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Association between cognitive impairment and oral anticancer agent use in older patients with metastatic renal cell carcinoma

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Abstract

Background—Kidney cancer is the fastest-growing cancer diagnosis in the developed world. About 16% of new cases are stage IV, which has a low five-year survival rate. Many patients with metastatic renal cell carcinoma (mRCC) are older and may have mild cognitive impairment or dementia (MCI/D). Given prior reports of patients with dementia initiating less cancer therapy and the importance of oral anticancer agents (OAAs) in mRCC treatment, we investigated the prevalence of preexisting MCI/D in patients with mRCC and their OAA use.

Methods—SEER-Medicare patients were analyzed who were ≥65 years, diagnosed with mRCC between 2007 and 2015, and had Medicare part D coverage. Patterns and predictors of a) OAA utilization within the 12 months following mRCC diagnosis and b) adherence (percent of days covered [PDC] ≥ 80%) during the first 90 days following treatment initiation were assessed.

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Authors' Contributions

Dr. Dinan conceptualized the study and Drs. Dinan, Pritchard, and Wilson acquired the data. Dr. Wilsons and Ms. Greiner performed quality control of data and algorithms, and statistical analysis. Drs. Pritchard and Wilson prepared and edited the manuscript. All authors participated in study design, data interpretation, and manuscript review, and approved the final manuscript.

Ethics Review

The Duke University Health System Institutional Review Board determined this study to be exempt from its oversight (Protocol #Pro00101962).

Results—Of the 2,792 eligible patients, 268 had preexisting MCI/D and 907 initiated OAA treatment within 12 months of mRCC diagnosis. Patients with preexisting MCI/D were less likely to begin an OAA than those without MCI/D (fully-adjusted HR 0.53, 95% CI 0.38 – 0.76). Among OAA initiators, a preexisting MCI/D diagnosis did not alter the likelihood that a person would be adherent (adjusted RR 0.84, 95% CI 0.55 – 1.28).

Conclusions—Patients with preexisting MCI/D were half as likely to start an OAA during the year following mRCC diagnosis than patients without comorbid MCI/D. The 90-day adherence of OAA initiators was not significantly different between those with and without preexisting MCI/D. In light of this, clinicians should assess mRCC patients for cognitive impairment and take steps to optimize OAA utilization by those with MCI/D.

Keywords

Renal cell carcinoma; cognitive impairment; dementia; targeted therapy; metastatic cancer

INTRODUCTION

Kidney cancer is the fastest-growing cancer diagnosis in the United States, with an estimated 79,000 new cases and 13,920 deaths during in 2022.[1,2] Renal cell carcinoma (RCC) comprises about 85% of all kidney cancers and the average age at diagnosis is 64 years.[3] Though overall survival remains low[4,5], the advent of oral anticancer agents (OAAs) in 2008 improved the overall survival of patients with metastatic RCC (mRCC) by about 40% over the cytokine-based regimens available previously.[6] OAAs were also an alternative to the intravenous and subcutaneous mRCC treatment regimens available during this period[7–11]; cancer patients generally prefer oral drugs to those given intraveneously[12]. OAA regimens remain important components of care even as multi-drug, combination regimens and immunotherapies have been added in recent years.[3,9]

Cognitive impairment occurs on a spectrum of decline in complex attention, executive function, learning and memory, language, perceptual-motor, and/or social cognition. Dementia, or major neurocognitive disorder, is characterized by a significant cognitive decline that impairs independence in activities of daily living. People with mild cognitive impairment (MCI), or mild neurocognitive disorder, experience less severe cognitive decline and can perform everyday tasks without assistance.[13] Comorbid cognitive impairment is a concern in older patients with cancer, as the prevalence of MCI and dementia both increase with age.[14–16] However, it is not known whether there are disparities in OAA usage by patients with mRCC and preexisting MCI or dementia (MCI/D).

In this retrospective study of insurance claims and cancer registry data, we explored the relationship between preexisting cognitive impairment and OAA initiation and adherence in older patients with mRCC.

METHODS

Study Sample

This retrospective, cohort study of Surveillance, Epidemiology and End Results (SEER)-Medicare data analyzed patients ≥65 years of age diagnosed with mRCC from 2007 – 2015. Supplementary Figure S1 describes full cohort selection. Each patient was required to have ≥12 months of continuous enrollment in Medicare fee-for-service Parts A and B before SEER RCC diagnosis, and Parts A, B, and D for 12 months after the metastatic index date (mRCC diagnosis date) or until death. We excluded patients who were <65 years old at metastatic diagnosis, had a second primary diagnosis of cancer at another site between the initial SEER RCC diagnosis date and metastatic index date, or if metastatic diagnosis occurred at autopsy or death.

Assessment of Pre-existing Mild Cognitive Impairment and Dementia

We considered a patient to have preexisting MCI/D if there was a MCI/D diagnosis code (Supplemental Appendix A) in any diagnosis position on an inpatient, outpatient, carrier, or home health Medicare claim during the 12 months prior to the metastatic index date.[17]

Patient and Clinical Characteristics

With the exception of comorbid conditions, patient and clinical characteristics were derived from the SEER registry. We assessed these characteristics on the metastatic index date, unless otherwise noted: race/ethnicity, age, sex, stage at initial RCC diagnosis, histology at initial RCC diagnosis, marital status, United States geographic region of residence[18], metropolitan residence[19], and ZIP code-level socioeconomic status (SES) characteristics (proportions of Black residents, adults ≤25 years old without a high school diploma or equivalent, and households at or below the poverty threshold). Race was derived from patient records; it was assigned to individuals using the local methodology of the facility that enrolled a patient in the SEER registry. The SEER algorithm that assigned ethnicity and the groups within the “other” race category are described in the Supplemental Methods.

We used validated coding algorithms to assess patient comorbidities of interest during the 12 months prior to the metastatic index date using diagnosis codes (Supplemental Appendix B) from inpatient, outpatient, and carrier Medicare claims files.[20–24]

Initiation of OAA Treatment

OAA utilization was indicated by a Part D prescription drug claim for sorafenib, sunitinib, pazopanib, everolimus, or axitinib in the 12 months following the metastatic index date. Utilization was treated as a binary indicator, and the date OAA initiation corresponded to a patient’s earliest OAA claim. These drugs are taken once- or twice-daily, with dose adjustments made as needed. Certain treatment regimens suggest scheduled breaks of either one or two weeks between cycles of oral treatment.[25–29]

Adherence to OAAs

Patients in the subcohort of OAA initiators had Part D coverage from the OAA initiation date through 90 days or until death. Their percentage of days covered (PDC) during

this period was calculated from the number of days' supply of OAAs provided on the prescription fill record and fill claim dates. Drug switching was permitted. Sunitinib adherence calculations accounted for the standard dosing of 4 weeks on followed by 2 weeks off by substituting 42 days of coverage for a 28-day prescription fill. Adherence was analyzed as a binary variable: we defined adherent as PDC ≥ 80% and non-adherent as PDC < 80%, per previously-reported thresholds.[30–33]

Receipt of and Adherence to Oral Antihypertensive Drugs by Patients with Preexisting Hypertension

For comparison of OAA use patterns to those of more commonly-used oral agents, we assessed receipt of and adherence to a prescribed oral antihypertensive drug (Supplemental Appendix C) by a subgroup of our mRCC patient cohort with a preexisting diagnosis of hypertension. Receipt of an oral antihypertensive drug may represent initiation or continued use of a chronic drug. Adherence was calculated during the 90 days following the first fill after the metastatic index date or until death using the same approach as described for OAA adherence. Oral antihypertensive drugs were selected because of their widespread usage by older adults, continuous dosing schedule, and low barriers for use (e.g., low toxicity and inexpensive options). None of the selected antihypertensive agents were contraindicated for use with the OAAs under investigation.[25–29]

Statistical Methods

Descriptive statistics were calculated for patient characteristics by MCI/D status at baseline; group differences were tested using Chi-square, t-tests, and Cochran Mantel-Haenzel tests, as appropriate. Cumulative incidence of OAA initiation and oral antihypertensive drug receipt were calculated at 12 months from mRCC diagnosis based on the cumulative incidence function to account for the high risk of death in this population. Patients were censored at 12 months following cohort entry or at death, whichever occurred first. Differences in initiation by preexisting MCI/D status were evaluated using Gray's test.

Fully-adjusted Cox proportional hazards regression analyses estimated the associations between preexisting MCI/D and OAA initiation in both the mRCC cohort and hypertensive subcohort, and between MCI/D and the first oral antihypertensive drug fill after metastatic diagnosis in the hypertensive subcohort. The proportional hazards assumption was assessed using Kaplan-Meier curve and Schoenfeld residuals testing. Full models were adjusted for all aforementioned patient and clinical characteristics. Minimally-adjusted models were only adjusted for patient age in years and MCI/D status at metastatic diagnosis.

Among OAA initiators, log-binomial regression analysis was used to assess the association between preexisting MCI/D and 90-day OAA adherence (PDC ≥ 80%), with full adjustment for patient clinical and demographic characteristics.

Ethics Review

The Duke University Health System Institutional Review Board determined this study to be exempt from its oversight (Protocol #Pro00101962).

RESULTS

Patient Demographics

A total of 2,792 patients with a mRCC diagnosis during 2007 – 2015 met the study inclusion criteria (Table 1 and Supplementary Figure S1). Of these, 268 (9.6%) patients had preexisting MCI/D at the time of metastatic diagnosis (Table 1).

Compared to patients without MCI/D, those with preexisting MCI/D were more likely to be older (mean age: 81.6 years vs. 75.9 years; $p < 0.001$), White non-Hispanic (73.1% vs. 75.6%; $p = 0.02$), unmarried (62.7% vs. 46.8%; $p = 0.02$), and dual-enrolled in Medicare and Medicaid (47.0% vs. 28.9%; $p < 0.001$). About half (53.4%) of the MCI/D subgroup were 81 years of age or older, whereas the patients without preexisting MCI/D were more evenly distributed across age groups (65 – 70 years, 30.7%; 71 – 75 years, 26.6%; 76 – 80 years, 20.5%; ≥81 years, 22.2%). White non-Hispanic patients comprised the vast majority of the subgroup, with the balance composed of Black non-Hispanic (MCI/D, 11.6%; no MCI/D, 6.5%), Hispanic (MCI/D, 10.1%; no MCI/D, 10.9%) and other race/ethnicity (MCI/D, 5.2%; no MCI/D, 7.1%) patients. The cohorts with and without preexisting MCI/D were similar for the other demographic, geographic, ZIP code-level SES, and RCC-specific measures examined. (Table 1)

Initiation of OAA treatment by patients with mRCC and preexisting MCI/D

OAA initiation was evaluated in the full study cohort, stratified by MCI/D status. Forty-six percent of patients without preexisting MCI/D initiated an OAA within a year of mRCC diagnosis, compared to twenty-six percent of patients with MCI/D (Figure 1); in fully-adjusted models, patients with preexisting MCI/D were about half as likely as their counterparts to initiate OAAs during the same time period (Figure 2, Table 2, and Supplementary Table S1; fully-adjusted HR 0.53, 95% CI 0.38 – 0.76). Adjustment for comorbidities and patient demographics, ZIP code-level SES measures, and RCC-specific characteristics did not appreciably alter the likelihood that a patient with preexisting MCI/D would begin OAA treatment (Figure 2, and Supplementary Table S1; preexisting MCI/D: minimal vs. full adjustment).

We analyzed OAA and oral antihypertensive drug claims in a subset of the mRCC cohort that had preexisting hypertension to see whether OAA use differed from other oral drugs' during the year following mRCC diagnosis (Supplementary Figure S2 and Supplementary Tables S2 – S3). The impact of MCI/D status was similar for the subset of patients with preexisting hypertension and the overall cohort (Table 2 and Supplementary Table S1 vs. Supplementary Table S3). Preexisting MCI/D was associated with lower risk of filling an oral antihypertensive drug after metastatic diagnosis, but the magnitude of the effect was less than that observed for OAAs (Table 2, Figure 1 vs. Supplementary Figure S2, and Supplementary Table S2 vs. Supplementary Table S3).

OAA adherence by patients with mRCC and preexisting MCI/D

Fewer than half of OAA initiators were adherent to treatment (Supplementary Table S6), and a preexisting MCI/D diagnosis did not alter the likelihood that a person would be adherent (Figure 3A, Table 2, and Supplementary Table S4, adjusted RR 0.84, 95% CI 0.55 – 1.28).

Antihypertensive drug adherence by patients with mRCC, preexisting hypertension, and comorbid MCI/D

Among the subset of patients with mRCC and preexisting hypertension who were treated with an oral antihypertensive drug, patients with concomitant MCI/D were 29% less likely to adhere to an oral antihypertensive drug regimen compared to patients without MCI/D (Figure 3B, Table 2, and Supplementary Table S5, adjusted RR 0.71, 95% CI 0.59 – 0.86). Additionally, median PDC and the proportion of the sample meeting the 80% adherent threshold were both 25 percentage points lower for those with preexisting MCI/D, as compared to those without MCI/D (Supplementary Table S6).

DISCUSSION

This study is the first characterization of OAA treatment patterns in patients with mRCC and pre-existing MCI/D. In this retrospective study of older patients who developed mRCC, we found that nearly 10% of patients had comorbid MCI/D at the time of mRCC diagnosis. Patients with comorbid MCI/D were less likely to initiate OAAs than their counterparts, but initiators had comparable adherence.

Patients with preexisting MCI/D tended to be older and were more often White non-Hispanic. They were also about 1.6-fold more likely to be dual-enrolled in Medicare and Medicaid than patients without preexisting MCI/D, consistent with the prior characterization of Medicare beneficiaries with dementia.[34]

Compared to those without MCI/D, patients with preexisting MCI/D were about half as likely to initiate an OAA in the first year following mRCC diagnosis. In this study, oral antihypertensive drugs were used, in part, to approximate baseline patient attitudes, barriers, and behaviors underlying oral medication usage. Cognitively impaired patients with hypertension were less likely to fill an OAA than an oral antihypertensive drug during the year following mRCC diagnosis, which suggests that the disparity between OAA initiation by patients with and without comorbid MCI/D was not due solely to an unwillingness or inability to obtain an oral medication. We posit that there may have been unique or more pronounced provider- and/or patient-level factors that were heavily influenced by MCI/D and deterred OAA initiation.

Patients with preexisting dementia generally are less likely to pursue cancer treatment or receive guideline-concordant care.[35,36] Providers report that efficacy, toxicity, and a patient's anticipated adherence, physical impairment, and cognitive status all influence their cancer treatment recommendations.[37,38] Aspects of physical frailty are captured in common risk factor criteria that guide providers' mRCC treatment recommendations.[39] Additionally, frailty has been reported as risk factor for cognitive impairment[40], so the mRCC patient population with comorbid MCI/D may be frailer than those who are not

cognitively impaired. Unfortunately, this study was unable to assess frailty because cognitive impairment is included in its algorithms.[41–49] Providers may assume that patients with MCI/D will not be able to adhere to an OAA dosing regimen since lower cognition has been reported to correlate with reduced adherence in other contexts[50–52]; this assumption might lead providers to steer patients with MCI/D towards other options, since poor adherence increases the risk of disease progression[53]. A comprehensive geriatric assessment is useful for guiding treatment decisions for older patients with cancer; a systematic review found that 28% of patients (median; range 8 – 54%) had altered treatment plans following geriatric assessment; most patients moved to a less intensive option.[54] While there are several types of geriatric assessments available[54,55], clinicians concerned about the potential for OAA non-adherence may wish to include the Lawton Instrumental Activities of Daily Living Scale (self-rated version), which addresses compliance to drug regimens[56]. Patients with MCI/D or their caregivers may also be less willing to accept the toxicities that accompany OAA use. Though there are conflicting reports about OAAs' impact on cognition[57–65], concerns that OAAs could exacerbate MCI/D might influence patient and provider willingness to use these drugs in patients with preexisting cognitive impairment. Finally, the high cost of OAAs may deter some patients from initiating treatment. Elevated costs may be of particular concern to patients with preexisting MCI/D, as patients with dementia are more likely to experience financial strain than those without dementia.[66]

In the current study, MCI/D status was not a predictor of a patient's likelihood to be adherent during the first 90 days of OAA use. This is surprising because patients with MCI/D tend to have smaller incomes, experience more financial strain, and have lower cognitive test scores, which are all risk factors for poor medication adherence.[14,15,50–52,66–69] One explanation for our finding is that there was channeling bias in favor of patients predisposed to be adherent, since MCI/D negatively impacted OAA initiation but not adherence. For example, providers may have favored patients with more financial resources, social support, or cognitive capabilities when prescribing OAAs. Unfortunately, the small sample size precluded further analysis of OAA adopters with preexisting MCI/D, nor did our dataset include clinical measures. Another possible explanation is that prior studies linking adherence and cognition used cognitive testing and self-reported adherence or pill counts[50,51] rather than diagnostic codes and prescription fill records, as we did. Future research using electronic health record information or patient and provider surveys could identify predictors of OAA initiation and adherence within the general and MCI/D population. It is also possible that MCI/D was not predictive of adherence (PDC ≥ 80%) because these patients were indeed capable of following the recommended dosing schedule. If so, the low initiation rate may be the result of providers inappropriately recommending against OAA treatment, which has the potential to adversely affect patient outcomes.

Both the proportion of adherent patients and median PDC were lower for OAAs than oral antihypertensive drugs, suggesting that adherence was undermined by considerations and behaviors specific to OAA treatment. For example, the high cost of OAA treatment may have interfered with a patient's ability to maintain a continuous drug supply. Privately-insured patients <65 years paid about $76 out-of-pocket for antihypertensive medications during 2014 and their adherence had an inverse relationship to monthly drug costs.[67]

In contrast, privately-insured patients <65 years who were diagnosed with RCC between 2003 and 2010 had an average out-of-pocket cost of $2,576 for the first year of OAA treatment[70]; patients who pay >$200 out-of-pocket for newly prescribed OAAs were more than twice as likely to abandon treatment than those who paid ≤$100[71]. Additionally, our group previously reported that mRCC patients treated with OAAs in the first year following metastatic diagnosis have total Medicare costs about 50% higher than those who do not receive OAAs.[72] A meta-analysis of 159 studies on patients with cancer found consistent reports that adverse events and high out-of-pocket costs negatively impacted adherence.[73] Additionally, toxicities contributed to patients requiring dose modifications or discontinuing OAA treatment[74,75], leading to a lower overall PDC.

The SEER-Medicare dataset is a powerful resource, but has limitations. The SEER database includes cancer registry data from 22 geographic areas, representing approximately 48% of the United States (US) population[76,77]. Results from the SEER-Medicare dataset may not be generalizable to countries other than the United States, or to regions of the United States without contributing cancer registries. Compared to the general US population, there is a higher proportion of urban-dwelling, foreign-born, and non-White, and Hispanic constituents in the SEER database[78–80]. Sex and age distributions are similar for people 65 years and older[78]. We confined analysis to those ≥65 years old because this is the age at which most Medicare beneficiaries enroll, so findings may vary for younger patients. Between 2012 and 2016, there were comparably fewer people in the SEER-Medicare sample than the general population who lived in impoverished census tracts and proportionally more living in areas with the highest density of adults who had not completed a high school education[78]. Our investigation was restricted to fee-for-service Medicare beneficiaries; there may be differences between their treatment and those with other health insurance plans or no insurance. We did not explicitly exclude or censor patients enrolled in hospice or residents of long-term care facilities, as we wanted to include the full lifecycle of outcomes for these patients. There are known challenges identifying patients with recurrent or progressive metastases in the SEER-Medicare data[81]; it is possible that some of these patients were excluded from our study cohort, but unlikely that this significantly altered our findings since most of our cohort was diagnosed with stage IV RCC. Another analytical challenge and potential limitation was that the MCI diagnostic codes have not been validated in the literature, though this does not negate the importance of this population or relevance of these findings. SEER-Medicare data lacks clinical information, such as clinical test results or other indicators of the severity or progression of MCI/D, as well as a full picture of the patient's health status and level of physical frailty - factors that inform physician and patient treatment decisions. Frailty may be particularly influential in treatment decisions[39], but we were unable to include it in our models because cognitive impairment is a component of the common validated frailty algorithms[41–49] and strongly correlated with dementia in this study (data not shown); including a frailty index would introduce substantial collinearity. We used prescription drug claims and standard dosing regimens[25–29] to approximate adherence because drug administration records and physicians' dosing instructions were not available. The source data also lacked information about patients', caregivers', surrogates', and providers' decision-making process about whether and how to proceed with treatment. Finally, our analyses were constrained by the number of patients in the MCI/D subcohort.

We lacked sufficient statistical power to stratify patients with mRCC and preexisting MCI/D by OAA initiation status. Likewise, there were too few patients with mRCC, MCI/D, and hypertension to compare antihypertensive agent and OAA usage in this subset.

CONCLUSIONS

About 1 in 10 Medicare-insured patients ≥65 years had MCI/D at the time of their mRCC diagnoses. Cognitive impairment profoundly impacted OAA initiation during the first year following mRCC diagnosis; affected patients were about half as likely to start an OAA as their counterparts without comorbid MCI/D. The 90-day adherence of all OAA initiators was low, and was not significantly different between those with and without preexisting MCI/D. In light of this, clinicians should assess patients with mRCC for cognitive impairment and take steps to optimize OAA utilization by those with MCI/D, while continuing to monitor OAA adherence in all patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Drs. Pritchard, Wilson, Miller, Greiner, Cohen, Kaye, and Dinan have no competing interests.

Conflicts of Interest

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Data Availability

The SEER-Medicare data that were used in this study are available from the National Institutes of Health National Cancer Institute. The authors obtained these data under a study-specific data use agreement that does not permit sharing. However, data may be purchased directly from the data provider.

ABBREVIATIONS

CI	confidence interval
HR	hazard ratio
MCI	mild cognitive impairment
MCI/D	mild cognitive impairment/dementia
mRCC	metastatic renal cell carcinoma
NA	not applicable
OAA	oral anticancer agent
PDC	percent of days covered
RCC	Renal cell carcinoma
Ref	reference group
SD	standard deviation
SEER	Surveillance, Epidemiology and End Results cancer registry
SES	socioeconomic status

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Impact Statement:

We certify that this work is novel research. The content of this manuscript has not been presented at a conference or symposium. This study is the first characterization of oral anticancer agent treatment patterns in patients with metastatic renal cell carcinoma and pre-existing cognitive impairment.

Key Points:

- About 1 in 10 older patients (65+ years) who had metastatic renal cell carcinoma also had preexisting cognitive impairment.
- Patients with cognitive impairment were 47% less likely than those without cognitive impairment to start an oral anticancer agent within a year of metastatic renal cell carcinoma diagnosis.
- Less than half of all oral anticancer agent users were adherent during the first three months of treatment, and there was no detectable difference between the adherence of those with and without cognitive impairment.

Why does this matter?

Patients with preexisting cognitive impairment were less likely to receive the standard of care treatment for metastatic renal cancer, an oral anticancer agent. However, among patients prescribed an oral anticancer agent, preexisting cognitive impairment was not associated with lower adherence. The clinical implication of this is that providers should assess and consider cognitive status when prescribing oral anticancer agents, but should not exclude impaired patients based on diagnosis alone because some cognitively impaired patients are capable of adherence – a broader context should be considered. Providers should also take steps to optimize the adherence of all OAA users, regardless of cognitive status.

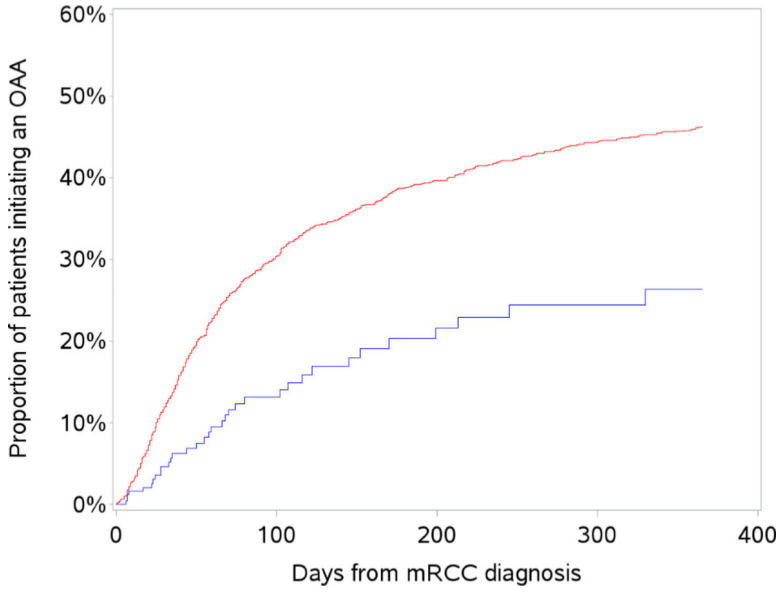

Figure 1. Cumulative incidence of patients with metastatic renal cell carcinoma (mRCC) (N=2,792) initiating an oral anticancer agent (OAA) during the year following mRCC diagnosis, stratified by preexisting preexisting mild cognitive impairment or dementia (MCI/D) status.

Red: Without preexisting mild cognitive impairment or dementia

Blue: With preexisting mild cognitive impairment or dementia

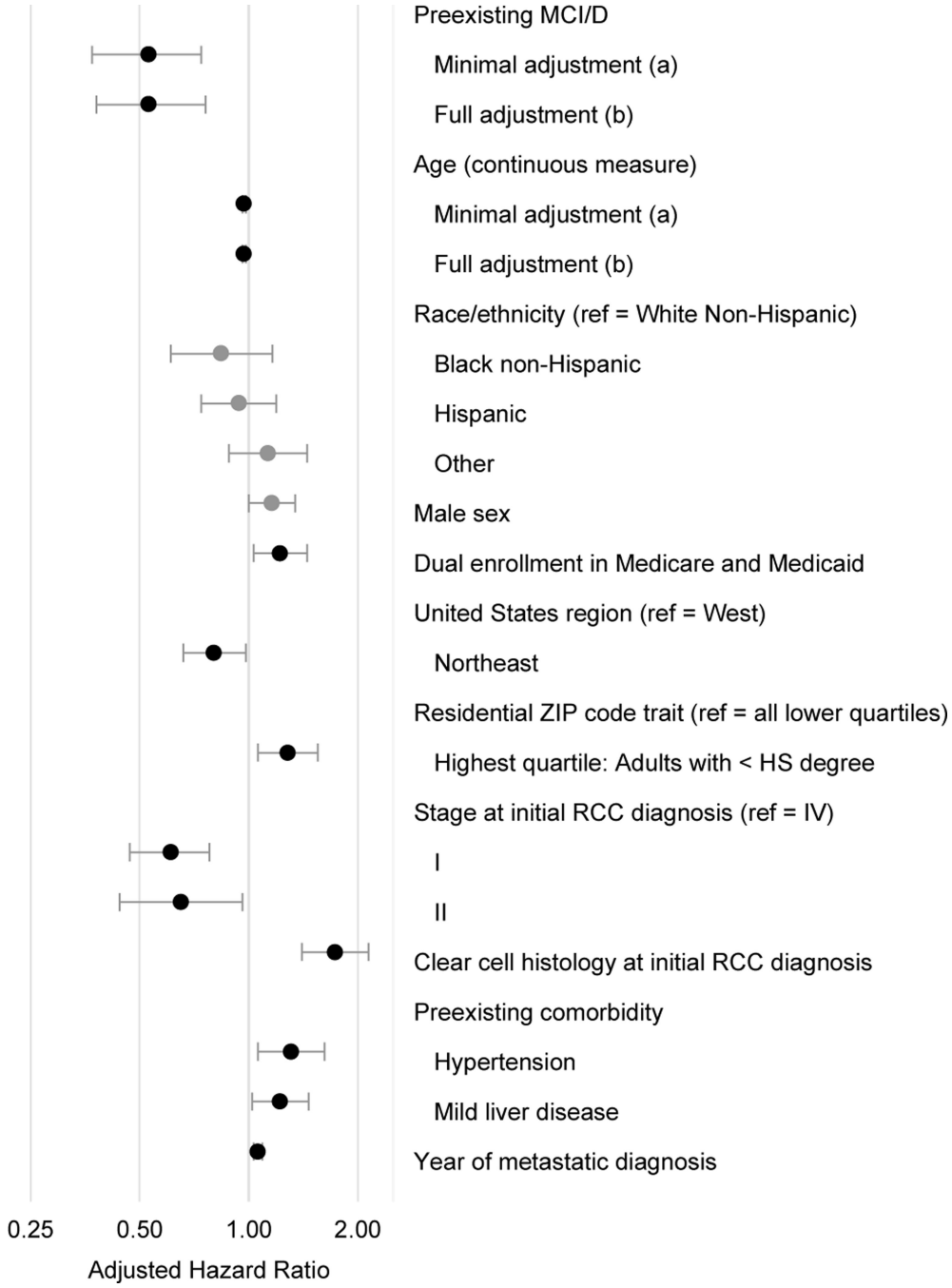

Figure 2. Likelihood of a patient initiating an oral anticancer agent (OAA) during the year following metastatic renal cell carcinoma (mRCC) diagnosis.

Cox proportional hazards regression was performed for patients with mRCC (N=2,792). Only age, race/ethnicity, sex, and statistically significant results are shown; statistically-significant results are black. Results are fully-adjusted unless otherwise noted.

Abbreviations: HS, high school; MCI/D, mild cognitive impairment/dementia; Ref, reference group.

[a] The minimally-adjusted model included only age and MCI/D status.

[b] Full adjustment included demographic, cancer, comorbidity, and socioeconomic traits.

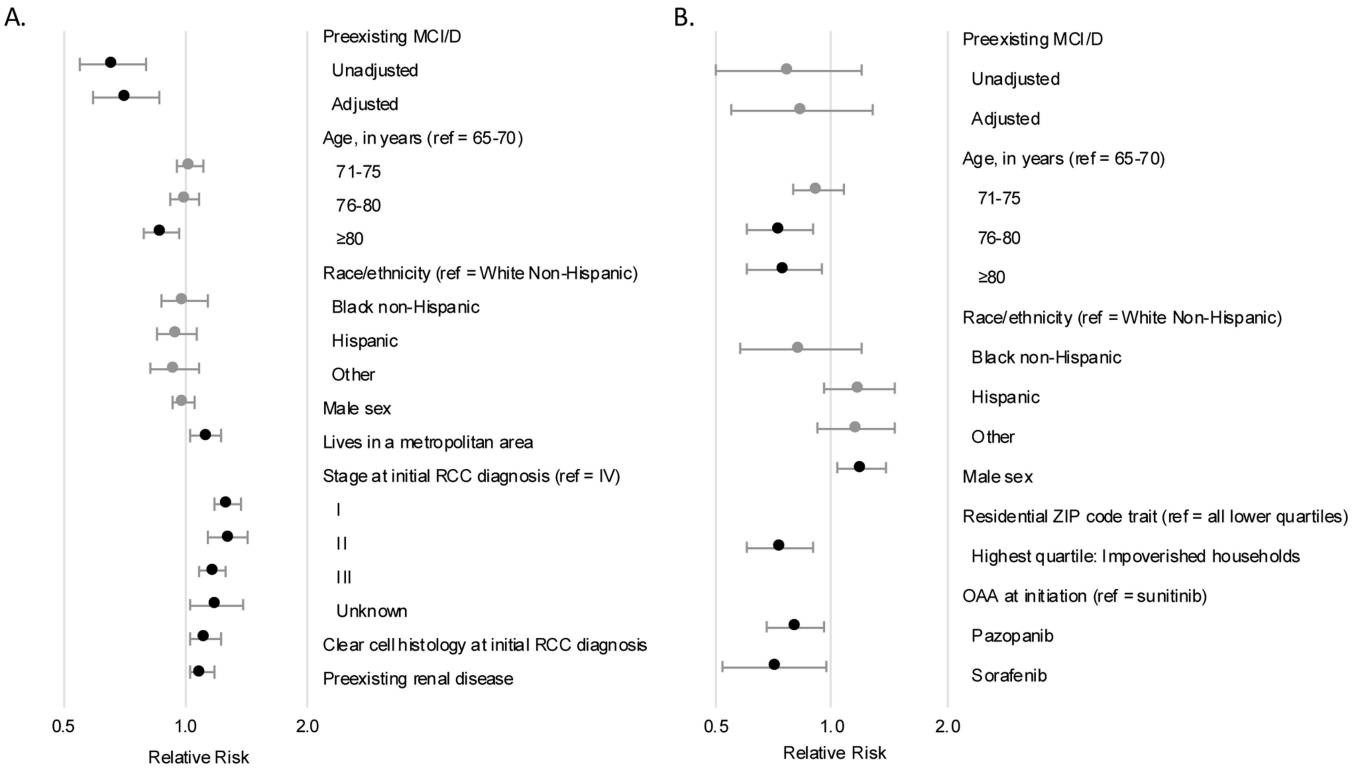

Figure 3.

A. Likelihood of a patient with metastatic renal cell carcinoma (mRCC) and preexisting mild cognitive impairment or dementia (MCI/D) adhering to an oral anticancer agent (OAA). Log-binomial regression evaluated the association between prevalent MCI/D and binary OAA adherence (percent days covered [PDC] ≥ 80%) during the first 90 days following initiation (N=907 initiating OAA). Only age, race/ethnicity, sex, and statistically significant results are shown; statistically-significant results are black. Results are fully-adjusted[a] unless otherwise noted. Abbreviation: Ref, reference group

B. Likelihood of a patient with mRCC and preexisting MCI/D and hypertension adhering to an oral antihypertensive drug. Log-binomial regression assessed association between prevalent MCI/D and binary oral antihypertensive drug adherence (PDC ≥ 80%) in the 90 days after the first antihypertensive drug claim following mRCC diagnosis, among patients with mRCC who filled an antihypertensive prescription (N=1,780). Results are fully-adjusted[a] unless otherwise noted.

[a] Full adjustment included demographic, cancer, comorbidity, and socioeconomic traits.

Table 1.

Baseline characteristics of patients with metastatic renal cell carcinoma (mRCC), stratified by preexisting mild cognitive impairment or dementia (MCI/D) status.

All characteristics were determined at the time of metastatic diagnosis unless otherwise indicated. Abbreviations: NA, not applicable; Ref, reference group; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results; ZIP, Zone Improvement Plan

Variable	Preexisting MCI/D	No MCI/D	p-value[a]
N	268	2,524	
Patient Characteristics			
Age, in years; mean (SD)	**81.6 (7.6)**	**75.9 (6.7)**	**< 0.001**
Age, in years			**< 0.001**
65–70	33 (12.3%)	775 (30.7%)	
71–75	35 (13.1%)	672 (26.6%)	
76–80	57 (21.3%)	517 (20.5%)	
≥81	143 (53.4%)	560 (22.2%)	
Race/ethnicity			**0.02**
White non-Hispanic	196 (73.1%)	1907 (75.6%)	
Black non-Hispanic	31 (11.6%)	164 (6.5%)	
Hispanic	27 (10.1%)	275 (10.9%)	
Other	14 (5.2%)	178 (7.1%)	
Male sex	149 (55.6%)	1,466 (58.1%)	0.43
Married	**100 (37.3%)**	**1,344 (53.2%)**	**< 0.001**
Dual-enrolled in Medicare and Medicaid	**126 (47.0%)**	**729 (28.9%)**	**< 0.001**
Lives in metropolitan area	217 (81.0%)	2,006 (79.5%)	0.56
Lives in rural area	<11[b]	82 (3.2%)	0.57
United States region			**0.02**
Midwest	19 (7.1%)	323 (12.8%)	
NA	16 (6.0%)	199 (7.9%)	
Northeast	57 (21.3%)	506 (20.0%)	
South	59 (22.0%)	433 (17.2%)	
West	117 (43.7%)	1,063 (42.1%)	
Residential ZIP code trait (ref = all lower quartiles)			
Highest quartile: Black race	76 (28.4%)	609 (24.1%)	0.13
Highest quartile: adults ≥25 years with less than a high school education	76 (28.4%)	609 (24.1%)	0.13
Highest quartile: Impoverished households	68 (25.4%)	617 (24.4%)	0.74
Stage at initial SEER diagnosis			**0.02**
I	30 (11.2%)	248 (9.8%)	
II	<11[b]	87 (3.4%)	
III	18 (6.7%)	332 (13.2%)	
IV	205 (76.5%)	1,784 (70.7%)	

Variable	Preexisting MCI/D	No MCI/D	p-value[a]
Unknown	<11[b]	73 (2.9%)	
Clear cell histology at initial RCC diagnosis	217 (81.0%)	2,083 (82.5%)	0.52
Prior nephrectomy			0.57
Partial	<11[b]	45 (1.8%)	
Radical	>15[b]	234 (9.3%)	
Preexisting comorbidity			
Myocardial infarction	**45 (16.8%)**	**240 (9.5%)**	**< 0.001**
Hypertension	**221 (82.5%)**	**2,192 (86.8%)**	**0.046**
Peripheral vascular disease	**111 (41.4%)**	**650 (25.8%)**	**< 0.001**
Congestive heart failure	**95 (35.4%)**	**557 (22.1%)**	**< 0.001**
Cerebrovascular disease	**106 (39.6%)**	**544 (21.6%)**	**< 0.001**
Chronic obstructive pulmonary disease	93 (34.7%)	815 (32.3%)	0.42
Rheumatologic disease	19 (7.1%)	120 (4.8%)	0.09
Peptic ulcer disease	12 (4.5%)	75 (3.0%)	0.18
Mild liver disease	38 (14.2%)	382 (15.1%)	0.68
Moderate/severe liver disease	<11[b]	<11[b]	0.40
Renal disease	**95 (35.4%)**	**747 (29.6%)**	**0.047**
Diabetes with complications	47 (17.5%)	398 (15.8%)	0.45
Hemiplegia or paraplegia	**14 (5.2%)**	**57 (2.3%)**	**0.003**
Year of metastatic diagnosis			0.90
2007	21 (7.8%)	225 (8.9%)	
2008	26 (9.7%)	236 (9.4%)	
2009	23 (8.6%)	234 (9.3%)	
2010	23 (8.6%)	244 (9.7%)	
2011	39 (14.6%)	281 (11.1%)	
2012	32 (11.9%)	305 (12.1%)	
2013	39 (14.6%)	353 (14.0%)	
2014	35 (13.1%)	354 (14.0%)	
2015	30 (11.2%)	292 (11.6%)	

[a] Bolded variables have statistically significant differences between groups with and without preexisting MCI/D.

[b] Suppressed to protect patient privacy

Table 2.

Summary of medication usage by patients with metastatic renal cell carcinoma (mRCC) and preexisting mild cognitive impairment or dementia (MCI/D).

Center column: Cox proportional hazards regression was performed for patients with mRCC (mRCC cohort; N=2,792) or mRCC and preexisting hypertension (mRCC with hypertension; N = 2,413) to determine the likelihood of an oral anticancer agent (OAA) or antihypertensive drug usage during the 12 months following mRCC diagnosis. Right column: Log-binomial regression evaluated the association between prevalent MCI/D and binary medication adherence (percent days covered ≥ 80%) during the first 90 days following its initial use following mRCC diagnosis (N=907 OAA initiators, N=1,780 antihypertensive drug initiators). Abbreviations: CI, confidence interval; HR, hazard ratio; Ref, reference group; RR, risk ratio

		Use Post-mRCC Diagnosis (fully-adjusted HR [95% CI])[a]		**Adherence (adjusted RR [95% CI])[a]**	
Cohort	**Medication**	**- MCI/D**	**+ MCI/D**	**- MCI/D**	**+ MCI/D**
mRCC	OAA	Ref.	**0.53 (0.38 – 0.76)**	Ref.	0.84 (0.55 – 1.28)
mRCC with hypertension	OAA	Ref.	**0.58 (0.40 – 0.84)**	*Insufficient cohort size*	
	Antihypertensive drug	Ref.	**0.77 (0.63 – 0.93**	Ref.	**0.71 (0.59 – 0.86)**

[a]Bolded variables have statistically significant differences between groups with and without preexisting MCI/D.