

End-of-Life Care for Patients With Metastatic Renal Cell Carcinoma in the Era of Oral Anticancer Therapy

Hannah E. Dzimitrowicz, MD¹; Lauren E. Wilson, PhD²; Bradford E. Jackson, PhD³; Lisa P. Spees, PhD^{3,4}; Christopher D. Baggett, PhD^{3,5}; Melissa A. Greiner, MS²; Deborah R. Kaye, MD, MS^{6,7}; Tian Zhang, MD, MHS^{8,9}; Daniel George, MD^{1,7}; Charles D. Scales Jr, MD, MSHS^{2,6}; Jessica E. Pritchard, PhD²; Michael S. Leapman, MD^{10,11}; Cary P. Gross, MD^{11,12}; Michaela A. Dinan, PhD^{12,13}; and Stephanie B. Wheeler, PhD, MPH^{3,4}

QUESTION ASKED: What are the prevalence of and factors associated with end-of-life (EOL) care quality among a diverse population of patients with metastatic renal cell carcinoma (mRCC)?

SUMMARY ANSWER: Prior oral anticancer agent (OAA) use was associated with increased likelihood of receiving systemic therapy in the last 30 days of life in two unique cohorts. Prior OAA use was also associated with increased likelihood of hospice use in the last 30 days of life. Younger patients experienced more aggressive EOL care with higher likelihood of inpatient death, inpatient admission, and systemic therapy use in the last 30 days of life in both cohorts. Other factors associated with low-quality EOL care included dual enrollment in Medicare and Medicaid, non-White race, male sex, rural location, northeast region, and recurrent metastatic disease.

WHAT WE DID: Using two distinct cohorts of patients with mRCC—a national population-based registry-linked Medicare claims data set (SEER-Medicare) and a unique, cancer registry-linked multipayer claims data set from North Carolina (Cancer Information and Population Health Resource [CIPHR])—we used multivariable logistic regression to assess associations between OAA use, patient and provider characteristics, and EOL care. As measures of EOL care quality, we assessed hospice use in the last 30 days of life (measure of high-quality EOL care) and existing measures of poor-quality EOL care: systemic therapy, hospital admission, intensive care unit admission, and > 1 emergency department (ED) visit in the last 30 days of life, hospice initiation in the last 3 days of life, and in-hospital death.

WHAT WE FOUND: In the CIPHR and SEER-Medicare cohorts, 53.4% and 43.5% of decedents received an

OAA, respectively. Prior OAA use was associated with increased systemic therapy in the last 30 days of life in both cohorts, increased in-hospital death and > 1 ED visit in the last 30 days of life in CIPHR, and increased hospice in the last 30 days of life in SEER-Medicare. Older patients were less likely to receive systemic therapy or be admitted in the last 30 days of life or die in hospital.

BIAS, CONFOUNDING FACTORS, DRAWBACKS: Although CIPHR represents a novel cohort of patients with mRCC from multiple payers, the data from CIPHR are limited to patients who were diagnosed and received care in North Carolina and may not be reflective of care patterns elsewhere. SEER-Medicare, while encompassing patients across the United States, is limited to older patients and may not be generalizable to patients under age 66 years. Because our study ended with claims through 2016, EOL patterns of care might have changed in the context of increasing available therapies.

REAL-LIFE IMPLICATIONS: This study provides valuable assessment of EOL care quality for patients with RCC and for patients with cancer taking OAAs, now common in oncology treatment. Patients receiving OAAs remained on therapy near the EOL more frequently; however, they were also more likely to enroll in hospice care. Overall, younger patients received more aggressive EOL care. In the context of multiple available therapy modalities for advanced cancer, OAA receipt in clinically declining patients may be a potential marker of aggressive EOL care, which presents an opportunity to focus on optimizing EOL care for these patients through interventions such as early engagement of palliative care specialists.

ASSOCIATED CONTENT

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Appendix

Author affiliations and disclosures are available with the complete article online.

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CORRESPONDING AUTHOR

Hannah E. Dzimitrowicz, MD, Department of Medicine, Duke University School of Medicine, DUMC Box 3841, 2301 Erwin Rd, Durham, NC 27710; Twitter: @hannahdzmd; e-mail: hannah.dzimitrowicz@duke.edu.

EOL care may be influenced by other demographic characteristics, which vary between registries. Therefore, using two distinct cohorts of patients with mRCC—a national population-based registry-linked Medicare claims data set and a unique, cancer registry-linked multipayer claims data set from North Carolina—we sought to identify prevalence of and factors associated with poor-quality EOL care with the above measures in the mRCC population.

METHODS

Study Populations

We conducted a retrospective study of decedent patients with mRCC in two separate cohorts that we analyzed in parallel: a cohort of patients age 18 years and older drawn from the University of North Carolina Cancer Information Population Health Resource (CIPHR) and a cohort of patients age 66 years and older sourced from the SEER-Medicare database. CIPHR links the North Carolina Central Cancer Registry data to administrative claims data from private health insurance, Medicare, and Medicaid plans,⁷ whereas SEER-Medicare links data from the SEER registries covering approximately 30% of the US population to administrative claims data from fee-for-service Medicare only.⁸ Appendix Figure A1 (online only) illustrates how patients were selected. Eligible patients included those identified in cancer registry data from each cohort diagnosed with stage I-IV RCC (January 1, 2004, to December 31, 2015, for CIPHR and January 1, 2007, to December 31, 2015, for SEER-Medicare; Appendix Table A1, online only). Index date was defined as the RCC diagnosis date from the registry for patients with stage IV disease or the date of the first of two metastatic diagnosis claims for patients diagnosed as stage I-III. Patients were included if they survived ≥ 90 days after the index date and died within the follow-up period (through December 31, 2016). Patients were required to have continuous insurance and prescription medication coverage from their index date until death.

EOL Care Quality Outcomes

Using information drawn from the linked insurance claims, we assessed established measures of poor-quality EOL care: receipt of systemic therapy, hospital admission, ICU admission, and > 1 ED visit within the last 30 days of life; in-hospital death; and hospice initiation within the last 3 days of life.⁶ Receipt of systemic therapy included both intravenous systemic anticancer therapies and OAAs. Codes used to assess receipt of intravenous and oral chemotherapies are given in Appendix Table A2 (online only). As a high-quality EOL care indicator, we examined hospice use in the last 30 days of life.

Prior Use of an OAA

OAA use during the period from the patient's metastatic diagnosis until 30 days before death was identified using prescription drug files and pharmacy claims by reviewing

generic and brand names and national drug codes for sorafenib (approved 2005), sunitinib (2006), pazopanib (2009), everolimus (2009), and axitinib (2012).

Patient- and Provider-Level Variables

We examined other potential factors expected to influence EOL care, including age at mRCC diagnosis, race/ethnicity (non-Hispanic White *v* Others), sex, residence in a rural or urban area,⁹ insurance status (CIPHR: private *v* Medicare only *v* any Medicaid; SEER-Medicare: Medicare only *v* dual enrollment in Medicare and Medicaid), number of comorbid conditions in the 12 months pre-mRCC diagnosis (Appendix Table A3, online only), Fautot Frailty score,¹⁰ stage at diagnosis (stage IV *v* $< IV$), percentage of Medicare beneficiaries in the hospital referral region who died in-hospital the year of metastatic diagnosis,¹¹ and US geographic region (for SEER-Medicare only).¹² Sex and race were categorized on the basis of abstracted data from medical records included in the cancer registries.¹³ Because of small cell sizes, race and ethnicity were grouped into two categories—non-Hispanic White and Others, which included Asian/Pacific Islander, Hispanic Black, Hispanic Others, Hispanic White, non-Hispanic American Indian, non-Hispanic Black, non-Hispanic Others, unknown ethnicity Black, and unknown ethnicity White.¹³ Patients were assigned a modal provider, the physician identified most frequently on claims with a diagnosis code of RCC or metastatic cancer between 2 months before and 3 months after the index date. The rural practice location for the modal provider was assessed using Rural-Urban Commuting Area codes for the provider's zip code.⁹

Statistical Analysis

Descriptive statistics for each cohort were calculated using means and medians for continuous variables and frequencies and percentages for binary and categorical variables. The distributions of EOL care outcomes were stratified by OAA use; unadjusted group differences were tested using the chi-square test. We estimated odds ratios (ORs) and corresponding 95% confidence limits (CL) using multivariable logistic regression models for the associations between OAA use, patient characteristics, and the EOL quality outcomes. Multicollinearity of covariates was assessed using a variance inflation factor threshold of 5, where no covariates exceeded this threshold.

RESULTS

Study Population

The study samples comprised 410 and 1,508 patients with the median age of 69 and 75 years for the CIPHR and SEER-Medicare populations, respectively (Table 1). Compared with the SEER-Medicare cohort, patients in CIPHR were less often female (34% in CIPHR; 43% in SEER-Medicare) and less frequently lived in an urban area (62%; 80%). Patients in CIPHR were less frequently diagnosed with de novo metastatic disease and had fewer

comorbid conditions. In addition, 53% and 44% of decedents received an OAA in CIPHR and SEER-Medicare cohorts, respectively. Among patients who did not receive an OAA, 70% and 67% did not receive any systemic therapy in CIPHR and SEER-Medicare, respectively. Patients who did not receive OAAs but received another systemic therapy received targeted therapy/immunotherapy (49% SEER-Medicare; 47% CIPHR), traditional cytotoxic chemotherapy (44% SEER-Medicare; 35% CIPHR), and cytokine therapy (< 5% in SEER-Medicare).

Relationship Between Prior OAA Use and EOL Quality Indicators

Overall, 19.3% of decedents in CIPHR and 16.8% in SEER-Medicare received systemic therapy in the 30 days before death (Table 2). Patients who previously received OAAs more frequently received any systemic therapy in the 30 days before death compared with patients who had not previously received OAAs in both CIPHR (26.5% v 11.0%; $P < .001$) and SEER-Medicare (23.4% v 11.7%; $P < .001$). Among patients who received OAAs previously, 16% and 14% received an OAA in the 30 days before death in CIPHR and SEER-Medicare, respectively. The overall proportion of decedents with any hospice use in the last 30 days of life was 48.5% in CIPHR and 42.2% in SEER-Medicare. Prior OAA use was associated with any hospice in the 30 days before death in SEER-Medicare (47.5% v 40.6%; $P = .007$). In SEER-Medicare, hospice initiation in the 3 days before death was higher among prior OAA users compared with nonusers (13.7% v 10.3%; $P = .042$). In CIPHR, prior OAA use was associated with ICU admission in the 30 days before death (19.6% v 12.0%; $P = .037$) and with > 1 ED visit in the 30 days before death (16.9% v 6.8%; $P = .002$). The proportion of patients who died in hospital was similar in both cohorts (21%); however, the difference between prior OAA use and nonuse was only statistically significant in the CIPHR cohort (24.7% v 15.7%; $P = .025$).

Inpatient Admission Within the 30 Days Before Death

Prior OAA use (v no prior OAA use) was not associated with inpatient admission in the 30 days before death in both cohorts. Older patients were less likely to be admitted in the 30 days before death in both cohorts (CIPHR: OR = 0.82 [95% CL, 0.72 to 0.92]; SEER-Medicare: OR = 0.80 [95% CL: 0.73 to 0.87]; Fig 1). In SEER-Medicare, patients were more likely to be admitted in the 30 days before death if they were male (v female; OR, 1.34; 95% CL, 1.08 to 1.66) or living in the Northeast United States (v west; OR, 1.63; 95% CL, 1.21 to 2.19; Fig 1 and Appendix Table A4, online only).

ICU Admission Within the 30 Days Before Death

Prior OAA (v no prior OAA use) use was not associated with ICU admission in the 30 days before death in both cohorts. Patients were more likely to be admitted to an ICU in the

30 days before death if they were diagnosed with recurrent mRCC (v de novo mRCC) in both cohorts (CIPHR: OR = 2.20 [95% CL, 1.16 to 4.18]; SEER-Medicare: OR = 1.46 [95% CL, 1.09 to 1.94]). In SEER-Medicare, patients were less likely to be admitted to an ICU in the 30 days before death if they were older (OR, 0.75; 95% CL, 0.67 to 0.85) but more likely to be admitted to an ICU in the 30 days before death if they were not non-Hispanic White (v non-Hispanic White; OR, 1.48; 95% CL, 1.05 to 2.07) or lived in the Northeast United States (v west; OR, 1.55; 95% CL, 1.08 to 2.23).

Death in Hospital

Patients in CIPHR were more likely to die in hospital if they previously received an OAA (v no prior OAA; OR, 1.84; 95% CL, 1.03 to 3.28; Fig 1). In both cohorts, older patients were less likely to die in hospital (CIPHR: OR = 0.75 [95% CL, 0.65 to 0.88]; SEER-Medicare: OR = 0.80 [95% CL, 0.71 to 0.89]). In SEER-Medicare, patients with dual Medicaid insurance (compared with Medicare only) were more likely to die in hospital (OR, 1.40; 95% CL, 1.02 to 1.93) as were patients living in a rural location (v urban; OR, 1.60; 95% CL, 1.13 to 2.28).

Systemic Therapy Within the 30 Days Before Death

Compared with patients who had not previously received an OAA, patients who previously received an OAA were more likely to receive systemic therapy in the last 30 days of life in both cohorts (CIPHR: OR = 2.58 [95% CL, 1.35 to 4.91]; SEER-Medicare: OR = 2.00 [95% CL, 1.50 to 2.66]; Fig 1). Older patients less often received systemic therapy in the 30 days before death in both cohorts (CIPHR: OR = 0.84 [95% CL, 0.72 to 0.99]; SEER-Medicare: OR = 0.78 [95% CL, 0.69 to 0.89]).

Hospice Initiation Within the 3 Days Before Death

In SEER-Medicare, patients were more likely to initiate hospice in the last 3 days of life if they had previously received an OAA (OR, 1.45; 95% CL, 1.05 to 2.02), were male (v female; OR, 1.45; 95% CL, 1.03 to 2.04), or lived in the northeast (v west; OR, 1.85; 95% CL, 1.22 to 2.81). In SEER-Medicare, patients were less likely to initiate hospice in the last 3 days of life if they lived in a rural location (v urban; OR, 0.39; 95% CL, 0.23 to 0.68).

More Than One ED Visit Within the 30 Days Before Death

In CIPHR, patients were more likely to have > 1 ED visit in the 30 days before death if they had previously received an OAA (OR, 3.23; 95% CL, 1.48 to 7.04) and less likely if they were older (OR, 0.82; 95% CL, 0.69 to 0.98). In SEER-Medicare, patients were more likely to have > 1 ED visit in the 30 days before death if they lived in a rural location (OR, 2.88; 95% CL, 1.63 to 5.09).

Any Hospice Within the 30 Days Before Death

To identify variables associated with hospice use at EOL, a measure of high-quality care, we examined any hospice

TABLE 1. Descriptive Characteristics of the CIPHR and SEER-Medicare Cohorts

Characteristic	CIPHR (n = 410)	SEER-Medicare (n = 1,508)
OAA use, ^a No. (%)		
No	191 (46.6)	852 (56.5)
Yes	219 (53.4)	656 (43.5)
Race, No. (%)		
Non-Hispanic White	317 (77.3)	1,135 (75.3)
Others ^b	93 (22.7)	373 (24.7)
Sex, No. (%)		
Male	271 (66.1)	866 (57.4)
Female	139 (33.9)	642 (42.6)
Age, years, median (IQR)	69 (59-76)	74.9 (70.5-80.6)
Stage at initial diagnosis, No. (%)		
Recurrent	170 (41.5)	441 (29.2)
De novo	240 (58.5)	1,067 (70.7)
Frailty score, median (IQR)	0.04 (0.03-0.12)	0.06 (0.03-0.12)
No. of comorbid conditions, No. (%)		
0	77 (18.8)	100 (6.6)
1	125 (30.5)	415 (27.5)
2+	208 (50.7)	993 (65.8)
Patient residence, No. (%)		
Rural	154 (37.6)	298 (19.8)
Urban	256 (62.4)	1,210 (80.2)
% Medicare inpatient deaths, mean (SD) ^c	25.1 (4.66)	24.0 (4.7)
Modal provider location, No. (%)		
Rural only	29 (7.1)	< 11 (< 0.7)
Rural and urban	91 (22.2)	—
Urban only	290 (70.7)	> 1,490 (> 98.8)
Insurance at diagnosis (CIPHR only), No. (%)		
Private	79 (19.3)	—
Any Medicaid ^d	88 (21.5)	426 (28.2)
Medicare only	243 (59.3)	1,082 (71.8)
US geographic region (SEER-Medicare only), No. (%)		
Midwest	—	184 (12.2)
Northeast	—	305 (20.2)
South	—	276 (18.3)
West	—	631 (41.8)
Missing	—	112 (7.4)

Abbreviations: CIPHR, Cancer Information Population Health Resource; IQR, interquartile range; mRCC, metastatic renal cell carcinoma; OAA, oral anticancer agent; SD, standard deviation.

^aOAA use between mRCC diagnosis and 30 days before death.

^bBecause of small cell sizes, racial and ethnic categories of Asian/Pacific Islander, Hispanic Black, Hispanic Others, Hispanic White, non-Hispanic American Indian, non-Hispanic Black, non-Hispanic Others, unknown ethnicity Black, and Unknown ethnicity White are grouped.

^cMeasured at the Hospital Referral Region level.

^dIn SEER-Medicare, these are dual enrollees.

use in the 30 days before death (Fig 1). In SEER-Medicare, prior OAA use was associated with increased hospice use in the 30 days before death (OR,

1.30; 95% CL, 1.04 to 1.61). Compared with patients with Medicare alone, patients with dual Medicaid and Medicare had lower odds of hospice use in the 30 days before death (OR, 0.71; 95% CL, 0.54 to 0.94) in SEER-Medicare.

DISCUSSION

We report the first description, to our knowledge, of EOL care in patients with mRCC and in patients receiving OAAs as part of routine oncologic care. Our data, drawn from two complementary cohorts, illuminate real-world patterns of EOL care and factors associated with these care components during the era of OAAs. Prior OAA use was associated with increased likelihood of receiving systemic therapy in the last 30 days of life in both cohorts. Prior OAA use was also associated with increased likelihood of hospice use in the last 30 days of life. Younger patients experienced more aggressive EOL care with higher likelihood of inpatient death, inpatient admission, and systemic therapy use in the last 30 days of life in both cohorts. In SEER-Medicare, patients who were dual-enrolled in Medicare and Medicaid, a traditionally vulnerable population, had more aggressive EOL care including higher likelihood of in-hospital death and lower likelihood of any hospice use in the last 30 days of life. Other factors associated with low-quality EOL care included non-White race, male sex, rural location, northeast region, and recurrent metastatic disease.

In the time between metastatic diagnosis and 30 days before death, 53% of patients in CIPHR and 43% of patients in SEER-Medicare received an OAA. In the last 30 days of life, 27% and 23% of these patients in CIPHR and SEER-Medicare, respectively, continued to receive systemic therapy, some of whom continued OAA use. The use of systemic therapy near EOL has been shown not to improve quality of life, while subjecting patients to unnecessary toxicities.¹⁴ Studies characterizing the negative impact of systemic therapy near EOL have largely included patients receiving traditional cytotoxic chemotherapy, before widespread use of newer targeted OAAs and ICIs. In one study using 2012-2013 Massachusetts private insurance claims, OAA use sharply declined during the last 30 days of life and even more so at 14 days before EOL in multiple cancer types, but they did not examine how OAA use may affect other aspects of EOL care.¹⁵

One potential explanation for the increased likelihood of hospice enrollment for patients on OAAs is that these patients may be more likely to see a medical oncologist,^{16,17} and in previous studies, patients with advanced cancer cared for by medical oncologists were more likely to enroll in hospice.¹⁸ Alternatively, concurrent increases in OAA use and national increases in hospice enrollment over the past two decades may account for the increased likelihood of hospice enrollment for patients on OAAs.¹⁹ However, rates

TABLE 2. End-of-Life Quality Indicators in CIPHR and SEER-Medicare Decedent Cohorts, overall and Stratified by OAA Use^a

End-of-life Quality Outcome	CIPHR				SEER-Medicare			
	Overall (n = 410)	OAA Use (n = 219)	No OAA Use (n = 191)	P	Overall (n = 1,508)	OAA Use (n = 656)	No OAA Use (n = 852)	P
Systemic therapy in the 30 days before death, No. (%)	79 (19.3)	58 (26.5)	21 (11.0)	< .001	254 (16.8)	154 (23.4)	100 (11.7)	< .001
Inpatient admission in the 30 days before death, No. (%)	219 (53.4)	125 (57.1)	94 (49.2)	.111	696 (46.2)	313 (47.7)	383 (44.9)	.277
ICU stay in the last 30 days before death, No. (%)	66 (16.1)	43 (19.6)	23 (12.0)	.037	273 (18.1)	128 (19.5)	145 (16.9)	.208
Any hospice in the 30 days before death, No. (%)	199 (48.5)	108 (49.3)	91 (47.6)	.736	636 (42.2)	302 (47.5)	353 (40.6)	.007
Hospice initiated in the 3 days before death, No. (%)	59 (14.4)	32 (14.6)	27 (14.14)	.891	178 (11.8)	90 (13.7)	88 (10.3)	.042
Died in hospital, No. (%)	84 (20.5)	54 (24.7)	30 (15.7)	.025	315 (20.9)	135 (20.6)	180 (21.1)	.804
Two or more emergency department visits in the 30 days before death, No. (%)	50 (12.2)	37 (16.9)	13 (6.8)	.002	52 (3.4)	25 (3.8)	27 (3.2)	.495

NOTE. P values are from chi-square tests.

Abbreviations: CIPHR, Cancer Information Population Health Resource; ICU, intensive care unit; OAA, oral anticancer agent.

^aOAA use between metastatic diagnosis and 30 days before death.

of OAA use for patients with mRCC increased significantly from 2007 to 2015 in SEER-Medicare, but in CIPHR, OAA use rates varied with no consistent trend over this time period.^{20,21}

Previous studies of patients with multiple cancer types have demonstrated similar trends to our study with younger patients and dual-eligible beneficiaries receiving more aggressive EOL care.²²⁻²⁴ We did not see differences in EOL care metrics among racial or ethnic groups except for increased risk of ICU admission in the last 30 days of life for non-White patients in SEER-Medicare. Although it is encouraging not to see differences in EOL care quality by race or ethnicity, we exercise caution when interpreting these findings, given the small number of non-White patients and conflicting findings in other treatment settings and cancer types.^{22,25-27}

This study provides a valuable view of real-world patterns in EOL care for patients with mRCC, many receiving OAAs as part of routine treatment, but is subject to the limitations that are part of retrospective analyses of registry and claims databases. CIPHR represents a novel cohort of patients with mRCC from multiple payers. However, the data are limited to patients who were diagnosed and received care in North Carolina and may not reflect patterns of care in other regions. SEER-Medicare, while encompassing patients across the United States, is limited to older patients and may not be generalizable to patients under age 66 years. In addition, there are limitations to the use of SEER-Medicare data to identify patients with localized RCC with later progression to

mRCC, so it is possible that some of these patients were excluded from our study cohort.²⁸ Our study included patients treated between 2004 and 2016, which encompassed the approval times of most OAAs used in RCC; however, frontline management of mRCC has subsequently changed to include ICIs alone and in combination with OAAs, which might have influenced more recent EOL patterns of care. Because ICIs are commonly combined with OAAs, we believe that the implications of this study will remain largely unchanged by these developments but still warrant future studies. We defined OAA use at EOL as having a prescription drug claim within 30 days of death, as has been performed in previous studies evaluating OAA use near EOL.^{15,27} This methodology does not capture whether patients took the prescribed OAA and may incorrectly identify patients who stop taking an OAA despite having filled the prescription. Finally, decisions around EOL care are highly personal and complicated, incorporating unique patient preferences and physician guidance, which are not captured in these data. Although higher-quality EOL care is generally characterized as less aggressive care, specifics of EOL care are personal decisions and not captured in a retrospective study.

Despite these limitations, to our knowledge, our study is the first to describe patterns of EOL care for patients with mRCC in the OAA era. Patients receiving OAAs, common in contemporary oncology treatment, remained on therapy near the EOL more frequently; however, they were also more likely to enroll in hospice care. For clinicians, these data suggest that OAA receipt in clinically declining patients may be a marker of aggressive EOL care,

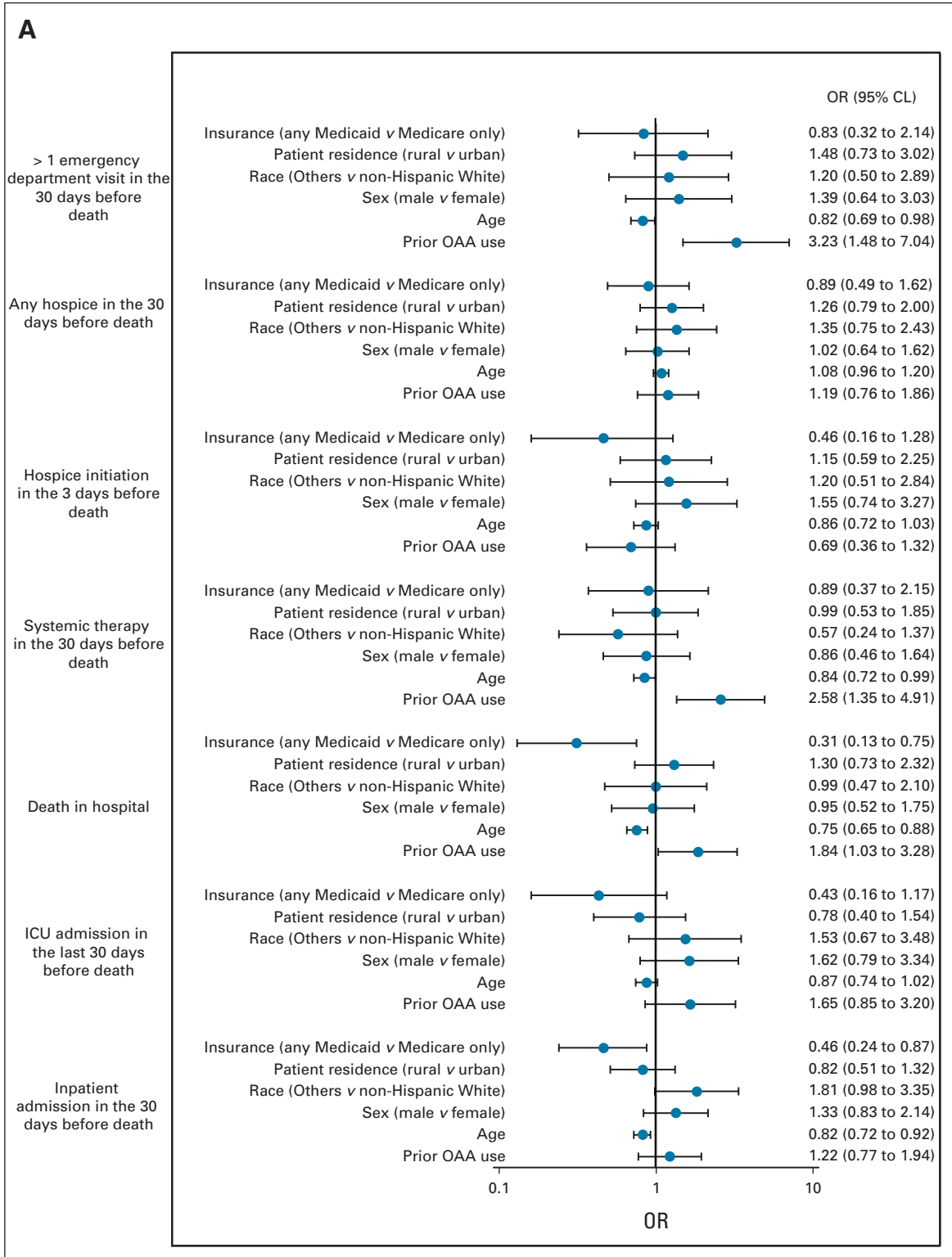


FIG 1. Adjusted ORs for end-of-life care outcomes in (A) CIPHR and (B) SEER-Medicare decedent cohorts. Results are shown for prior OAA use (v no prior OAA use), age^a, sex (male v female), race^b (Others v non-Hispanic White), patient residence (rural v urban), and insurance at mRCC diagnosis (any Medicaid v Medicare only). Full results are presented in Appendix [Table A4](#). ^aAge is scaled to 5-year intervals. ^bBecause of small cell sizes, racial and ethnic categories of non-Hispanic Black, Hispanic Black, non-Hispanic American Indian, non-Hispanic Others, Hispanic White, Hispanic Others, unknown ethnicity White, Unknown ethnicity Black, and Asian/Pacific Islander were grouped. CIPHR, Cancer Information Population Health Resource; ICU, intensive care; mRCC, metastatic renal cell carcinoma; OAA, oral anticancer agent; OR, odds ratio; RCC, renal cell carcinoma. (continued on following page)

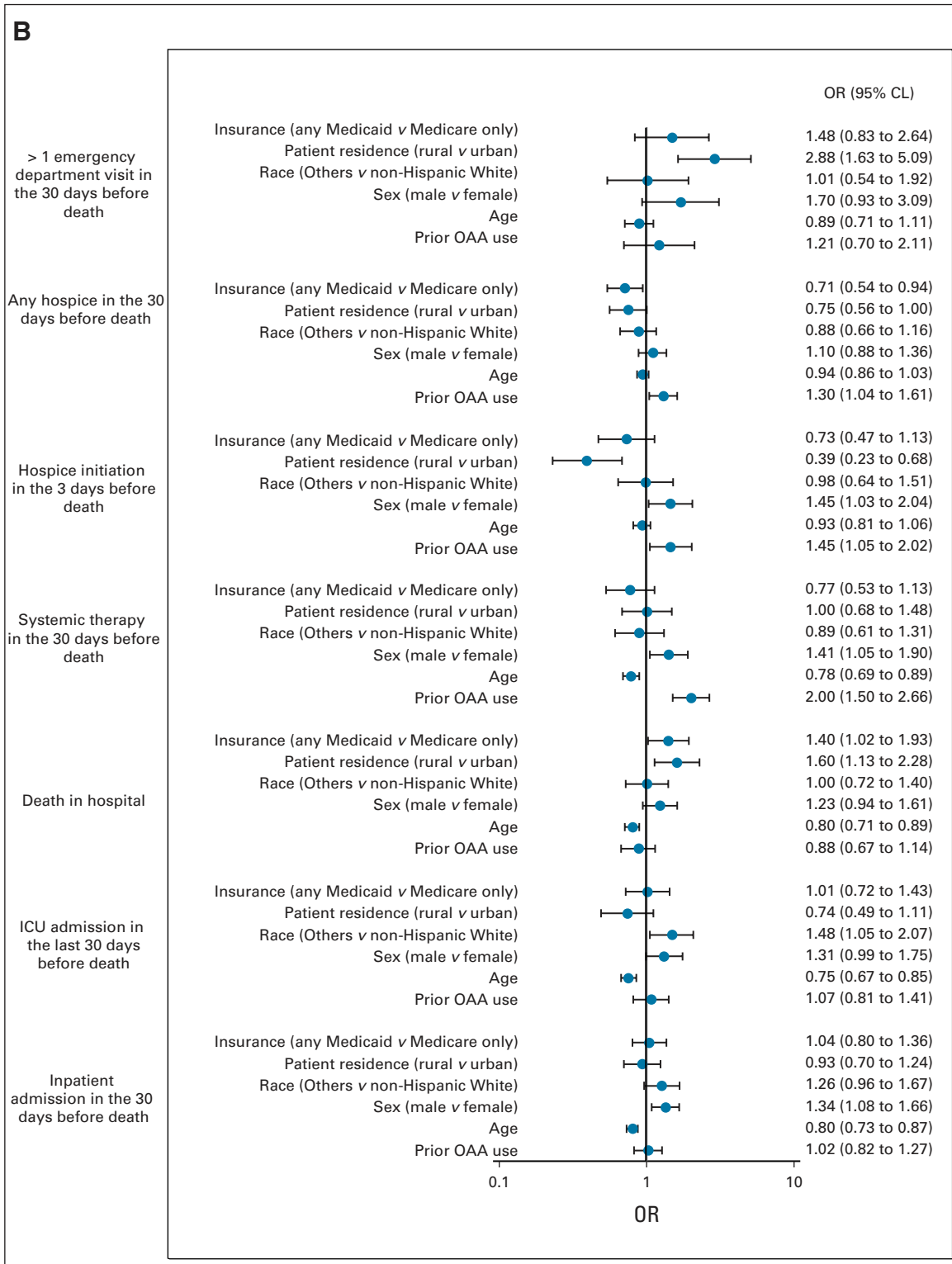


FIG 1. (Continued).

presenting an opportunity to optimize EOL care through interventions such as early palliative care engagement. Better understanding of the unique factors influencing

physician and patient decision making around EOL care, particularly for patients receiving OAAs, warrants continuous evaluation to optimize EOL care.

AFFILIATIONS

¹Department of Medicine, Duke University School of Medicine, Durham, NC

²Department of Population Health Sciences, Duke University School of Medicine, Durham, NC

³Lineberger Comprehensive Cancer Center, UNC-CH, Chapel Hill, NC

⁴Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill (UNC-CH), Chapel Hill, NC

⁵Department of Epidemiology, Gillings School of Global Public Health, UNC-CH, Chapel Hill, NC

⁶Department of Surgery (Urology), Duke University School of Medicine, Durham, NC

⁷Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC

⁸Division of Hematology and Oncology, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX

⁹Division of Medical Oncology, Department of Medicine, Duke University, Durham, NC

¹⁰Department of Urology, Yale School of Medicine, New Haven, CT

¹¹Yale Cancer Outcomes, Public Policy, and Effectiveness Research Center, New Haven, CT

¹²Department of Medicine, Yale School of Medicine, New Haven, CT

¹³Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT

CORRESPONDING AUTHOR

Hannah E. Dzimitrowicz, MD, Department of Medicine, Duke University School of Medicine, DUMC Box 3841, 2301 Erwin Rd, Durham, NC 27710; Twitter: @hannahdzmd; e-mail: hannah.dzimitrowicz@duke.edu.

DISCLAIMER

The ideas and opinions expressed herein are those of the author(s), and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Hannah E. Dzimitrowicz, Lauren E. Wilson, Melissa A. Greiner, Daniel George, Charles D. Scales, Jessica E. Pritchard, Cary P. Gross, Michaela A. Dinan, Stephanie B. Wheeler

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Administrative support: Jessica E. Pritchard, Stephanie B. Wheeler

Provision of study materials or patients: Stephanie B. Wheeler

Collection and assembly of data: Hannah E. Dzimitrowicz, Bradford E. Jackson, Melissa A. Greiner, Daniel George, Stephanie B. Wheeler

Data analysis and interpretation: Hannah E. Dzimitrowicz, Lauren E. Wilson, Bradford E. Jackson, Lisa P. Spees, Christopher D. Baggett, Melissa A. Greiner, Deborah R. Kaye, Tian Zhang, Daniel George, Charles D. Scales, Jessica E. Pritchard, Michael S. Leapman, Stephanie B. Wheeler

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

End-of-Life Care for Patients with Metastatic Renal Cell Carcinoma in the Era of Oral Anticancer Therapy

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Deborah R. Kaye

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Speakers' Bureau: Sanofi, Bayer, Exelixis

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Charles D. Scales Jr

Research Funding: Pfizer (Inst), Exelixis (Inst), Merck (Inst), Bristol Myers Squibb-Ono Pharmaceutical (Inst), Astellas Pharma (Inst)

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APPENDIX

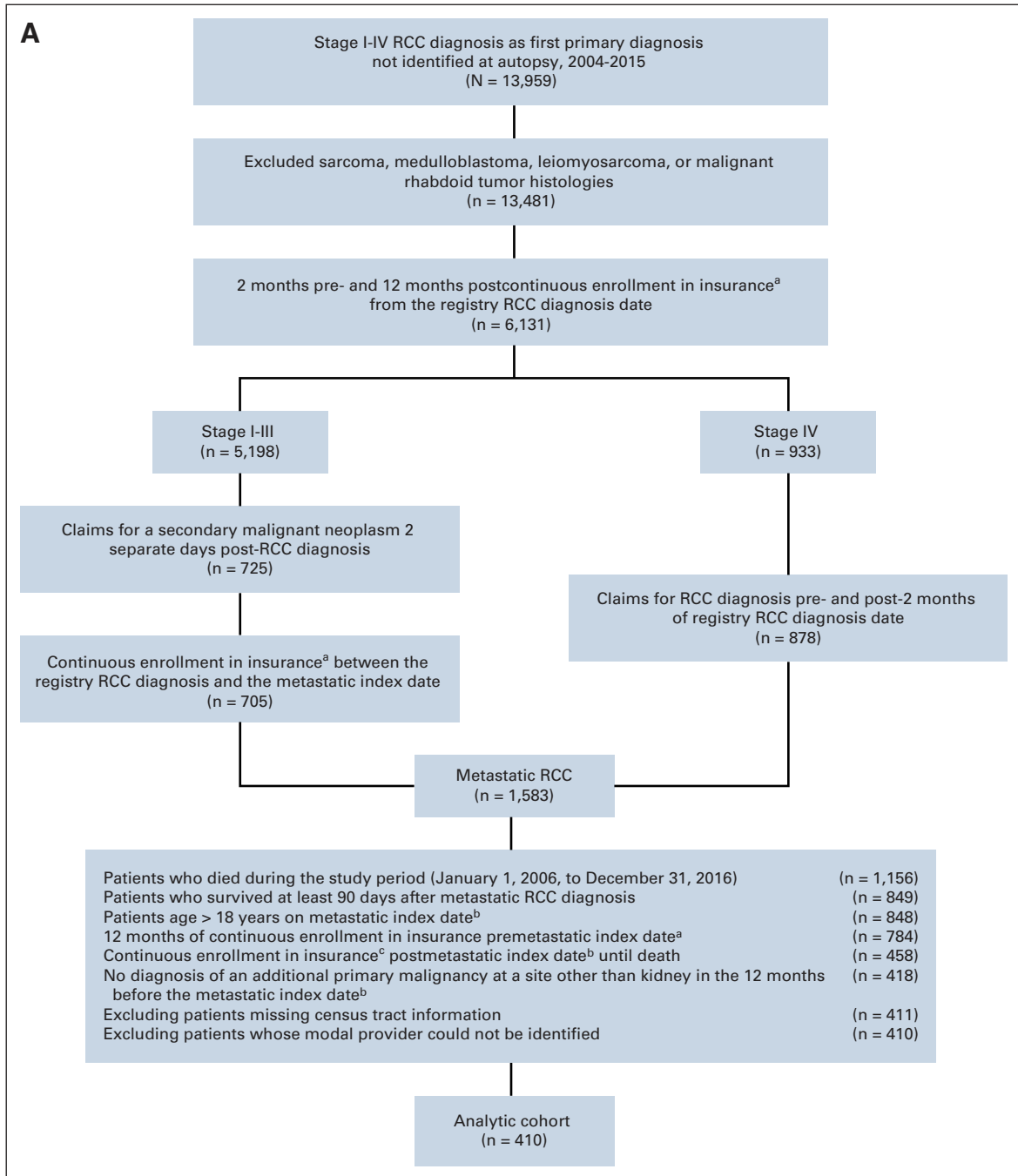


FIG A1. Cohort selection diagrams for (A) CIPHR and (B) SEER-Medicare. ^aRequired continuous enrollment in parts A and B for Medicare patients. ^bMetastatic index date was the first metastatic claim date for both stages I-III and earliest metastatic claim date for stage IV. ^cRequired continuous enrollment in parts A, B, and D for Medicare patients. CIPHR, Cancer Information and Population Health Resource. (continued on following page)

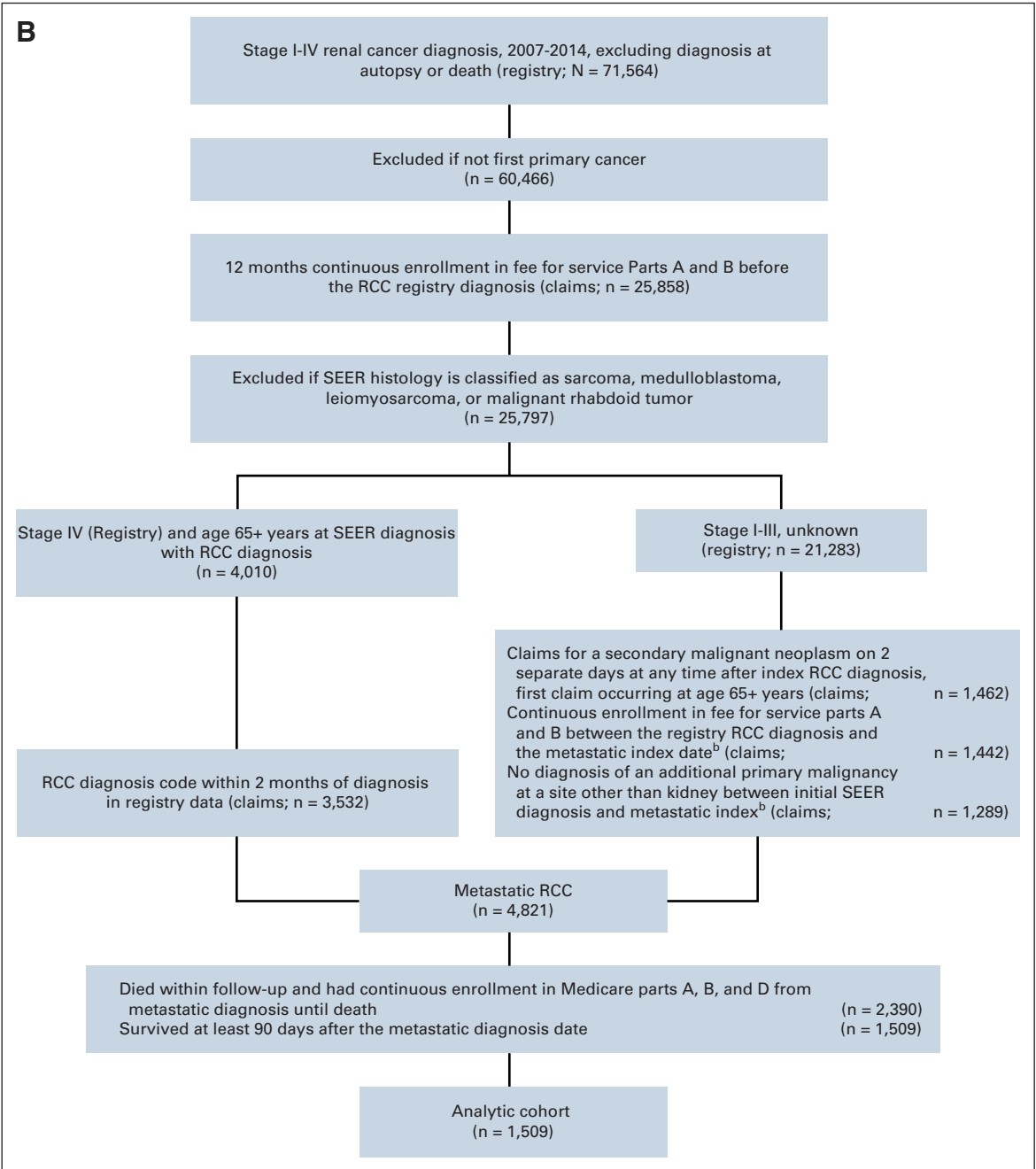


FIG A1. (Continued).

TABLE A1. Codes to Identify Renal Cell Carcinoma and Metastatic Cancer

Diagnosis or Procedure	Codes
RCC or metastatic cancer diagnosis in the first diagnosis position	ICD-9 or ICD-10: 189.*, 196.*, 197.*, 198.*, C77.*, C78.*, C79.*, C46.1*, C46.2*, C46.9*

TABLE A2. Codes and Generic Drug Names Used to Identify the Receipt of Intravenous and Oral Chemotherapies

Procedure	Codes/Identification
Administration of intravenous chemotherapy	CPT codes: Q0083-Q0085, G0355-G0363, J8501-J9999, 96400-96549
Receipt of oral chemotherapy	Generic drug names: sunitinib, pazopanib, sorafenib, everolimus, axitinib

TABLE A3. Coding Definitions for Patient Comorbid Conditions

Comorbid Condition	Corresponding Codes
Myocardial infarction	ICD-9-CM code 410.* , 412.* or ICD-10-CM I21.* , I22.* , I25.2*
Congestive heart failure	ICD-9-CM codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4*, 425.5*, 425.7*, 425.8*, 425.9*, 428.* , ICD-10-CM codes I09.81, I11.0*, I13.0*, I13.2*, I42.0*, I42.5*, I42.6*, I42.7*, I42.8*, I42.9*, I43.* , I50.*
Peripheral vascular disease	ICD-9-CM codes 093.0*, 437.3*, 440.* , 441.* , 443.1*, 443.2*, 443.8*, 443.9*, 447.1*, 557.1*, 557.9*, V43.4* ICD-10-CM codes A52.01, E08.51, E08.52, E09.51, E09.52, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, I67.0*, I67.1*, I70.* , I71.* , I73.1*, I73.8*, I73.9*, I77.7*, I79.* , K55.1*, K55.8*, K55.9*, Z95.82
Hypertension	ICD-9-CM codes 401.* , 402.* , 403.* , 404.* , 405.* , 437.2* ICD-10-CM codes I10.* , I11.* , I12.* , I13.* , I15.0*, I15.2*, I15.8*, I15.9*, I16.* , I67.4*
Dementia	ICD-9-CM codes 290.* , 294.1* , 331.2* ICD-10-CM codes F01.* , F02.* , F03.9* , G31.1*
Cerebrovascular disease	ICD-9-CM codes 362.34, 430.* , 431.* , 432.* , 433.* , 434.* , 435.* , 436.* , 437.* , 438.* ICD-10-CM codes G45.0*, G45.1*, G45.2*, G45.4*, G45.8*, G45.9*, G46.* , H34.0*, I60.* , I61.* , I62.* , I63.* , I65.* , I66.* , I67.1*, I67.2*, I67.4*, I67.5*, I67.6*, I67.7*, I67.81, I67.82, I67.84, I67.89, I67.9*, I68.* , I69.*
Chronic pulmonary disease	ICD-9-CM codes 416.8*, 416.9*, 490.* , 491.* , 492.* , 493.* , 494.* , 495.* , 496.* , 500.* , 501.* , 502.* , 503.* , 504.* , 505.* , 506.4*, 508.1*, 508.8* ICD-10-CM codes I27.2*, I27.81, I27.89, I27.9*, J40.* , J41.* , J42.* , J43.* , J44.* , J45.2*, J45.3*, J45.4*, J45.5*, J45.90, J45.99, J47.* , J60.* , J61.* , J62.* , J63.* , J64.* , J65.* , J66.* , J67.* , J68.4*, J70.1*, J70.2*, J70.3*, J70.4*, J70.8*
Rheumatologic disease	ICD-9-CM codes 446.5*, 710.0*, 710.1*, 710.2*, 710.3*, 710.4*, 714.0*, 714.1*, 714.2*, 714.8*, 725.* ICD-10-CM codes M05.* , M06.* , M31.5*, M31.6*, M32.* , M33.* , M34.* , M35.0*, M35.3*, M36.0*

(continued in next column)

TABLE A3. Coding Definitions for Patient Comorbid Conditions

Peptic ulcer disease	ICD-9-CM codes 531.* , 532.* , 533.* , 534.* ICD-10-CM codes K25.* , K26.* , K27.* , K28.*
Mild liver disease	ICD-9-CM codes 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6*, 070.9*, 570.* , 571.* , 573.3*, 573.4*, 573.8*, 573.9*, V42.7* ICD-10-CM codes B17.9*, B18.0*, B18.1*, B18.2*, B19.0*, B19.9*, K70.0*, K70.1*, K70.2*, K70.3*, K70.40, K70.9*, K71.0*, K71.10, K71.2*, K71.3*, K71.4*, K71.5*, K71.6*, K71.7*, K71.8*, K71.9*, K72.00, K73.* , K74.0*, K74.1*, K74.2*, K74.3*, K74.4*, K74.5*, K74.6*, K75.2*, K75.3*, K75.4*, K75.8*, K75.9*, K76.0*, K76.1*, K76.2*, K76.3*, K76.4*, K76.5*, K76.89, K76.9*, K77.* , Z48.23, Z94.4*
Diabetes (mild to moderate)	ICD-9-CM codes 250.0*, 250.1*, 250.2*, 250.3*, 250.8*, 250.9* ICD-10-CM codes E10.1*, E10.618, E10.62, E10.63, E10.64, E10.65, E10.69, E10.8*, E10.9*, E11.0*, E11.1*, E11.618, E11.62, E11.63, E11.64, E11.65, E11.69, E11.8*, E11.9, E13.00, E13.01, E13.10, E13.11, E13.618, E13.62, E13.63, E13.64, E13.65, E13.69, E13.8*, E13.9*
Hemiplegia or paraplegia	ICD-9-CM codes 334.1*, 342.* , 343.* , 344.0*, 344.1*, 344.2*, 344.3*, 344.4*, 344.5*, 344.6*, 344.9* ICD-10-CM codes G04.1*, G11.4*, G80.* , G81.* , G82.* , G83.0*, G83.1*, G83.2*, G83.3*, G83.4*, G83.9*
End-stage renal disease	585.6, N18.6 or ESRD eligibility flag
Diabetes with complication	ICD-9-CM codes 250.4*, 250.5*, 250.6*, 250.7* ICD-10-CM codes E10.2*, E10.3*, E10.4*, E10.5*, E10.610, E11.2*, E11.3*, E11.4*, E11.5*, E11.610, E13.2*, E13.3*, E13.4*, E13.5*, E13.610
Moderate or severe liver disease	ICD-9-CM codes 456.0*, 456.1*, 456.2*, 572.2*, 572.3*, 572.4*, 572.8* ICD-10-CM codes I85.* , K70.41, K71.11, K72.01, K72.1*, K72.9*, K76.6*, K76.7*
Acquired immunodeficiency syndrome (AIDS)	ICD-9-CM codes 042.* , 043.* , 044.* ICD-10-CM codes B20.*

TABLE A4. Adjusted ORs for End-of-Life Care Outcomes in CIPHR and SEER-Medicare Decedent Cohorts

Characteristic	Inpatient Admission in the 30 Days Before Death		ICU Stay in the Last 30 Days Before Death		Death in Hospital		Systemic Therapy in the 30 Days Before Death		Hospice Initiation in the 3 Days Before Death		Any Hospice in the 30 Days Before Death		Two or More Emergency Department Visits in the 30 Days Before Death	
	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare
Prior OAA use														
No prior OAA	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Prior OAA use	1.22 (0.77 to 1.94)	1.02 (0.82 to 1.27)	1.65 (0.85 to 3.20)	1.07 (0.81 to 1.41)	1.84 (1.03 to 3.28)	0.88 (0.67 to 1.14)	2.58 (1.35 to 4.91)	2.00 (1.50 to 2.66)	0.69 (0.36 to 1.32)	1.45 (1.05 to 2.02)	1.19 (0.76 to 1.86)	1.30 (1.04 to 1.61)	3.23 (1.48 to 7.04)	1.21 (0.70 to 2.11)
Age ^a	0.82 (0.72 to 0.92)	0.80 (0.73 to 0.87)	0.87 (0.74 to 1.02)	0.75 (0.67 to 0.85)	0.75 (0.65 to 0.88)	0.80 (0.71 to 0.89)	0.84 (0.72 to 0.99)	0.78 (0.69 to 0.89)	0.86 (0.72 to 1.03)	0.93 (0.81 to 1.06)	1.08 (0.96 to 1.20)	0.94 (0.86 to 1.03)	0.82 (0.69 to 0.98)	0.89 (0.71 to 1.11)
Sex														
Female	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Male	1.33 (0.83 to 2.14)	1.34 (1.08 to 1.66)	1.62 (0.79 to 3.34)	1.31 (0.99 to 1.75)	0.95 (0.52 to 1.75)	1.23 (0.94 to 1.61)	0.86 (0.46 to 1.64)	1.41 (1.05 to 1.90)	1.55 (0.74 to 3.27)	1.45 (1.03 to 2.04)	1.02 (0.64 to 1.62)	1.10 (0.88 to 1.36)	1.39 (0.64 to 3.03)	1.70 (0.93 to 3.09)
Race														
Non-Hispanic White	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Others ^b	1.81 (0.98 to 3.35)	1.26 (0.96 to 1.67)	1.53 (0.67 to 3.48)	1.48 (1.05 to 2.07)	0.99 (0.47 to 2.10)	1.00 (0.72 to 1.40)	0.57 (0.24 to 1.37)	0.89 (0.61 to 1.31)	1.20 (0.51 to 2.84)	0.98 (0.64 to 1.51)	1.35 (0.75 to 2.43)	0.88 (0.66 to 1.16)	1.20 (0.50 to 2.89)	1.01 (0.54 to 1.92)
Patient residence														
Urban	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Rural	0.82 (0.51 to 1.32)	0.93 (0.70 to 1.24)	0.78 (0.40 to 1.54)	0.74 (0.49 to 1.11)	1.30 (0.73 to 2.32)	1.60 (1.13 to 2.28)	0.99 (0.53 to 1.85)	1.00 (0.68 to 1.48)	1.15 (0.59 to 2.25)	0.39 (0.23 to 0.68)	1.26 (0.79 to 2.00)	0.75 (0.56 to 1.00)	1.48 (0.73 to 3.02)	2.88 (1.63 to 5.09)
% of Medicare Beneficiaries dying in hospital	1.03 (0.98 to 1.08)	1.04 (1.01 to 1.06)	0.94 (0.87 to 1.01)	1.02 (0.99 to 1.05)	1.07 (1.00 to 1.14)	1.07 (1.04 to 1.11)	1.00 (0.93 to 1.07)	0.99 (0.95 to 1.02)	1.00 (0.93 to 1.08)	1.00 (0.96 to 1.04)	0.95 (0.91 to 1.00)	0.97 (0.94 to 0.99)	0.98 (0.91 to 1.06)	0.88 (0.83 to 0.94)
Stage at initial diagnosis														
De novo	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Recurrent	1.00 (0.63 to 1.58)	1.12 (0.89 to 1.42)	2.20 (1.16 to 4.18)	1.46 (1.09 to 1.94)	1.61 (0.91 to 2.83)	1.13 (0.85 to 1.50)	0.92 (0.50 to 1.66)	0.79 (0.57 to 1.09)	0.50 (0.25 to 1.00)	0.98 (0.69 to 1.04)	0.75 (0.48 to 1.16)	1.07 (0.85 to 1.35)	1.00 (0.49 to 2.01)	1.29 (0.72 to 2.31)
Frailty score	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.01)	1.01 (0.99 to 1.03)	1.00 (0.99 to 1.01)	1.00 (0.98 to 1.02)	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.00)	0.99 (0.97 to 1.00)	0.97 (0.94 to 1.00)	1.00 (0.99 to 1.02)	0.99 (0.97 to 1.00)	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.01)	1.01 (0.99 to 1.02)
No. of comorbid conditions														
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	0.62 (0.32 to 1.19)	1.00 (0.64 to 1.58)	0.75 (0.30 to 1.88)	1.09 (0.58 to 2.07)	1.05 (0.48 to 2.27)	1.19 (0.66 to 2.16)	1.01 (0.45 to 2.23)	1.08 (0.61 to 1.92)	0.82 (0.35 to 1.94)	1.07 (0.53 to 2.16)	0.81 (0.43 to 1.52)	0.97 (0.62 to 1.52)	1.25 (0.42 to 3.71)	0.66 (0.23 to 1.89)
2+	0.90 (0.51 to 1.81)	1.11 (0.72 to 1.70)	0.81 (0.34 to 1.92)	1.51 (0.82 to 2.77)	0.93 (0.43 to 2.00)	1.50 (0.85 to 2.65)	1.29 (0.59 to 2.83)	0.98 (0.57 to 1.71)	0.70 (0.30 to 1.66)	1.03 (0.52 to 2.03)	0.84 (0.45 to 1.55)	0.89 (0.58 to 1.36)	2.13 (0.77 to 5.88)	0.65 (0.25 to 1.71)

(continued on following page)

TABLE A4. Adjusted ORs for End-of-Life Care Outcomes in CIPHR and SEER-Medicare Decedent Cohorts (continued)

Characteristic	Inpatient Admission in the 30 Days Before Death		ICU Stay in the Last 30 Days Before Death		Death in Hospital		Systemic Therapy in the 30 Days Before Death		Hospice Initiation in the 3 Days Before Death		Any Hospice in the 30 Days Before Death		Two or More Emergency Department Visits in the 30 Days Before Death	
	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare	CIPHR	SEER-Medicare
Provider location														
Urban	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Rural	0.86 (0.52 to 1.41)	0.72 (0.13 to 4.07)	0.37 (0.15 to 0.89)	—	0.89 (0.46 to 1.70)	2.39 (0.40 to 14.3)	0.44 (0.20 to 0.94)	—	0.80 (0.38 to 1.70)	—	0.83 (0.51 to 1.35)	1.52 (0.29 to 8.03)	0.73 (0.32 to 1.66)	—
Insurance at mRCC diagnosis														
Medicare only	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any Medicaid	0.46 (0.24 to 0.87)	1.04 (0.80 to 1.36)	0.43 (0.16 to 1.17)	1.01 (0.72 to 1.43)	0.31 (0.13 to 0.75)	1.40 (1.02 to 1.93)	0.89 (0.37 to 2.15)	0.77 (0.53 to 1.13)	0.46 (0.16 to 1.28)	0.73 (0.47 to 1.13)	0.89 (0.49 to 1.62)	0.71 (0.54 to 0.94)	0.83 (0.32 to 2.14)	1.48 (0.83 to 2.64)
Private	0.69 (0.34 to 1.39)	—	0.57 (0.22 to 1.49)	—	0.41 (0.17 to 0.97)	—	1.23 (0.53 to 2.84)	—	0.76 (0.29 to 1.97)	—	0.79 (0.40 to 1.56)	—	0.44 (0.15 to 1.30)	—
US geographic region														
West	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.
Midwest	—	1.25 (0.86 to 1.81)	—	0.84 (0.50 to 1.42)	—	0.63 (0.37 to 1.06)	—	0.66 (0.40 to 1.11)	—	1.55 (0.88 to 2.72)	—	1.02 (0.71 to 1.47)	—	1.42 (0.64 to 3.15)
Northeast	—	1.63 (1.21 to 2.19)	—	1.55 (1.08 to 2.23)	—	1.22 (0.86 to 1.73)	—	1.17 (0.80 to 1.72)	—	1.85 (1.22 to 2.81)	—	1.26 (0.94 to 1.70)	—	0.76 (0.22 to 2.59)
South	—	1.00 (0.73 to 1.36)	—	1.01 (0.67 to 1.52)	—	0.89 (0.61 to 1.30)	—	0.66 (0.42 to 1.02)	—	1.15 (0.69 to 1.93)	—	0.85 (0.62 to 1.16)	—	0.75 (0.33 to 1.69)
Missing	—	0.89 (0.58 to 1.39)	—	0.84 (0.45 to 1.55)	—	0.48 (0.25 to 0.93)	—	0.65 (0.36 to 1.18)	—	1.29 (0.65 to 2.57)	—	1.28 (0.83 to 1.96)	—	1.04 (0.49 to 2.23)

NOTE. Data are OR (95% CL). Bold estimates indicate $P < .05$.

Abbreviations: CIPHR, Cancer Information Population Health Resource; ICU, intensive care; MRCC, metastatic renal cell carcinoma; OAA, oral anticancer agent; OR, odds ratio.

^aAge is scaled to 5-year intervals.

^bBecause of small cell sizes, racial and ethnic categories of non-Hispanic Black, Hispanic Black, non-Hispanic American Indian, non-Hispanic Others, Hispanic White, Hispanic Others, unknown ethnicity White, unknown ethnicity Black, and Asian/Pacific Islander were grouped.