P, Sutharattanapong N, Disthabanchong S, Kantachuvesiri S, Kitiyakara C, Phakdeekitcharoen B, et al. Incidence of de novo post-transplant malignancies in Thai adult kidney transplant recipients: a single-center, population-controlled, retrospective cohort study at the highest volume kidney transplant center in Thailand. Transplant Int. 2024;37:11614.
62. Hsiao FY, Hsu WWY. Epidemiology of post-transplant malignancy in Asian renal transplant recipients: a population-based study. Int Urol Nephrol. 2014;46:833–8.
63. Franke TF. PI3K/Akt: getting it right matters. Oncogene. 2008;27:6473–88.
64. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007;26:3279–90.
65. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759–67.
66. Dantal J, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet. 1998;351:623–8.
67. Kao CC, Liu JS, Chang YK, Lin MH, Lin YC, Chen HH, et al. Cancer and mTOR inhibitors in kidney transplantation recipients. PeerJ. 2018;6:e5864.
68. Yokoyama I, Hayashi S, Kobayashi T, Yasutomi M, Uchida K, Takagi H. Immunosuppressive drugs and their effect on experimental tumor growth. Transplant Int. 1995;8:251–5.
69. Basu A, Contreras AG, Datta D, Flynn E, Zeng L, Cohen HT, et al. Overexpression of vascular endothelial growth factor and the development of post-transplantation cancer. Cancer Res. 2008;68:5689–98.
70. Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature. 1999;397:530–4.
71. Jung DH, Hwang S, Song GW, Ahn CS, Moon DB, Ha TY, et al. Survival benefit of early cancer detection through regular endoscopic screening for de novo gastric and colorectal cancers in Korean liver transplant recipients. Transplant Proc. 2016;48:145–51.
72. Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: What is the evidence? Clin J Am Soc Nephrol. 2008;3:S87–100.
73. Bini EJ, Kinkhabwala A, Goldfarb DS. Predictive value of a positive fecal occult blood test increases as the severity of CKD worsens. Am J Kidney Dis. 2006;48:580–6.
74. Wong G, Howard K, Craig JC, Chapman JR. Cost-effectiveness of colorectal cancer screening in renal transplant recipients. Transplantation. 2008;85:532.
75. Hadjiliadis D, Khoruts A, Zauber AG, Hempstead SE, Maisonneuve P, Lowenfels AB. Cystic fibrosis colorectal cancer screening consensus recommendations. Gastroenterology. 2018;154:736–45.e14.
76. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for colorectal cancer: updated evidence report and systematic review for the US preventive services task force. JAMA. 2021;325:1978.
77. Ashkar MH, Chen J, Shy C, Crippin JS, Chen CH, Sayuk GS, et al. Increased risk of advanced colonic adenomas and timing of surveillance colonoscopy following solid organ transplantation. Dig Dis Sci. 2022;67:1858–68.
78. Puttarajappa C, Yabes J, Bei L, Shah N, Bernardo J, McCauley J, et al. Cancer risk with alemtuzumab following kidney transplantation. Clin Transplant. 2013;27:E264–71.

AUTHOR CONTRIBUTIONS

BJH and OSE conceptualized the study. BJH, AO, MG, MM, LSLM, and OSE designed the review and meta-analysis methodology. LSLM conducted the literature search, while BJH, AO, and MG handled the review and data extraction. BJH curated the software and created the visualizations. BJH and MM performed the formal analysis. BJH and OSE drafted the manuscript, with AO, MG, HI, MDW, VV, RRR, OSE, and LSLM reviewing multiple iterations. All authors contributed to interpreting the results, had access to the raw data, and approved the final manuscript. OSE supervised the project.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval and consents to participate were not necessary for the study as it is a systematic review and meta-analysis of previously published, public data. No new human participant data were obtained and includes studies that were conducted in accordance to relevant ethical guidelines and regulations.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41416-025-02994-7.

Correspondence and requests for materials should be addressed to Oliver S. Eng.