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Research Article

Predictors of new-onset chronic kidney disease in patients managed surgically for T1a renal cell carcinoma: an Australian population-based analysis[1]

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Synopsis

Chronic kidney disease following nephrectomy for renal cell carcinoma (RCC) is common, however some patients are at greater risk than others. This study evaluates a large number of risk factors for postoperative kidney disease in patients who have been managed for T1a RCC to comprehensively evaluate risk. We identified that apart from commonly recognised risk factors,

rural place of residence increases a patient's risk, most likely due to differences in surgical service delivery models.

Abstract

Background

New-onset chronic kidney disease (CKD) following surgical management of kidney tumours is common. This study evaluated risk factors for new-onset CKD after nephrectomy for T1a renal cell carcinoma (RCC) in an Australian population-based cohort.

Methods

There were 551 RCC patients from the Australian states of Queensland and Victoria included in this study. The primary outcome was new-onset CKD (eGFR <60 mL/min per 1.73m^2) and the secondary outcome was new-onset moderate-severe CKD (<45 mL/min per 1.73m^2). Multivariable logistic regression was used to evaluate associations between patient, tumour and health-service characteristics and these outcomes.

Results

Forty percent (219/551) of patients developed new-onset CKD, and 12% (68/551) experienced new-onset moderate-severe CKD. Risk factors for new-onset CKD were age, lower preoperative eGFR, tumour size >20mm, radical nephrectomy, lower hospital caseloads (<20 cases/year), and rural place of residence. The associations between rural place of residence and low centre volume were a consequence of higher radical nephrectomy rates.

Conclusion

Risk factors for CKD after nephrectomy generally relate to worse baseline health, or likelihood of undergoing radical nephrectomy. Surgeons in rural centres and hospitals with low caseloads may benefit from formalised integration with specialist centres for continued professional development and case-conferencing, to assist in management decisions.

Introduction

In developed countries, the kidney is the eighth most common site for primary cancers, with renal cell carcinoma (RCC) accounting for approximately 90% of cases [1]. Greater use of abdominal imaging in routine clinical practice in recent decades has driven an increase in the proportion of incidentally detected renal cancers [2], from around 10% to 60% [3,4]. Accordingly, more than 65% of lesions are localised to the kidney at diagnosis [3,5].

Patients managed surgically for T1a RCC (localised tumours ≤4cm) have an excellent prognosis, with 10-year survival as high as 93% in some studies [6]. Considering the excellent survival times for patients managed with T1a RCC, concerns have arisen over adverse sequelae of renal parenchymal resection, particularly the potential for iatrogenic chronic kidney disease (CKD). CKD is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73m^2 and/or evidence of kidney damage, typically manifested as albuminuria, present for at least 3 months [7]. Patients who develop CKD after nephrectomy have a modest increase in mortality compared to those who do not, with risk increasing as postoperative eGFR declines [8,9]. In light of the CKD risk, partial nephrectomy (PN) rather than radical nephrectomy (RN) is recommended for managing localised renal masses where feasible, due to equivalent oncological control with better preservation of kidney function [10].

A number of studies have investigated factors associated with new onset CKD post nephrectomy for small renal cancers finding that older age, lower preoperative eGFR, and specific comorbidities are associated with increased risk [11-13]. However, many of these studies were undertaken in single-centre tertiary referral centres, and most have examined a limited set of potential risk factors. The aims of the present study were therefore to evaluate a range of patient, tumour, and health-service factors associated with the development of new-onset CKD (eGFR <60 mL/min per 1.73m^2) and new-onset moderate-severe CKD (eGFR <45 mL/min per 1.73m^2)

in a large population-based sample of patients, with preoperative kidney function ≥60 mL/min per 1.73m^2 who were managed surgically for T1a RCC. We also aimed to evaluate whether associations differed by nephrectomy type. Identification of factors which associate with CKD development may assist in the assessment and management of patients with T1a tumours.

Patients and Methods

Study Design and Population

The present analysis is part of a broader study of the patterns of care for patients newly diagnosed with RCC whose usual place of residence was within the Australian states of Queensland and Victoria. Between January 2012 and December 2013, all patients aged ≥18 years who were notified to either the Queensland or Victorian Cancer Registries with newly diagnosed RCC were ascertained. Reporting cancer diagnoses to state-based cancer registries is a legal requirement in Australia, therefore it is likely that ascertainment was close to complete. The registries provided trained study staff with sufficient identifying information to enable location of each patient's clinical records. The registries also provided information on the sex, age at diagnosis, and date of diagnosis, as well as codes for the patients' area of residence (based on the Accessibility/Remoteness Index of Australia [ARIA] + 2011) [14]; and area-level socioeconomic status (SES) (Socioeconomic Indexes for Areas [SEIFA], Index of Relative Socioeconomic Disadvantage 2011) [15]. Information about clinical presentation, investigations, patient comorbidities and functional status, diagnosis, staging, management and outcomes was extracted from the medical records. Data were then de-identified and returned to the research teams based at QIMR Berghofer Medical Research Institute and Cancer Council Victoria. Overall, data from 2,323 patients with RCC (all stages) were available (986 from Queensland; 1,337 from Victoria).

The current analysis included only the patients with T1a tumours without nodal involvement or distant metastases. Those with higher stage tumours, preoperative eGFR <60 mL/min per

1.73m^2, or an abnormal contralateral kidney determined on imaging were excluded (Figure 1). Patients missing pre- or postoperative eGFR values were also excluded from the main analysis. Tumour stage was predominantly determined on imaging, although 17 patients coded as having a cT1b lesions on imaging but a pT1a lesion in the pathology report were included. Overall, 551 patients were included in the primary analysis.

Ethical Considerations

Approval to access medical records without patient consent was obtained under the Queensland Public Health Act and the human research ethics committee (HREC) of Cancer Council Victoria. This study was also approved by the QIMR Berghofer HREC and Metro South Health HREC in Queensland. Additional ethics and individual site-specific approvals were obtained for each healthcare provider as required.

Exposures

Pre- and postoperative eGFR was calculated from serum creatinine measurements, using the CKD Epidemiological Collaborative equation [16]. Age at diagnosis, body mass index (BMI), and preoperative eGFR were grouped by clinically relevant categories. A modified Charlson comorbidity index was calculated using information extracted from medical records, and grouped as scores of 0, 1 or ≥2 (excluding the kidney cancer diagnosis from the calculation) [17]. SES was grouped as more and less disadvantaged (deciles 1-5 and 6-10). Area of residence was categorised as major city, inner regional and rural (outer regional/remote/very remote). Exophytic properties and tumour polarity were grouped based on RENAL nephrometry score thresholds (http://www.nephrometry.com/) by 1 and ≥2 points for each corresponding criterion. Tumour size was grouped as <20 and 20-40mm, as the American Urological Association guidelines recommend active surveillance be considered for tumours <20mm [18]. Surgical approach was assigned as open, laparoscopic (including laparoscopic-to-open) and robot-assisted. Hospital volume was the mean number of patients/year treated for RCC at each site.

Outcomes

Kidney function was evaluated by postoperative eGFR, calculated from serum creatinine recorded on follow-up. The minimal follow-up time considered was three postoperative months; however, most values were recorded at approximately 12 months after surgery, with the latest value for each patient considered. The primary outcome of our study was new-onset CKD (postoperative eGFR <60 mL/min per 1.73m^2). As there are concerns about the clinical significance of using such a broad definition of CKD following kidney surgery [19,20], we also considered postoperative eGFR <45 mL/min per 1.73m^2 (new-onset moderate-severe CKD) as a secondary outcome. Both groups were compared with patients who had a postoperative eGFR ≥60 mL/min per 1.73m^2. These cut-offs were selected based on KDIGO guidelines for CKD diagnosis [7], and literature demonstrating worse survival outcomes for nephrectomy patients whose eGFR falls below either threshold [8,9]. We also analysed postoperative eGFR as a continuous variable and the change from pre- to postoperative eGFR was evaluated descriptively.

Statistical Analysis

Statistical analysis was performed using Stata 13.0 (StataCorp, College Station, TX, USA). The characteristics of the patients were presented overall and grouped by primary and secondary outcome, and compared on categorical data by Pearson's chi-square test or continuous data by a Mann-Whitney U-test.

We evaluated associations between exposure variables and the primary and secondary outcomes using univariable and multivariable logistic regression, including cases with complete data for exposures and potential confounders to estimate odds ratios (ORs) and 95% CI. Multivariable models were initially adjusted only for confounders, not mediators, which were identified using directed acyclic graphs [21]. Clustering for hospital volume was accounted for by hospital code,

using robust sandwich estimators. Postoperative eGFR was evaluated as a continuous variable using multivariable linear regression, with adjustment for preoperative eGFR.

As previous studies have reported very strong associations between nephrectomy type and postoperative eGFR [22], we wanted to investigate whether the magnitude of other associations might differ by nephrectomy type. Analysis of the primary outcome was stratified by nephrectomy type, and the statistical significance of interactions between nephrectomy type and the exposure of interest were assessed.

Analyses were also performed to investigate relationships between variables identified to be significantly associated with the primary outcome and whose effects were hypothesised *a priori* to be mediated by the decision to perform RN (age, place of residence, and hospital volume). This was initially done by adding nephrectomy type to each model and assessing the effect on the variables of interest. We then undertook formal mediation analysis using generalised structural equation modelling, adjusting for exposure-outcome, mediator-outcome, and exposure-mediator confounding. Effect size was assessed by the logistic coefficient, using the product method: direct effects (β_{xy}), indirect effects ($\beta_{xm}\,\beta_{my}$) and total effects ($\beta_{xy} + \beta_{xm}\,\beta_{my}$); where x = independent variable, y = dependent variable and m = mediator [23]. The mediation proportion was defined as indirect ÷ total effects × 100 [24].

A sensitivity analysis was performed using multiple imputation to estimate values for included cases (Figure 1), for whom there were missing data for exposures or outcomes. Of 643 patients, some had missing data for height (16%), weight (15%), tumour diameter (7%), smoking status (16%), tumour polarity (7%), and postoperative eGFR (4%), respectively. The estimates calculated using multiple imputation models were compared to the primary analysis on percentage change in adjusted OR (aOR).

Results

The main analysis included 551 patients managed surgically for T1a RCC with a preoperative eGFR ≥60 mL/min per 1.73m^2, and postoperative eGFR recorded at a median follow-up time of 11.8 months [interquartile range (IQR) 9.5-13.3]. Forty percent (219/551) of patients developed the primary outcome of new-onset CKD, and 12% (68/551) experienced the secondary outcome of new-onset moderate-severe CKD. The median postoperative eGFR was 67.3 [IQR 52.2-87.4] mL/min per 1.73m^2, and the median decrease in eGFR between baseline and follow-up was 21.6 [IQR 7.0-33.4] mL/min per 1.73m^2 (Supplementary Figure 1).

Patient characteristics by CKD outcomes are summarised in Table 1, and ORs and 95% CI for the associations between selected factors and CKD outcomes are presented in Tables 2 and 3.

The patient characteristics most strongly associated with new-onset CKD were age (OR per 5 year increase: 1.5, 95% CI: 1.4-1.7), and preoperative eGFR (aOR per 5 mL/min per 1.73m^2 decrease: 1.3, 95% CI: 1.2-1.4). Living outside a major city (reference group) was also associated with an increased likelihood of experiencing the primary outcome (aOR: 1.8, 95% CI: 1.1-2.8 and aOR: 2.1, 95% CI: 1.2-3.6, for patients living in inner regional and rural/remote areas, respectively). These associations were similar for the secondary outcome of moderate-severe CKD. Sex, BMI, area-level SES, and smoking status were not significantly related to CKD development. We evaluated whether individual comorbidities (diabetes mellitus, hypertension, and any cardiovascular disease), was associated with CKD risk; all were related in univariable analyses (data not shown), but when adjusted for age the associations were not significant. A Charlson comorbidity index ≥2 was associated with a modest increase in the odds of CKD, although the estimate was not statistically significant, (aOR: 1.6, 95% CI: 0.9-2.9). This association strengthened and became statistically significant when the outcome was restricted to those with moderate-severe CKD (aOR: 3.5, 95% CI: 1.4-9.2). Having a tumour >20mm was

associated with new-onset CKD (aOR: 2.5, 95% CI: 1.4-4.2) and moderate-severe CKD (aOR: 3.6, 95% CI: 1.3-10.0).

Of the health-service characteristics assessed, RN had the strongest association with both new-onset CKD and moderate-severe CKD (aOR: 19.0, 95% CI: 9.1-39.0, and aOR: 14.0, 95% CI: 4.0-48.0, respectively *vs.* PN). The odds for laparoscopic approach (*vs.* open) were elevated in unadjusted analyses, but this association was no longer statistically significant after nephrectomy type was included in the model. Whether the treating hospital was public or private was unrelated to the outcomes; but, when compared with hospitals with ≥20 RCC cases treated per year, being managed at a hospital with <20 cases per year was associated with an increased likelihood of developing new-onset CKD (aOR: 1.6, 95% CI: 1.1-2.4). The associations was similar when the outcome was restricted to eGFR <45 mL/min per 1.73m^2 (aOR: 1.7, 95% CI: 1.1-2.8).

Stratified analysis of the primary outcome by nephrectomy type is presented in Figure 2; most associations were similar to the main analysis although there was a statistically significant interaction between preoperative eGFR and nephrectomy type (P=0.02), such that patients with an eGFR of 70-79 mL/min per 1.73m^2 who underwent RN were significantly more likely to experience new-onset CKD than patients falling inside the same eGFR range who underwent PN (Supplementary Table 1).

Given that factors such as age, place of residence, and hospital volume, can influence the type of nephrectomy (PN *vs.* RN) performed, we investigated how much of the observed associations between these factors and postoperative CKD might be explained by the type of nephrectomy received. Adding nephrectomy type to each multivariable model considerably attenuated these associations (data not shown), and formal mediation analysis (Supplementary Table 2) indicated that approximately 54% of the effect of greater age and 99% of the effect of lower hospital volume was explained by greater likelihood of RN. For area of residence, 74% of the association

appeared to be mediated by surgery type, although the estimate did not reach statistical significance.

Postoperative eGFR as a continuous variable was assessed as a secondary analysis (Supplementary Table 3). All associations were similar to those of the main analysis, with the exception of area-level SES, where patients from the least disadvantaged category on average had a postoperative eGFR that was 3.9 mL/min per 1.73m^2 (95% CI: 1.0-6.9) higher than that of the most disadvantaged group.

Given there were missing data for patients who met the inclusion criteria, a sensitivity analysis was conducted using multiple imputation to estimate missing values. Results were almost identical to complete case analysis (Supplementary Table 4). When comparing aORs, the median percentage change was 0% [IQR -7, 0] when considering the primary outcome.

Discussion

As expected, the strongest associations with both new-onset CKD and moderate-severe CKD were increasing age, lower preoperative eGFR, RN (*vs.* PN), and a larger tumour diameter. In addition, we found that rural place of residence and low hospital volume were associated with increased odds of both outcomes. High scores on the Charlson comorbidity index were associated with both outcomes, although this was statistically significant only for moderate-severe CKD.

The associations between both rural place of residence and hospital volume with new-onset CKD following nephrectomy have not been evaluated previously in Australia. These two measures likely represented similar information, as hospitals in rural areas are generally lower-volume [25]. Poorer access to healthcare is associated with worse health outcomes in rural communities, and inequalities relating to cancer care and outcomes are well recognised [26]. We found that the effect of both hospital volume and rural place of residence was likely largely

mediated by surgery type with RN being performed more frequently in these settings (RN leading to greater nephron loss than PN and thereby eGFR reduction [22]). RN is a less technically-difficult procedure than PN, and may be favoured in lower-volume centres due to surgeon preference/expertise or resource availability.

Previous studies in Australia have demonstrated that less technically-difficult procedures with equivalent efficacy for oncological control are favoured in rural settings, for example, total mastectomy was more common in rural hospitals than breast-sparing surgery for breast cancer [27]; and in lower volume settings, where permanent colostomy was more common than temporary ileostomy for stoma creation during colorectal cancer management [28]. Previous studies from Victoria have demonstrated that PN rates were lower in rural areas compared with metropolitan [5,29], and a population-based study of all kidney cancer patients managed in New South Wales between 2001-2009 identified that a caseload of >8 cases/year increased the likelihood of receiving PN (OR: 2.4, 95% CI: 1.5-3.8) [30]. Further, in direct parallel with our findings, a large multicentre retrospective study of 913 patients who underwent surgical management for localised renal masses in the USA demonstrated that centres with >20 cases/year had a higher rate of PN than lower-volume centres, which was associated with better postoperative kidney function [31].

Addressing the complex issues that cause variation in health outcomes according to type or location of health service is challenging. Although service centralisation might provide one solution, this is unlikely to be feasible or desirable at either a patient or health-service level. Reasons for lower PN rates in smaller/rural centres likely relate in part to infrastructural limitations. Professional isolation may also play a role, particularly as higher complication rates following PN may require after-hours intervention, which may not be feasible in lower volume settings. With these limitations in mind, we advocate for surgical service delivery models that support professionally-isolated surgeons. Formal integration with high-volume tertiary referral

centres may provide benefit by facilitating continuing professional development, and through telehealth case-conferencing and multidisciplinary meetings, to support appropriate patient evaluation, case selection, and surgical technique.

Apart from surgery type we also found that factors that contribute to reductions in kidney function or indicate the baseline health of the kidney were associated with increased risk of postoperative CKD. This is similar to other studies, for example, the Charlson comorbidity index was found to associate with clinically-significant CKD in a Canadian population-based study [32]. The association between age and postoperative new-onset CKD is also a common finding [33]. As the effect of age was only partially mediated by nephrectomy type indicates that age associates with CKD through other paths, which is reflective of the general population, where the average annual eGFR reduction for persons aged ≥40 years is 0.75-1.00 mL/min per 1.73m^2 [34]. However, we did find that 50% of the association with age was attributable to the type of surgery performed, which invites discussion as to whether PN could be considered more readily for appropriately-selected older patients [35].

The association between CKD development and poorer baseline kidney function is also well known [36,37]. In the present study, preoperative eGFR was the only variable found to have a significant interaction with nephrectomy type, such that even those with relatively high eGFR measures preoperative (70-79 mL/min per 1.73m^2) who underwent RN were substantially more likely to develop new CKD than those with lower preoperative eGFR (60-69 mL/min per 1.73m^2) who underwent PN. Again, this reflects greater nephron loss occurring with RN compared with PN (Supplementary Figure 1B).

Patients with larger T1a tumours were more likely to develop CKD in the present study; but, stratification by nephrectomy type (Figure 2) indicated that this positive association was present only for patients managed with PN. This is concordant with previous reports evaluating kidney functional changes using renal scintigraphy after PN [38,39]. To ensure negative surgical

margins, the amount of functional parenchyma removed during PN is determined by tumour size and complexity [40], whereas that is not the case with RN. As a larger volume of resected functional parenchyma during PN associates with worse postoperative kidney function [41].

Limitations of this study should be considered in the interpretation of our results. There was a modest amount of missing data on kidney function (12% of cases assessed for inclusion in this study), particularly in Victoria, which may have introduced bias. There were no major differences in demographics between complete and missing cases, however PN was more likely performed in excluded patients, which is a consequence of different PN rates between states. Imputed results including patients with missing data showed minimal differences to complete cases, supporting the assumption that our data are generally representative.

This analysis is based on patients treated up to five years ago, and it is possible that practice has changed since that time. Definitions of CKD in this study are limited by the use of a single measure of eGFR, and the absence of albuminuria measurements (clinically-significant albuminuria has been reported in 17% of patients with T1 RCC before surgery) [42]. Additionally, all information was collected retrospectively from medical records, which may have introduced error. For example, the Charlson index was calculated using comorbidities recorded in the medical chart, and may underestimate the actual index.

The goal of this study was to identify patterns in the care of patients managed surgically for kidney cancer. Although every attempt has been made to minimise bias, the observational nature of the study's design introduces risk of selection and ascertainment bias. Accordingly, results should be interpreted in this context. Nevertheless, our results are consistent with findings in the literature and are biologically plausible, supporting their validity.

Strengths of the present study include its sample size, and the approach taken to statistical modelling to ensure minimisation of bias and maximisation of effect detection. Furthermore, its

population-based design reflected real-world outcomes beyond those from selected specialist centres.

Novel findings of this study demonstrated that surgically-managed patients with T1a RCC from rural areas and attending lower-volume centres have a greater likelihood of developing CKD. We have confirmed that RN (compared to PN), lower preoperative eGFR, comorbidity burden, and older age are also risk factors for lower postoperative eGFR. This may have implications for current practice in terms of risk stratification and case selection. This was the first population-based study evaluating postoperative kidney function after surgical management of renal tumours to be conducted in Australia.

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Figure Legends

Figure 1. Overview of study population.

Exclusion criteria at data collection level were: neoplasms other than renal cell carcinoma (RCC), usual place of residence outside specified state, previous RCC diagnosis, or inability to access patient records. eGFR, estimated glomerular filtration rate.

Figure 2. Associations between selected factors and new-onset chronic kidney disease (CKD) stratified by nephrectomy type.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) estimated using logistic regression. BMI, body mass index; eGFR, estimated glomerular filtration rate; SES, area-level socioeconomic status. *Significant interaction between exposure and nephrectomy type

(*P*=0.02). Refer to Supplementary Table 1 for comparisons of the estimates and *P* values for interactions for radical and partial nephrectomy.

Supplementary Figure 1. Change in estimated glomerular filtration rate.

Waterfall plots comparing change in estimated glomerular filtration rate (ΔeGFR) across **A:** patients with a preoperative eGFR ≥90 mL/min per 1.73m^2 (blue) and <90 mL/min per 1.73m^2 (red); **B:** patients who underwent radical (red) and partial (blue) nephrectomy. The median decrease in eGFR between baseline and follow-up was 21.6 [6.8-33.5], 7.2 [3.0-17.0] and 30.4 [23.3-39.7] mL/min per 1.72m^2 in all patients, and patients managed with partial and radical nephrectomy, respectively.

Table 1 – Patient, tumour and health-service characteristics of study population grouped by postoperative eGFR

		Postoperative eGFR (mL/min per 1.73m^2)		
	All (*N*, %)	≥60 (*N*, %)	<60 (*N*, %)	*P* value [a]
Patient Characteristics	(*N* = 551)	(*N* = 332)	(*N* = 219)	
Age at diagnosis—years				
Median [IQR]	60 [52-68]	56 [48-63]	65 [58-72]	<0.001
<50	107 (19)	96 (29)	11 (5)	<0.001
50-59	151 (27)	100 (30)	51 (23)	
60-69	183 (33)	105 (32)	78 (36)	
≥70	110 (20)	31 (9)	79 (36)	
Sex				
Female	216 (39)	137 (41)	79 (36)	0.22
Male	335 (61)	195 (59)	140 (64)	
Body mass index—kg/m^2				
Median [IQR]	29 [26-34]	29 [26-34]	29 [26-33]	0.80
<25	83 (15)	53 (16)	30 (14)	0.78
25-30	162 (29)	105 (32)	57 (26)	
>30	178 (32)	109 (33)	69 (32)	
Missing	128 (23)	65 (20)	63 (29)	
Area-level socioeconomic status				
Most disadvantaged	247 (45)	141 (42)	106 (48)	0.17
Least disadvantaged	304 (55)	191 (58)	113 (52)	
Place of residence				
Major city	366 (66)	238 (72)	128 (58)	0.005
Inner regional	114 (21)	57 (17)	57 (26)	
Rural/Remote [b]	71 (13)	37 (11)	34 (15)	
Charlson comorbidity index (score)				
Low (0)	308 (56)	193 (58)	115 (53)	0.22
Medium (1)	134 (24)	81 (24)	53 (24)	
High (≥2)	109 (20)	58 (17)	51 (23)	
Smoker status				
Former/Never	359 (65)	206 (62)	153 (70)	0.12
Current	107 (19)	73 (22)	34 (15)	
Missing	85 (15)	53 (16)	32 (15)	
Preoperative eGFR—ml/min per 1.73m^2				

Median [IQR]	89 [77-102]	97 [84-108]	79 [70-89]	<0.001
≥90	259 (47)	211 (63)	48 (22)	<0.001
80-89	111 (20)	60 (18)	51 (23)	
70-79	105 (19)	39 (12)	66 (30)	
60-69	76 (14)	22 (7)	54 (25)	
State				
Queensland	342 (62)	214 (64)	128 (58)	0.16
Victoria	209 (38)	118 (36)	91 (42)	
Tumour Characteristics				
Tumour histology				
Clear cell	392 (71)	241 (73)	151 (69)	0.35
Other	159 (29)	91 (27)	68 (31)	
Tumour crossed polar lines				
No	319 (58)	197 (59)	122 (56)	0.52
Yes	196 (36)	112 (34)	84 (38)	
Missing	36 (6)	31 (7)	13 (6)	
Exophytic properties				
≥50%	219 (40)	142 (43)	77 (35)	0.18
<50%	32 (6)	19 (6)	13 (6)	
Missing	300 (54)	171 (51)	129 (59)	
Diameter—mm				
Median [IQR]	29 [23-35]	27 [20-34]	30 [25-37]	<0.001
<20	101 (18)	78 (23)	23 (11)	<0.001
20-40	405 (74)	232 (70)	173 (79)	
Missing	45 (8)	22 (7)	23 (10)	
Health-Service Characteristics				
Nephrectomy type				
Partial	262 (48)	223 (67)	39 (18)	<0.001
Radical	289 (52)	109 (33)	180 (82)	
Surgical approach (intention to treat)				
Open	138 (25)	103 (31)	35 (16)	<0.001
Laparoscopic	364 (66)	188 (57)	176 (80)	
Robot-assisted	49 (9)	41 (12)	8 (4)	
Hospital type				
Public	297 (54)	184 (55)	113 (52)	0.38
Private	254 (46)	148 (45)	108 (48)	
Hospital volume—RCC cases/year				
Median [IQR]	26 [18-43]	28 [20-44]	25 [16-43]	0.03
>40	178 (32)	119 (36)	59 (27)	0.007
20-40	209 (38)	130 (49)	79 (36)	
<20	164 (30)	83 (25)	81 (37)	

Characteristics of patients with preoperative eGFR ≥60 ml/min per 1.73m^2 who underwent nephrectomy for T1a RCC, grouped by postoperative eGFR. *P* value compares patients with a postoperative eGFR above and below specified thresholds, using Pearson's chi-squared test on categorical data and a Mann Whitney u-test on continuous data. Missing category not included in statistical analysis. eGFR, estimated glomerular filtration rate; IQR, interquartile range; RCC, renal cell carcinoma.

[a] *P* value compares patients with a postoperative eGFR ≥60 ml/min per 1.73m^2 to patients with a postoperative eGFR <60 ml/min per 1.73m^2

[b] Includes residents of regions classified as outer regional, remote, and very remote.

Table 2 – Associations between patient, tumour and health-service characteristics and the development of new-onset chronic kidney disease (eGFR <60 mL mL/min per 1.73m^2) among patients managed surgically for T1a renal cell carcinoma (*N* = 551)

	New-onset CKD (*N* = 219)	
	Crude OR (95% CI)	Adjusted OR [a] (95% CI)
Patient Characteristics		
Age at diagnosis—years		
<50	1	
50-59	4.5 (2.2-9.0)	

60-69	6.5 (3.3-13.0)	-
≥70	22.0 (11.0-47.0)	
Per 5 year increase	1.5 (1.4-1.7)	
P value	<0.001	
Sex		
Female	1	1
Male	1.2 (0.9-1.8)	1.3 (0.9-1.9)
P value	0.22	0.23
Body mass index—kg/m^2		
<25	1	1
25-30	1.0 (0.6-1.7)	0.9 (0.5-1.7)
>30	1.1 (0.7-1.9)	1.4 (0.8-2.5)
P value	0.60	0.18
Area-level socioeconomic status		
Most Disadvantaged	1	1
Least Disadvantaged	0.8 (0.6-1.1)	0.7 (0.5-1.0)
P value	0.17	0.09
Place of residence		
Major city	1	1
Inner regional	1.9 (1.2-2.9)	1.8 (1.1-2.8)
Rural/Remote [b]	1.7 (1.0-2.9)	2.1 (1.2-3.6)
P value	0.005	0.003
Charlson comorbidity index (score)		
Low (0)	1	1
Medium (1)	1.1 (0.7-1.7)	0.7 (0.4-1.2)
High (≥2)	1.5 (0.9-2.3)	1.6 (0.9-2.9)
P value	0.10	0.21
Smoker status		
Former/Never	1	1
Current	0.6 (0.4-1.0)	1.0 (0.6-1.6)
P value	0.05	0.93
Preoperative eGFR—ml/min per 1.73m^2		
≥80	1	1
70-79	4.6 (2.9-7.3)	2.3 (1.3-4.2)
60-69	6.7 (3.9-12.0)	3.8 (1.8-8.0)
Per 5 unit decrease	1.4 (1.3-1.5)	1.3 (1.2-1.4)
P value	<0.001	<0.001
Preoperative eGFR compared by nephrectomy type (Partial Nephrectomy) [c]		
≥80	0.1 (0.1-0.2)	0.1 (0.1-0.2)
70-79	0.3 (0.2-0.7)	0.2 (0.1-0.4)
60-69	1.1 (0.5-2.3)	0.7 (0.3-1.8)
(Radical Nephrectomy) [c]		
≥80	1	1
70-79	22.0 (6.6-73.0)	17.0 (3.9-74.0)
60-69	8.9 (3.4-24.0)	5.9 (1.6-22.0)
P value	<0.001	<0.001
Tumour Characteristics		
Tumour histology		
Clear cell	1	1
Other	1.2 (0.8-1.7)	1.0 (0.6-1.8)
P value	0.36	0.86
Tumour crossed polar lines		
No	1	1
Yes	1.2 (0.8-1.7)	1.2 (0.8-1.7)
P value	0.30	0.30
Diameter—mm		
≤20	1	1
>20	2.5 (1.5-4.2)	2.5 (1.4-4.2)
P value	0.001	0.001
Health-Service Characteristics		
Nephrectomy type		
Partial	1	1
Radical	11.0 (5.9-21.0)	9.7 (4.3-22.0)
P value	<0.001	<0.001
Surgical approach (intention to treat)		

Open	1	1
Laparoscopic	2.8 (1.8-4.3)	0.7 (0.3-1.4)
Robot-assisted	0.6 (0.2-1.3)	1.3 (0.5-3.7)
P value	0.01	0.70
Hospital type		
Public	1	1
Private	1.2 (0.8-1.6)	1.1 (0.7-1.5)
P value	0.38	0.79
Hospital volume—RCC cases/year [d]		
≥20	1	1
<20	1.8 (1.2-2.6)	1.6 (1.1-2.4)
P value	0.005	0.05

Odds ratio (OR) and 95% confidence intervals (CI) for the associations between selected factors and likelihood of new-onset CKD in patients with T1a renal cell carcinoma (RCC) who were managed surgically. Crude and adjusted OR and 95% CI estimated using logistic regression.

[a] Estimates adjusted for confounders only, not potential mediators. Adjustment variables: Sex – age; Area-level socioeconomic status (SES) – age; Body mass index (BMI) – age, sex, SES; Place of residence – age, state; Charlson comorbidity index – age, sex, SES; Smoker status – age, sex, SES, Charlson comorbidity index; Preoperative estimated glomerular filtration rate (eGFR) – age, sex, BMI, Charlson comorbidity index, SES, smoker status; Tumour histology – age, sex, BMI, Charlson comorbidity index, smoker status, preoperative eGFR; Location relative to polar lines – tumour histology; Diameter – age, Charlson comorbidity index, tumour histology; Nephrectomy type – age, place of residence, BMI, Charlson comorbidity index, preoperative eGFR, tumour size; Surgical approach – age, BMI, Charlson comorbidity index, nephrectomy type, hospital volume, state; Hospital type – age, SES, Charlson comorbidity index; Hospital volume – place of residence, state.

[b] Includes residents of regions classified as outer regional, remote, and very remote

[c] A significant interaction ($P = 0.02$) between nephrectomy type and preoperative eGFR is reflected in the calculation of the OR and 95% confidence interval.

[d] Robust sandwich estimators used to account for clustering by hospital code.

Table 3 – Associations between patient, tumour and health-service characteristics and the development of new-onset moderate-severe chronic kidney disease among patients managed surgically for T1a renal cell carcinoma

	Postoperative eGFR (ml/min per 1.73m^2) ≥60	<45	Crude OR (95% CI)	Adjusted OR [a] (95% CI)
Patient Characteristics	(*N* = 332)	(*N* = 68)		
Age at diagnosis—years				
<50	96 (29)	4 (6)	1	
50-59	100 (30)	13 (19)	3.1 (1.0-9.9)	
60-69	105 (32)	15 (22)	3.4 (1.1-11.0)	-
≥70	31 (9)	36 (53)	28.0 (1.1-84.0)	
P value	<0.001		<0.001	
Sex				
Female	137 (41)	26 (38)	1	1
Male	195 (59)	42 (62)	1.0 (0.7-1.9)	1.2 (0.7-2.2)
P value	0.64		0.64	0.51
Body mass index—kg/m^2				
<25	53 (16)	14 (21)	1	1
25-30	105 (32)	13 (19)	0.5 (0.2-1.1)	0.4 (0.2-1.0)
>30	109 (33)	18 (26)	0.6 (0.3-1.4)	0.7 (0.3-1.5)
P value	0.18		0.40	0.85
Area-level socioeconomic status				
Most Disadvantaged	141 (42)	24 (35)	1	1
Least Disadvantaged	191 (58)	44 (65)	1.4 (0.8-2.3)	1.2 (0.6-2.2)
P value	0.27		0.28	0.53
Place of residence				
Major city	238 (72)	43 (63)	1	1
Inner regional	57 (17)	15 (22)	1.5 (0.8-2.8)	1.4 (0.7-2.9)
Rural/Remote [b]	37 (11)	10 (15)	1.5 (0.7-3.2)	2.7 (1.1-6.5)
P value	0.38		0.18	0.03
Charlson comorbidity index (score)				
Low (0)	193 (58)	31 (46)	1	1
Medium (1)	81 (24)	18 (26)	1.4 (0.7-2.6)	0.6 (0.2-1.6)
High (≥2)	58 (17)	19 (28)	2.0 (1.1-3.9)	3.5 (1.4-9.2)
P value	0.08		0.03	0.03
Smoker status				

Former/Never	206 (62)	48 (71)	1	1
Current	73 (22)	7 (10)	0.4 (0.2-1.0)	0.6 (0.2-1.6)
P value	0.03		0.04	0.32
Preoperative eGFR—ml/min per 1.73m^2				
≥80	271 (81)	13 (20)	1	1
70-79	39 (12)	31 (45)	17.0 (8.0-34.0)	5.3 (2.2-13.0)
60-69	22 (7)	24 (35)	23.0 (10.0-51.0)	6.8 (2.2-21.0)
P value	<0.001		<0.001	0.001
Tumour Characteristics				
Tumour histology				
Clear cell	241 (73)	44 (65)	1	1
Other	91 (27)	24 (35)	1.4 (0.8-2.5)	1.4 (0.5-3.9)
P value	0.19		0.19	0.55
Tumour crossed polar lines				
No	197 (59)	40 (59)	1	1
Yes	112 (34)	24 (35)	1.1 (0.6-1.8)	1.1 (0.6-1.9)
P value	0.85		0.92	0.92
Diameter—mm				
≤20	78 (23)	4 (6)	1	1
>20	232 (70)	59 (87)	4.9 (1.7-14.0)	4.1 (1.3-13.0)
P value	0.001		0.003	0.02
Health-Service Characteristics				
Nephrectomy type				
Partial	223 (67)	9 (13)	1	1
Radical	109 (33)	59 (87)	13.0 (6.4-28.0)	15.0 (6.0-38.0)
P value	<0.001		<0.001	<0.001
Surgical approach (intention to treat)				
Open	103 (31)	11 (16)	1	1
Laparoscopic	188 (57)	56 (82)	2.7 (1.4-5.5)	0.5 (0.2-1.7)
Robot-assisted	41 (12)	1 (1.5)	0.2 (0.1-1.9)	0.8 (0.1-8.6)
P value	<0.001		0.10	0.37
Hospital type				
Public	184 (55)	34 (50)	1	1
Private	148 (45)	34 (50)	1.2 (0.7-2.1)	1.0 (0.5-1.8)
P value	0.29		0.42	0.97
Hospital volume—RCC cases/year [c]				
≥20	249 (85)	42 (62)	1	1
<20	83 (25)	26 (38)	1.9 (1.1-3.1)	1.7 (1.1-2.8)
P value	0.07		0.02	0.04

Odds ratio (OR) and 95% confidence intervals (CI) for the associations between selected factors and likelihood of new-onset chronic kidney disease (CKD) and moderate-severe CKD in patients with T1a renal cell carcinoma (RCC) who were managed surgically. Crude and adjusted OR and 95% CI estimated using logistic regression. Where percentages do not add up to 100%, missing values constitute the discrepancy.

[a] Estimates adjusted for confounders only, not potential mediators. Adjustment variables: Sex – age; Area-level socioeconomic status (SES) – age; Body mass index (BMI) – age, sex, SES; Place of residence – age, state; Charlson comorbidity index – age, sex, SES; Smoker status – age, sex, SES, Charlson comorbidity index; Preoperative estimated glomerular filtration rate (eGFR) – age, sex, BMI, Charlson comorbidity index, SES, smoker status; Tumour histology – age, sex, BMI, Charlson comorbidity index, smoker status, preoperative eGFR; Location relative to polar lines – tumour histology; Diameter – age, Charlson comorbidity index, tumour histology; Nephrectomy type – age, place of residence, BMI, Charlson comorbidity index, preoperative eGFR, tumour size; Surgical approach – age, BMI, Charlson comorbidity index, nephrectomy type, hospital volume, state; Hospital type – age, SES, Charlson comorbidity index; Hospital volume – place of residence, state.

[b] Includes residents of regions classified as outer regional, remote, and very remote

[c] Robust sandwich estimators used to account for clustering by hospital code.

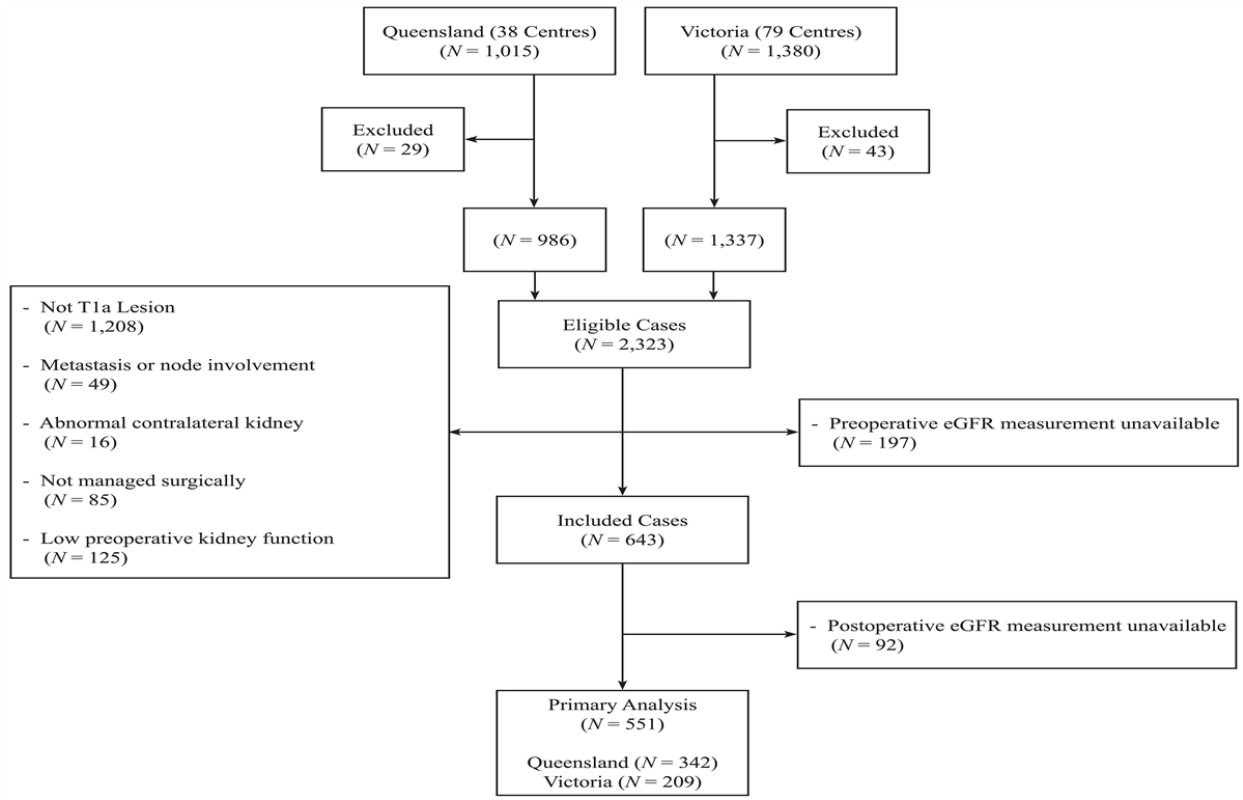


Figure 1 .

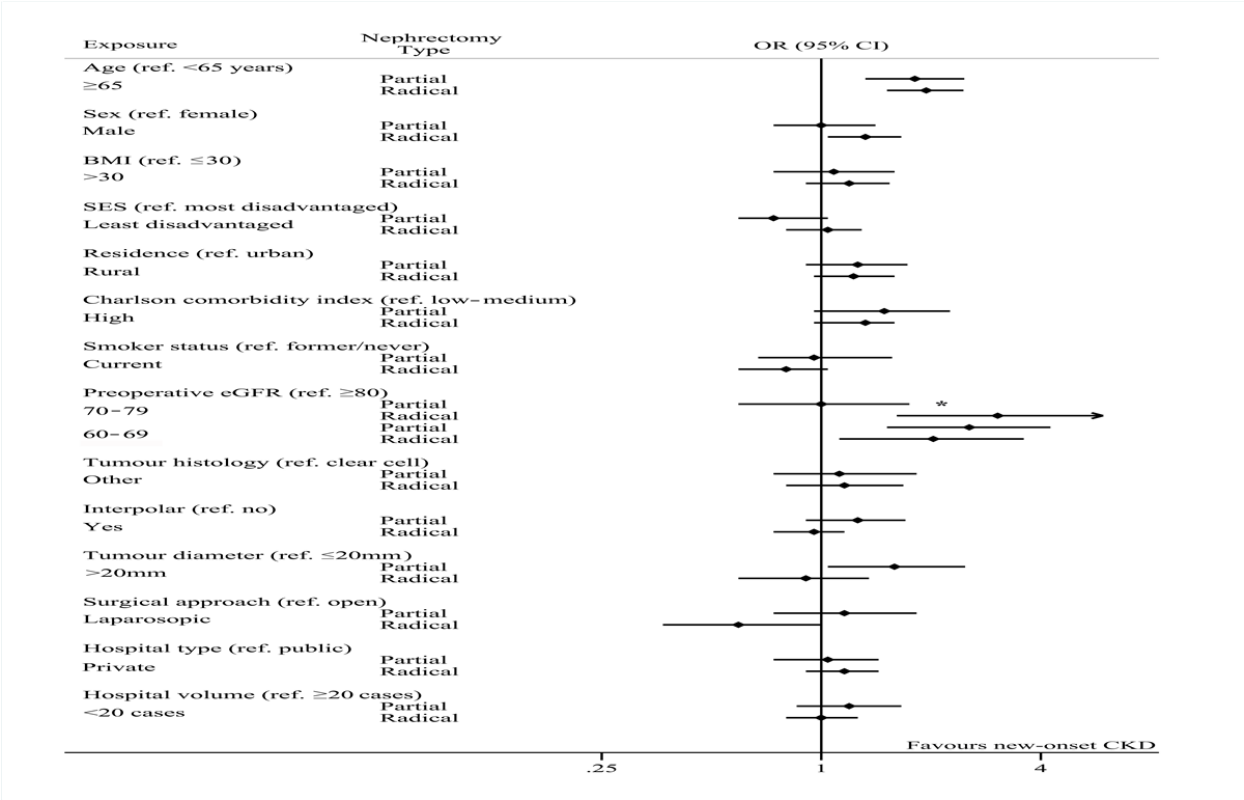
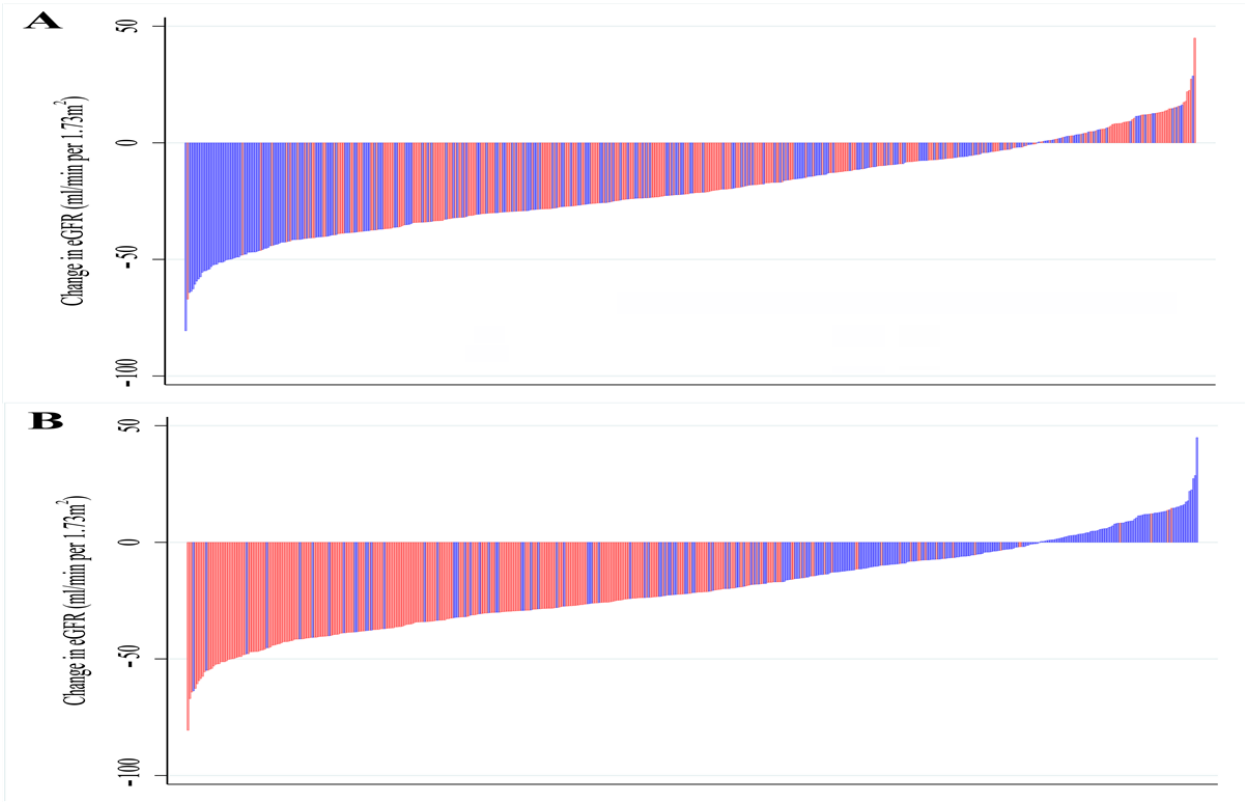


Figure 2 .



Supplementary Figure 1 .