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RESEARCH ARTICLE

SURVIVAL AND MORTALITY OF KIDNEY CANCER IN RELATION TO CARDIOVASCULAR DISEASES AND TREATMENTS: A POPULATION-BASED STUDY IN NORTHERN ITALY

Lucia **Mangone** [1,*], Luigi **Tarantini** [2], Francesco **Marinelli** [1], Isabella **Bisceglia** [1], Fortunato **Morabito** [3], Antonino **Neri** [4], Cristina **Masini** [5], Carmine **Pinto** [5]

[1] Epidemiology Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[2] Unit of Urology, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[3] Gruppo Amici Dell'Ematologia - Foundation-GrADE, Reggio Emilia, Italy
[4] Scientific Directorate, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[5] Medical Oncology Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[*] Correspondence to: lucia.mangone@ausl.re.it, https://orcid.org/0000-0002-5089-5178

ABSTRACT: Kidney cancer (KC) is a not very common neoplasm and has a good overall survival rate, especially for early forms. In this study we investigated, in a real-world context, the impact of stage and treatment on KC outcomes, particularly in patients with prior cardiovascular disease (CVD). Analyzing data from the Reggio Emilia Cancer Registry spanning 2003 to 2018, we examined 1,566 kidney cancer patients and 1,124 long-living patients. By comparing patients between 2003-2010 and 2011-2018 (target therapies were introduced in 2011), we aimed to assess any improvements in survival rates. Multivariable analysis shows an increased risk of death related to age (40-59 years [HR 2.97; 95% CI 1.21-7.31], 60-79 years [HR 6.90; 2-84-16-79], 80+ [HR 19.55; 95% CI 7.99-47.84]), and recent hospitalization for CVD [HR 1.76; 95% CI 1.24-2.51] while the risk is reduced in the more recent period [HR 0.78; 95% CI 0.67-0.91]. This reduction is linked partly to the increase in stage I recorded between the first and second periods (40.7% *vs*. 54.6%) and partly to the administration of Target Therapy to all patients with advanced disease in the second period. The study highlights that in addition to early diagnosis and innovative treatments, multidisciplinary cardio-oncological management of patients with kidney cancer is essential.

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Impact statement: Kidney cancer has a good prognosis and, with targeted therapies, profoundly changes treatment approaches. This study evaluates mortality and survival in a province in Northern Italy where the introduction of targeted therapy in 2011 seems to have changed the prognosis of kidney cancer. We have seen a decline in mortality that appears to be related to both the decline in advanced forms and the introduction of new drugs.

Key words: *kidney cancer; cardiovascular disease; survival; mortality; real-world setting.*

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INTRODUCTION

Annually, there are approximately 435,000 new cases of kidney cancer (KC) globally, making it the 14th most frequent neoplasm. It is the 16th leading cause of cancer-related mortality, accounting for approximately 156,000 deaths per year (1). The incidence and mortality rates of KC show significant geographic variability, with age-standardized incidence rates ranging from 1.6 x 100,000 in Africa to 12.6 x

100,000 in northern America (1). The 5-year survival rate of KC is approximately 78%, with survival rates significantly based on the stage of the disease: 93% for localized forms, 74% for regional forms, and 17% for metastatic forms (2). Despite the unknown etiology of KC, several risk factors have been identified that contribute to its pathogenesis. Among these, tobacco has been implicated, with smokers exhibiting almost nearly double the risk of developing KC compared to non-smokers (3, 4). Occupational exposure to carcinogenic substances, including arsenic, certain metal degreasers, and cadmium commonly used in mining operations, also significantly increases risk (5). Additionally, a positive family history of KC, obesity, hypertension, and male sex have been recognized as predisposing factors (6-8). Diagnostic modalities by imaging and histopathological examination are essential for cancer confirmation (9-10). The main treatment modality for KC is surgery, which may be utilized alone or in conjunction with radiotherapy, contingent on the cancer's stage and extent (11). Radical nephrectomy remains the predominant surgical procedure for kidney cancers (12), whereas partial nephrectomy is reserved for individuals presenting with a small tumor in one kidney (less than 4 cm), bilateral KC, or a solitary functioning kidney. The treatment of choice is surgery for localized forms while the availability of target therapies (TTs) in the last 20 years has changed the prognosis even in metastatic forms (13, 14). Observational data from real-world registries indicate that novel therapies are swiftly being integrated into routine clinical practice, in a scenario characterized by the growing clinical complexity of cancer patients (15). Patients with kidney cancers often exhibit a high incidence of cardiovascular (CV) risk factors, including arterial hypertension, obesity, dyslipidemia, and diabetes and are often excluded from randomized clinical oncology trials (16). The presence of arterial hypertension and other CV pathologies is associated with unfavorable prognostic outcomes in KC (17). However, the advent of tyrosine kinase inhibitors (TKIs) has contributed to improved prognoses, even among patients with concurrent CV comorbidities (18-21). Given the prolonged survival of KC patients, the identification of those at high risk of adverse events is of fundamental importance, as these individuals are more susceptible to CV events (22).The objective of this study is to investigate, in a real-world context, the impact of stage and treatment on KC mortality, in patients with prior CV disease (CVD), over 15 years of observation.

MATERIALS AND METHODS

Study setting

This study investigation utilized data extracted from the cancer registry of Reggio Emilia province. All incidences of KC cases recorded between 2003 and 2018 were included. The classification of KC was conducted in accordance with the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [23], with a specific emphasis on topography C64.9. The study was approved by the provincial Ethics Committee of Reggio Emilia, Protocol no. 2014/0019740, on 4 August 2014. Microscopic confirmations accounted for 89% of KC diagnoses, with occurrences of Death Certificate Only (DCO) cases constituting less than 0.1%. The Reggio Emilia Cancer Registry (RE-CR) covered a population of 532,000 inhabitants and the primary information sources were anatomic pathology reports, hospital discharge records, and mortality data, integrated with diagnostic reports, laboratory tests, and information from general practitioners.

Data sources

The incidence and mortality trend were made over the period 2003-2018 and the APCs were calculated. Since Target therapies were introduced starting from 2011, the case study was broken into two periods (2003-2010 and 2011-2018).

The stage was recovered for the two oldest years (2003-2004 and the two most recent years 2017-2018). The information on the treatment was retrieved directly from the pharmaceutical company and cross-referenced with the most recent cases.

Two inclusion criteria were applied to select subjects for this study:

a. Selection was restricted to hospitalizations for CVD within the 365 days preceding the date of incidence, where the 365-day period was calculated as the difference between the date of hospitalization admission and the date of incidence. Hospitalizations were identified using the following ICD-9 codes: Essential hypertension (401.x); Hypertensive heart disease (402.x); Ischemic heart disease (410.x-414.x); Conduction disorders (426. x); Cardiac dysrhythmias (427.x); Heart failure (428.x); and Ill-defined descriptions and complications of heart disease (429.x). These codes were queried across all medical locations.
b. The count of dispensing executed within the 180 days preceding the date of incidence for the three specified drugs was assessed. These drugs were

identified by their Anatomical Therapeutic Chemical (ATC) codes as follows: Antihypertensive (A10), Statins (C10), and Antidiabetic medications (C02, C03, C07, C08, C09).

Statistical methods

All cases identified through the cancer registry for the period spanning 2003 to 2018 were cross-referenced with the data derived from Hospital Discharge Records to ascertain the selection of hospitalizations and with the Direct Delivery Drugs database (only from 2017) and Territorial Pharmaceutical Assistance concerning drug-related information. Comparative analyses were conducted between two distinct periods 2003-2010 and 2011-2018, stratified by sex, year of diagnosis, and age at diagnosis. Additional stratification was performed based on CVD hospitalizations in the preceding year, which was defined as the presence of at least one hospitalization for specified pathologies within the 365 days prior to hospitalization, and CVD hospitalizations in the previous year in the primary position, denoting the presence of one of the specified ICD-9 codes as the principal diagnosis in any hospitalization within the preceding 365 days.

Analyses encompassed the entire cohort as well as a subgroup of long-lived patients, excluding individuals who died within 2 years of diagnosis.

Univariable and multivariable Cox proportional hazard regression models were constructed to investigate the association between the two periods, age, hospitalization for CVD, presence of hypertension, presence of drugs and overall survival. Time was expressed in years.

Analyses were conducted on the entire cohort and a subset comprising long-lived patients. Results were reported with 95% confidence intervals (CI). The Kaplan-Meier method was employed to analyze the time-to-event data, specifically overall survival, stratified by time periods for both the entire cohort and the sub-group. STATA 16.1 software was utilized for all statistical analyses.

RESULTS

The incidence and mortality trend over the entire period (**Figures 1A, B**) shows that compared to a slight increase in the period 2003-2013 (APC 1.4; 95% CI -0.3, 3) a significant decrease was observed in the period 2014-2020 (APC -3.3; 95% CI -5.9, -0.6). As regards mortality, a first decline was observed in 2003-2013 (APC -2.3; 95% CI -8.9, 4.8) followed by a more consistent, although not significant, decline in the period 2014-2020 (APC -10.3; 95% CI -22.9, 4.3). In the period between 2003 and 2018, 1,566 kidney tumors were registered (722 in 2003-2010 and 844 in 2011-2018). The majority of tumors affect male sex (64.9%), age 60-79 (52.2%), and were diagnosed in the two years preceding hospitalization (28.2%). Observing the CV pathological diagnoses, 25.1% had hospitalization in the year preceding the diagnosis of KC,

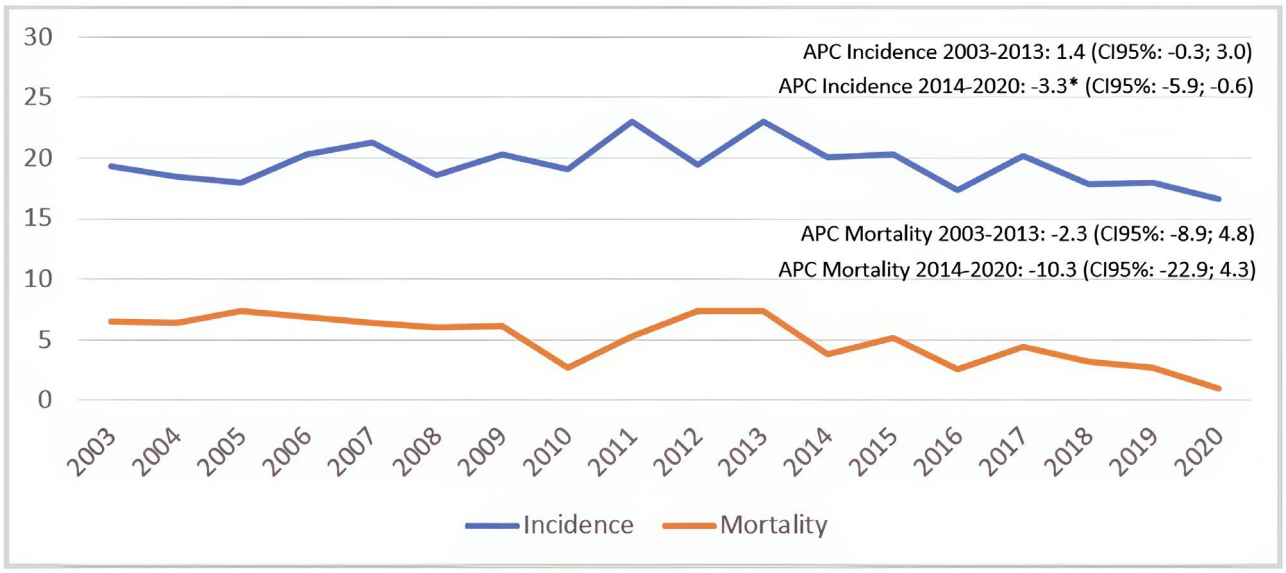


Figure 1. *Reggio Emilia Cancer Registry. Kidney Cancer 2003-2020. Incidence and mortality trend of kidney cancer.*

3.3% the diagnosis was in first position in the HDR, furthermore 64.8% used antihypertensive drugs, 20.6% of statins and 11.6 of antidiabetics. The comparison of the two periods shows a slight increase in tumors diagnosed at ages 40-59 and 80+ and in hospitalizations that occurred 2 to 10 years before diagnosis. Furthermore, there is an increase in hospitalizations for CVD and in therapies with antihypertensive drugs and statins (**Table 1**). The distribution by stage is shown in **Supplementary Table 1**. In the period 2003-2004 *vs*. 2017-2018, an increase in stage I was observed (40.7% *vs*. 54.6%) while stage IV remained stable (18.6% *vs*. 19.1%) but an interesting decline in unstaged forms was observed (12.8% *vs*. 5.1%).

Long-living patients (**Table 2**) were defined as individuals who remained alive and not lost at follow-up exceeding 2 years of observation after diagnosis. After excluding those who died and those lost to follow-up, the long-term survivor cohort included 1,124 patients. Of these long-living patients, 65.9% were male, predominantly aged between 60 and 79 years (54.8%), with no significant demographic differences compared to the overall patient population shown in **Table 1**.

Kaplan-Meier analysis (**Figure 2A**) revealed that among *all patients* at 5-year post-diagnosis, 56.6% of patients diagnosed in the years 2003-2010 are alive compared to 63.2% of 2011-2018 period, with a sta-

Table 1. *Analysis of Demographic and Clinical Characteristics among All Patients: a comparison 2003-2010 vs. 2011-2018.*

			PERIOD OF DIAGNOSIS			
	TOTAL (1,566)		2003-2010		2011-2018	
	N	%	N	%	N	%
Overall			**722**	**46.1**	**844**	**53.9**
Gender						
Male	1,018	64.9	465	64.4	553	65.5
Female	548	35.1	257	35.6	291	34.5
Age at diagnosis						
<40	48	3.1	27	3.7	21	2.5
40-59	359	22.9	156	21.6	203	24.1
60-79	817	52.2	388	53.7	429	50.8
80+	342	21.8	151	20.9	191	22.6
Years from diagnosis						
<2 years	442	28.2	221	30.6	221	26.2
2-5 years	485	31	112	15.5	373	44.2
6-10 years	388	24.8	138	19.1	250	29.6
10+ years	251	16	251	34.8	0	0
CVD hospitalization previous year						
No	1,175	74.9	570	78.9	605	71.7
Yes	391	25.1	152	21.1	239	28.3
CVD hospitalization previous year (first position)						
No	1,515	96.7	697	96.5	818	96.9
Yes	51	3.3	25	3.5	26	3.1
Antihypertensive						
No	552	35.2	274	37.9	278	32.9
Yes	1,014	64.8	448	62.1	566	67.1
Statins						
No	1,243	79.4	612	84.8	631	74.8
Yes	323	20.6	110	15.2	213	25.2
Antidiabetic						
No	1,384	88.4	642	88.9	742	88.4
Yes	182	11.6	80	11.1	102	11.6

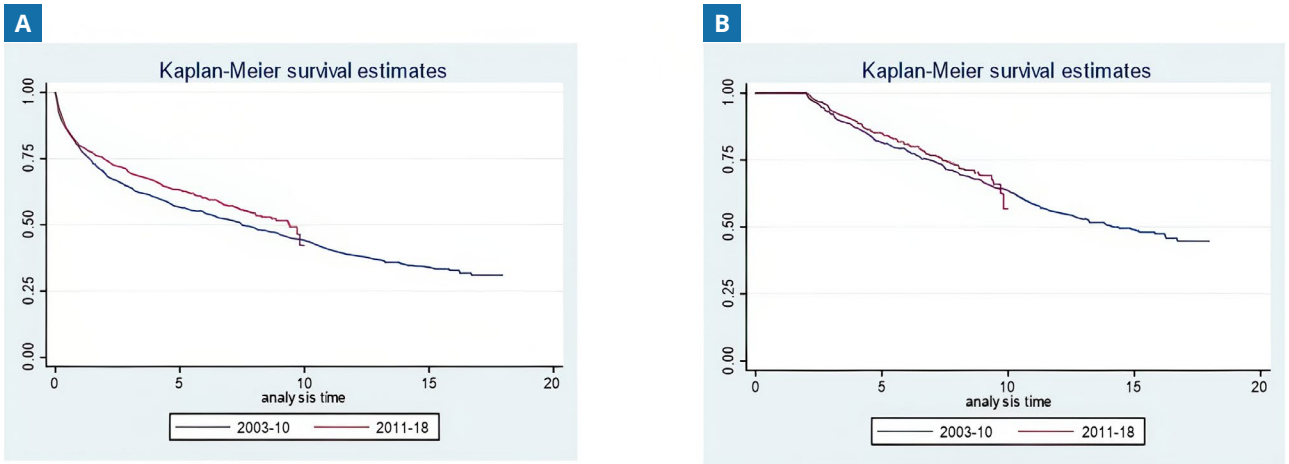
Table 2. *Analysis of Demographic and Clinical Characteristics among Long-Living Patients: a comparison 2003-2010 vs. 2011-2018.*

			PERIOD OF DIAGNOSIS			
	TOTAL (1,124)		2003-2010		2011-2018	
	N	%	N	%	N	%
Overall			**501**	**44.6**	**623**	**55.4**
Gender						
Male	741	65.9	323	64.5	418	67.1
Female	383	34.1	178	35.5	205	32.9
Age at diagnosis						
<40	44	3.9	26	5.2	18	2.9
40-59	310	27.6	140	27.9	170	27.3
60-79	616	54.8	270	53.9	346	55.5
80+	154	13.7	65	13	89	14.3
CVD hospitalization previous year						
No	857	76.2	404	80.6	453	72.7
Yes	267	23.8	97	19.4	170	27.3
CVD hospitalization previous year (first position)						
No	1,098	97.7	490	97.8	608	97.6
Yes	26	2.3	11	2.2	15	2.4
Antihypertensive						
No	433	38.5	211	42.1	222	35.6
Yes	691	61.5	290	57.9	401	64.4
Statins						
No	881	78.4	423	84.4	458	73.5
Yes	234	21.6	78	15.6	165	26.5
Antidiabetic						
No	997	88.7	447	89.2	550	88.3
Yes	127	11.3	54	10.8	73	11.7

tistically significant difference. Conversely, among *long-living patients*, the disparity diminishes (81.4% in the 2003-2010 cohort *vs*. 84.9% in the 2011-2018 cohort) (**Figure 2B**). Survival analysis demonstrates that 68.3% of patients with a history of hospitalization for CVD survived 24 months from diagnosis, whereas this figure rises to 77.3% for patients without such hospitalization. Notably, survival rates beyond 24 months stand at 51% among patients with CVD as the primary cause of hospitalization, compared to 72.7% among those without such hospitalization. Finally, multivariable analysis for *all patients* (**Table 3A**) showed in the most recent period a 18% reduction in the risk of death [HR 0.78; 95% CI 0.67-0.91], while the risk increased with age (40-59 years [HR 2.97; 95% CI 1.21-7.31], 60-79 years [HR 6.90; 2-84-16-79], 80+ [HR 19.55; 95% CI 7.99-47.84]), and the presence of prior hospitalization for CVD, particularly when it occurs as the primary diagnosis [HR 1.73; 95% CI 1.21- 2.46]. The risk reduction remains consistent at 18% even when analyzing *long-living patients*, although not significant [HR 0.78, 95% CI 0.61-1.00], while the age-related risk increase persists (**Table 3B**).

DISCUSSION

This study aimed to evaluate the mortality and survival outcomes of KC patients in the province of Reggio Emilia, Italy, analyzing a 15-year of registration. In particular, the study aims to highlight any changes in mortality and survival in relation to the stage of the disease and the introduction of new drugs which, in our province, were introduced starting from 2011-2012. For this reason, we decided to break the cohort into two periods, 2003-2010 and 2011-2018; in fact, the introduction of the drugs start-



Survival			
2003-10	**%**	**95% CI**	
3 years	64.0	60.3	67.3
5 years	56.6	52.9	60.1
8 years	48.9	45.2	52.5
2011-18			
3 years	69.6	66.4	72.6
5 years	63.2	61.0	66.5
8 years	54.4	50.2	58.5

Survival			
2003-10	**%**	**95% CI**	
3 years	92.0	89.3	94.1
5 years	81.4	77.7	84.5
8 years	70.3	66.1	74.1
2011-18			
3 years	93.5	91.1	95.2
5 years	84.9	81.4	87.7
8 years	73.1	68.0	77.5

Figure 2. *Province of Reggio Emilia, years 2003-2018. Kaplan-Meier survival estimates by period in the Province of Reggio Emilia: (**A**) all patients (1,566); (**B**) long-living patients (1,124).*

ing from 2011 highlighted a drop in mortality and this was clearly observed after a couple of years from the introduction of the new drugs: starting from 2014 a drop equal to 10% per year was observed, although not significant, which also persisted in subsequent years. The study was conducted both on all 1,566 patients with kidney cancer and then on a subgroup of 1,124 (individuals who remained alive and not lost at follow-up exceeding 2 years of observation after diagnosis). The data were also observed-corrected for hospitalization due to previous CV pathologies and for the use of drugs for CVD diseases. Indeed, the presence of CV events in patients with kidney cancers significantly influences survival outcomes and poses substantial clinical challenges (24). These events not only potentially foster tumor growth, metastasis, and resistance to treatment modalities but also impact treatment decisions and tolerability, potentially delaying surgery or complicating systemic therapies.

The first thing we observed in all patients is a slight shift in the most recent period of tumors observed in the 40-59 and 80+ age groups, as well as hospitalizations for CVD in the 2-10 years preceding the diagnosis of KC. Furthermore, there was a rise in patients with prior hospitalization for CVD, from 21.1% to 28.3%, potentially indicating either enhanced detection and reporting or a genuine increase in comorbidity conditions. The use of antihypertensive drugs and statins also increased in the second period, which may reflect broader statin use guidelines or improved management of comorbidity. In the subset of long-living patients, the comparison between the two periods, the increase in males, prior hospitalization for CVD (from 19% to 27%), and in the use of statins and antihypertensive drugs was also confirmed. This underlines the importance of a multidisciplinary approach to patients with KC which, in addition to eye care, requires correct management of cardiovascular pathology (25). The survival analysis shows a significant improvement in the 5-year survival rate in all patients, increasing significantly from roughly 56.6% to 63.2% across the two study periods. Although the 8-year survival rate also showed improvement (48.9% *vs*. 54.4%), this difference was not statistically significant. Among long-living patients, the 5-year survival rate increased from 81.4% in 2003-2010 to 84.9% in 2011-2018, with this trend persisting at the 8-year (70.3% *vs*. 73.1%).

In fact, in the two periods observed, we recorded a slight increase in early-stage tumors that are usually associated with excellent 5-year survival (26). In our study, this improvement also coincides with the introduction of TT drugs which, starting from 2011, had

Table 3. *Univariable and multivariable Cox regression analyses adjusted for drugs and several variables conducted in kidney cancer patients of Province of Reggio Emilia over the period 2003-2018. (**A**) All patients and (**B**) long living patients.*

A

CHARACTERISTICS	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
	HR	95% CI	HR	95% CI
Period				
2003-2010	1.00	Ref.	1.00	Ref.
2011-2018	0.86	0.74-0.99	0.78	0.67-0.91
Age at diagnosis				
<40	1.00	Ref.	1.00	Ref.
40-59	3.11	1.53-6.33	2.97	1.21-7.31
60-79	7.93	3.95-15.93	6.90	2.84-16.79
80+	20.86	10.33-42.14	19.55	7.99-47.84
CVD hospitalization previous year				
No	1.00	Ref.	1.00	Ref.
Yes	1.41	1.21-1.64	1.01	0.85-1.20
CVD hospitalization previous year (first position)				
No	1.00	Ref.	1.00	Ref.
Yes	2.09	1.50-2.91	1.73	1.21-2.46
Antihypertensive				
No	1.00	Ref.	1.00	Ref.
Yes	1.77	1.51-2.07	1.10	0.92-1.31

B

CHARACTERISTICS	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
	HR	95% CI	HR	95% CI
Period				
2003-2010	1.00	Ref.	1.00	Ref.
2011-2018	0.91	0.72-1.16	0.78	0.61-1.00
Age at diagnosis				
<40	1.00	Ref.	1.00	Ref.
40-59	5.21	1.65-16.46	8.37	1.15-60.70
60-79	14.91	4.79-46.49	21.70	3.02-155.79
80+	40.78	12.95-128.45	58.47	8.07-423.46
CVD hospitalization previous year				
No	1.00	Ref.	1.00	Ref.
Yes	1.61	1.28-2.02	1.15	0.89-1.48
CVD hospitalization previous year (first position)				
No	1.00	Ref.	1.00	Ref.
Yes	1.86	1.04-3.30	1.48	0.81-2.72
Antihypertensive				
No	1.00	Ref.	1.00	Ref.
Yes	1.88	1.50-2.36	1.15	0.89-1.48

an immediate impact on mortality which dropped starting from 2014. In fact, the introduction of new pharmacological strategies has notably enhanced survival rates for advanced KC. The initial implementation of antiangiogenic and mTOR TKI, followed by immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-CTLA4, has revolutionized treatment paradigms. Sunitinib, the first TKI introduced into clinical

practice for first-line therapy, significantly improved survival rates (27-29). Subsequent TKI targeting angiogenesis and the TOR pathway were incorporated across various lines of therapy (30-35). Finally, the introduction of immunotherapy (36) marked a substantial advancement. The use of ICIs in combination with TKIs has significantly improved the prognosis for patients with metastatic KC (37). Currently, four regimens are available for first-line therapy in advanced KC in Italy: pembrolizimab/axitinib, nivolumab/cabozantinib, pem-brolizumab/levantinib and ipilimumab/nivolumab (37-40).

Therefore, the double effect linked to the decline in advanced tumors and the presence of active and effective treatments in the clinical management of these could explain the decline in mortality recorded in recent years, in a population-based study.

This study has several strengths, making it a valuable contribution to understanding the interaction between KC treatment and CV comorbidities. This is a population-based study, which includes a 15-year period of registration. The large sample size improves the statistical power and generalizability of the study. Furthermore, an additional effort was made to retrieve information on CV comorbidities both linked to previous hospitalizations and the use of drugs. Even the recovery of information on stage and treatment, although for a few years, which is not routinely collected by CRs, represents a strong point of the work.

However, there are limitations largely linked to the fact that it is a single center, in a province characterized by high quality of healthcare systems and the variability of healthcare systems, patient demographics and treatment practices in different regions could influence the applicability of the results to other regions. The study does not provide detailed information on patient adherence to prescribed cardiovascular and anticancer therapies. Medication adherence is a critical factor in treatment efficacy and survival outcomes, and its omission constitutes a notable gap.

CONCLUSIONS

This real-world study confirms the promising trends inKC survival following the introduction of innovative drugs, suggesting a potential reduction in mortality rates, even in older patients and with greater hospitalizations for CVD. However, a history of CV comorbidities significantly influences the risk of death (41) as well as the presence of diabetes, obesity and metabolic syndrome (42) and hypertension (43) and the overall survival out-comes, emphasizing the need for integrated multidisciplinary care. Patients with prior hospitalization for CVD represent a high-risk cohort. This increased risk of death remains high, if not significant, even for long-living patients, thus requiring comprehensive management strategies. Awareness of the impact of new drugs and cardiovascular disease on kidney cancer survival underlines the importance of a multidisciplinary collaboration between cardiology and oncology specialists.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interests

The authors have declared no conflicts of interests.

Availability of data and materials

The data presented in this study are available on request from the Corresponding Author.

Authors' contributions

Conceptualization, investigation, writing-original draft, visualization, supervision: LM, LT; formal analysis: FM; writing-review and editing, supervision and visualization: IB; supervision: FM, AN, CM; conceptualization, writing-original draft, supervision: CP. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Human studies and subject - Institutional Review Board Statement

This population-based cohort study uses data from the Reggio Emilia Cancer Registry, approved by the Provincial Ethics Committee of Reggio Emilia (ref. no. 2014/0019740 of 4 August 2014). The Ethics Committee authorized, even in the absence of consent, the processing of personal data, including those suitable for revealing the state of health of patients who are deceased or untraceable for the execution of the study.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. Available from: https://gco.iarc.fr/en. Accessed: May 25, 2024.
2. Available from: https://www.cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html. Accessed: May 25, 2024.
3. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer. 2008;122(1):155-64. doi: 10.1002/ijc.23033.
4. Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR. Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study. BMC Cancer. 2008;8:387. doi: 10.1186/1471-2407-8-387.
5. Peters CE, Parent MÉ, Harris SA, Kachuri L, Latifovic L, Bogaert L, et al.; Canadian Cancer Registries Epidemiology Group. Workplace exposure to asbestos and the risk of kidney cancer in Canadian men. Can J Public Health. 2018;109(4):464-72. doi: 10.17269/s41997-018-0095-9.
6. Venkatesh N, Martini A, McQuade JL, Msaouel P, Hahn AW. Obesity and renal cell carcinoma: Biological mechanisms and perspectives. Semin Cancer Biol. 2023;94:21-33. doi: 10.1016/j.semcancer.2023.06.001.
7. Mittal B v, Singh AK. Hypertension in the Developing World: Challenges and Opportunities. Am J Kidney Dis. 2010;55(3). doi: 10.1053/j.ajkd.2009.06.044.
8. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, Mafakher L. Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. G Ital Nefrol. 2022;39(3):2022-vol3. PMID: 35819037.
9. Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(1):71-90. doi: 10.6004/jnccn.2022.0001.
10. Quencer KB. Renal Mass Biopsy. Tech Vasc Interv Radiol. 2021;24(4):100774. doi: 10.1016/j.tvir.2021.100774.
11. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, Mafakher L. Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. G Ital Nefrol. 2022;39(3):2022-vol3. PMID: 35819037.
12. Campos-Sañudo JA, Ballestero-Diego R, Zubillaga-Guerrero S, Rodríguez-SanJuan JC, Monge-Mirallas JM, Crespo-Santiago D. Impact of radical nephrectomy on kidney function and prognostic factors for adverse cardiovascular events. Actas Urol Esp (Engl Ed). 2020;44(4):239-44. English, Spanish. doi: 10.1016/j.acuro.2020.02.003.
13. Cardenas LM, Sigurdson S, Wallis CJD, Lalani AK, Swaminath A. Advances in the management of renal cell carcinoma. CMAJ. 2024;196(7):E235-E240. doi: 10.1503/cmaj.230356.
14. Tung I, Sahu A. Immune Checkpoint Inhibitor in First-Line Treatment of Metastatic Renal Cell Carcinoma: A Review of Current Evidence and Future Directions. Front Oncol. 2021;11:707214. doi: 10.3389/fonc.2021.707214.
15. Li P, Jahnke J, Pettit AR, Wong Y, Doshi JA. Comparative Survival Associated With Use of Targeted vs Nontargeted Therapy in Medicare Patients With Metastatic Renal Cell Carcinoma. JAMA Netw Open. 2019;2(6):e195806. doi: 10.1001/jamanetworkopen.2019.5806.
16. Bonsu J, Charles L, Guha A, Awan F, Woyach J, Yildiz V, et al. Representation of Patients With Cardiovascular Disease in Pivotal Cancer Clinical Trials. Circulation. 2019;139(22):2594-6. doi: 10.1161/CIRCULATIONAHA.118.039180.
17. Tini G, Sarocchi M, Tocci G, Arboscello E, Ghigliotti G, Novo G, et al. Arterial hypertension in cancer: The elephant in the room. Int J Cardiol. 2019;281:133-9. doi: 10.1016/j.ijcard.2019.01.082.
18. Beisland C, Johannesen TB, Klepp O, Axcrona U, Torgersen KM, Kowalski J, et al. Overall survival in renal cell carcinoma after introduction of targeted therapies: a Norwegian population-based study. Onco Targets Ther. 2017;10:371-385. doi: 10.2147/OTT.S123061.
19. Wagstaff J, Jones R, Hawkins R, Porfiri E, Pickering L, Bahl A, et al. Treatment patterns and clinical outcomes in patients with renal cell carcinoma in the UK: insights from the RECCORD registry. Ann Oncol. 2016;27(1):159-65. doi: 10.1093/annonc/mdv504.

20. Marschner N, Staehler M, Müller L, Nusch A, Harde J, Koska M, et al; RCC Registry Group. Survival of Patients With Advanced or Metastatic Renal Cell Carcinoma in Routine Practice Differs From That in Clinical Trials-Analyses From the German Clinical RCC Registry. Clin Genitourin Cancer. 2017;15(2):e209-e215. doi: 10.1016/j.clgc.2016.08.022.
21. Li P, Jahnke J, Pettit AR, Wong YN, Doshi JA. Comparative Survival Associated With Use of Targeted vs Nontargeted Therapy in Medicare Patients With Metastatic Renal Cell Carcinoma. JAMA Netw Open. 2019;2(6):e195806. doi: 10.1001/jamanetworkopen.2019.5806.
22. Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. J Clin Oncol. 2016;34(10):1122-30. doi: 10.1200/JCO.2015.64.0409.
23. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. International Classification of disease for Oncology, 3rd edition. World Health Organization 2013.
24. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31(2):171-90. doi: 10.1016/j.annonc.2019.10.023.
25. Paterson DI, Wiebe N, Cheung WY, Mackey JR, Pituskin E, Reiman A, et al. Incident Cardiovascular Disease Among Adults With Cancer: A Population-Based Cohort Study. JACC CardioOncol. 2022;4(1):85-94. doi: 10.1016/j.jaccao.2022.01.100.
26. Lewis G, Maxwell AP. Early diagnosis improves survival in kidney cancer. Practitioner. 2012;256(1748):13-6, 2. PMID: 22497103.
27. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24. doi: 10.1056/NEJMoa065044.
28. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584-90. Corrected and republished in: J Clin Oncol. 2023;41(11):1965-71. doi: 10.1200/JCO.2008.20.1293.
29. Procopio G, Claps M, Pircher C, Porcu L, Sepe P, Guadalupi V, et al. A multicenter phase 2 single arm study of cabozantinib in patients with advanced or unresectable renal cell carcinoma pre-treated with one immune-checkpoint inhibitor: The BREAKPOINT trial (MeetUro trial 03). Tumori. 2023;109(1):129-37. doi: 10.1177/03008916221138881
30. Rini BI. Targeted therapy for patients with renal-cell carcinoma. Lancet Oncol. 2011;12(12):1085-7. doi: 10.1016/S1470-2045(11)70276-5.
31. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31. doi: 10.1056/NEJMoa1303989.
32. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al.; METEOR Investigators. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1814-23. doi: 10.1056/NEJMoa1510016.
33. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015;16(15):1473-82. doi: 10.1016/S1470-2045(15)00290-9.
34. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al.; METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917-27. doi: 10.1016/S1470-2045(16)30107-3.
35. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med. 2017;376(4):354-66. doi: 10.1056/NEJMra1601333.
36. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al.; CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1803-13. doi: 10.1056/NEJMoa1510665.
37. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al.; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277-90. doi: 10.1056/NEJMoa1712126.
38. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al.; KEYNOTE-426 Investigators.

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116-27. doi: 10.1056/NEJMoa1816714.
39. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, et al.; KEYNOTE-564 Investigators. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med. 2021;385(8):683-94. doi: 10.1056/NEJMoa2106391.
40. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al.; CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021;384(14):1289-300. doi: 10.1056/NEJMoa2035716.
41. Ricardo AC, Anderson CA, Yang W, Zhang X, Fischer MJ, Dember LM, et al.; CRIC Study Investigators. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2015;65(3):412-24. doi: 10.1053/j.ajkd.2014.09.016.
42. Flammia RS, Tufano A, Proietti F, Gerolimetto C, DE Nunzio C, Franco G, et al. Renal surgery for kidney cancer: is preoperative proteinuria a predictor of functional and survival outcomes after surgery? A systematic review of the literature. Minerva Urol Nephrol. 2022;74(3):255-64. doi: 10.23736/S2724-6051.21.04308-1.
43. Flammia RS, Anceschi U, Tufano A, Tuderti G, Ferriero MC, Brassetti A, et al. Is Hypertension Associated with Worse Renal Functional Outcomes after Minimally Invasive Partial Nephrectomy? Results from a Multi-Institutional Cohort. J Clin Med. 2022;11(5):1243. doi: 10.3390/jcm11051243.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. *Reggio Emilia Cancer Registry. Distribution by stage in 2003-2004 and 2017-2018 years. Percentage values.*

STAGE	2003-2004	2017-2018
I	40.7%	54.6%
II	15.1%	5.8%
III	12.8%	15.4%
IV	18.6%	19.1%
unknown	12.8%	5.1%