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Economic burden of renal cell carcinoma among older adults in the targeted therapy era

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Abstract

Objective: This study examined the economic burden of renal cell carcinoma (RCC) among older adults. The study also examined healthcare costs by types of resources used and stage at which RCC was diagnosed.

Methods: The study analyzed the Surveillance Epidemiology and End Result—Medicare linked data. We included a prevalent cohort of RCC patients from 2013, diagnosed and continuously enrolled in Medicare from 2005 to 2013. RCC patients were matched to controls selected from a 5% sample of noncancer beneficiaries using propensity score matching to calculate incremental costs. Total healthcare costs (THC) were calculated using a phase-based approach, which classified patients into early, continuing, and late phases of care. Costs were also examined by types of resources used and stage at which RCC was diagnosed. Generalized linear models estimated annual incremental costs per patient. The number of older RCC patients was calculated using SEER-Stat and ProjPrev software. The average incremental THC was multiplied by the estimated number of RCC patients to calculate the total economic burden of RCC among older adults.

Results: The study included 10,392 each of RCC and control patients. The average annual THC associated with RCC was $7,419 for all phases, $22,752 for the initial phase, $4,860 for the continuing phase, and $13,232 for the late phase of care. The average THC was $4,584 for patients diagnosed at stage I, $4,727 for stage II, $9,331 for stage III, and $31,637 for stage IV. For patients diagnosed at stages I to III, hospital cost (approximately $1,500–$3,400) was the largest component of THC. For stage IV patients, prescription drug cost ($11,747) was the largest component of THC. The projected number of older RCC patients in 2015 was 204,256. The annual economic burden of RCC after weighting for proportion of patients diagnosed at various stages was estimated to be $2.1 billion.

Conclusions: RCC was associated with a significant economic burden on Medicare. Healthcare costs associated with RCC varied substantially between early stage and metastatic patients. This research provided a baseline that can be used to assess the economic value of emerging therapies among older RCC patients.

Keywords: Economic burden; RCC; Healthcare costs; mRCC; Resource Utilization; SEER-Medicare

1. Background

Renal cell carcinoma (RCC) is the most common type of kidney cancer. In 2017, approximately 63,990 new kidney cancer cases would be diagnosed and 14,440 people would die from this disease [1]. The median age of RCC diagnosis is 64 years. Medicare covers about 46% of RCC patients [2,3].

Treatment patterns of RCC have evolved over time. Smaller tumors (≤ 4 cm) are now typically managed with active surveillance and local therapies. Patients with localized but larger tumors (≥ 4 cm) are treated with nephrectomy [2,4,5]. Significant changes in treatment patterns also occurred for metastatic RCC (mRCC) patients. Until 2005, systemic therapy for mRCC included the use of interleukin-2 and interferon-alfa [6,7]. From 2005, several high-cost

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targeted therapies were approved to treat mRCC [8–12]. In 2016, the U.S. FDA also approved cabozantinib and nivolumab [13]. In addition, there is great interest in combination regimens such as nivulomab and ipilumimab [14]. As the landscape of therapies continues to evolve, patients are likely to receive more lines of therapies than they received in the past [20]. The costs of targeted therapies and administration, along with the costs of adverse events management, can be substantial. In addition, as the number of older adults continues to increase, the burden of RCC on Medicare will continue to grow.

Estimates from previous studies regarding the economic burden of RCC have ranged from $600 million to $5.19 billion, with annual per patient medical costs between $11,169 and $43,805 (2009 USD) [3,15–19]. However, a majority of studies were conducted prior to the targeted therapy era. Only Shih et al. (2011) assessed the economic burden of RCC at the beginning of the targeted therapy era (2005–2007); however, due to unavailability of Medicare Part D, costs from Shih et al. may not accurately represent the burden among older RCC patients on Medicare [18]. Additionally, none of the studies included targeted therapies approved since 2009 or projected the economic burden to the entire Medicare population with RCC.

The aim of this study was to assess the economic burden of RCC among older adults (aged 65 years and above) from Medicare's perspective. The study also assessed healthcare costs by types of resources used and stage at which RCC was diagnosed.

2. Methods

2.1. Data source

2.1.1. SEER-Medicare

The Surveillance Epidemiology and End Result (SEER) program collects information on cancer statistics in an effort to reduce the cancer burden among the U.S. population [21]. As of 2016, SEER registries covered 28% of the U.S. population [22]. Medicare data provides information on Part A (hospital), Part B (outpatient), and Part D (prescription drug) claims for Medicare beneficiaries. The SEER-Medicare linked database provides information about healthcare resource use and costs for Medicare patients living in SEER areas [21].

We used 2005 to 2013 SEER-Medicare linked data. The Patient Entitlement and Diagnosis Summary File was used to obtain demographics and cancer diagnosis-related information. Healthcare resource use and cost-related information were obtained from Medicare Provider Analysis and Review, outpatient, carrier, Part D event, home health agencies, hospice (HS), and durable medical equipment files. A 5% random sample of noncancer Medicare beneficiaries was used as controls. More details regarding SEER and Medicare files can be found on the SEER-Medicare website [21].

2.2. Study design and sample selection

The study used a prevalence-based design to quantify the economic burden of RCC. Patients diagnosed from 2005 to 2013 were identified using ICD-O (v.3) code C649 and relevant histology types. Healthcare costs were examined using 2013 claims. Patients in the control group were assigned a random date of pseudo-diagnosis between January 1, 2013 and December 31, 2013. To be included in the study, patients needed to be alive for at least 1 month in 2013. We excluded patients aged < 65 years at the time of diagnosis, diagnosed with another cancer, diagnosed on autopsy, with cancer reported by death certificate, or enrolled in health maintenance organizations (Fig. 1).

Total healthcare cost (THC) was estimated using a phase-based approach which classifies patients into early, continuing, and late phases of care [18,23,24]. In this study, the early phase included patients diagnosed in 2013 who remained alive at the end of 2013. Patients who died in 2013 represented the late phase. Patients diagnosed before 2013 who remained alive at the end of 2013 represented the continuing phase.

To reduce the effect of selection bias, RCC patients were matched in 1:1 ratio to control patients for each phase of care using propensity score matching (PSM). A propensity score was calculated using logistic regression which controlled for age, sex, race, SEER registry region, urban-rural status, and NCI Comorbidity Index score [25]. The quality of matching was assessed by comparing standardized scores and distributions for patient characteristics before and after matching. Standardized scores of <10% after matching indicated a good match [26,27]. Details about PSM by phase of care can be found in Appendices 2 to 6.

For estimating costs by stage at diagnosis, a separate statistical analysis was run using the same cases that were used for estimating cost of RCC. However, we could not match cases to controls because stage at diagnosis was not applicable to noncancer patients. Therefore, the regression included stage at diagnosis as a primary independent variable and noncancer group as the reference category. The analyses controlled for age at diagnosis, sex, race, SEER registry region, and NCI Comorbidity Index. Patients diagnosed at each stage of RCC were compared to the entire cohort of 10,392 noncancer patients. Estimates from regression models provided average incremental costs between patients diagnosed at each stage and noncancer control group.

2.3. Study measures

2.3.1. Healthcare cost

Because the study was conducted from Medicare's perspective, only direct medical costs were included. We calculated incremental cost, which is the average difference between the total health care cost incurred by a patient with RCC and a matched control, as the cost associated with RCC.

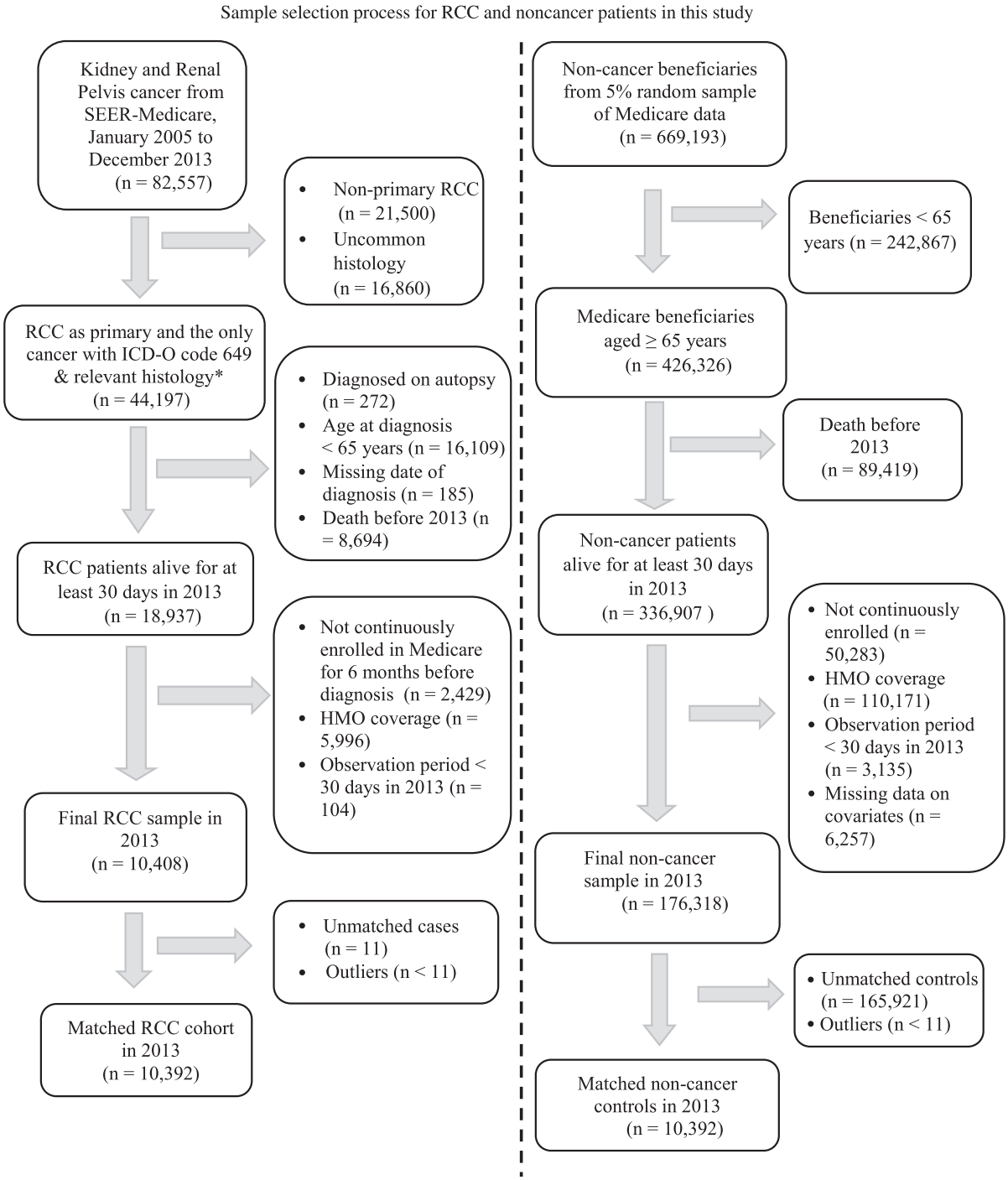

Fig. 1. RCC = renal cell carcinoma. *relevant histology types: ICD O-3 codes ’8260′, ’8310′, ’8312′, ’8316′, ’8317′, ’8318′.

2.3.2. Other variables

These variables included patient demographics, urban/rural status, SEER registry region, cancer stage, histology, and NCI Comorbidity Index. We used American Joint Committee on Cancer (AJCC 6th edition) criteria to classify patients into stages I to IV and unknown stage [28].

2.3.3. RCC prevalence/number of patients

We calculated the number of older RCC patients living in SEER registry regions using SEER Stat software [29]. This estimate was used to derive the number of older RCC patients in the United States using the Projected Prevalence Software developed by the National Cancer Institute [30].

Table 1
Characteristics of renal cell carcinoma and noncancer control group patients.

Characteristics	RCC (n = 10,408) n, (%)	Noncancer (n = 170,061) n, (%)	RCC (matched) (n = 10,392) n, (%)	Noncancer (matched) (n = 10,392) n, (%)	Standardized difference after matching
Age (mean, SD)[a,b]	73.8 (6.3)	75.5 (7.3)	73.8 (6.3)	74.9 (7.1)	0.1645
Age categories (y)[a,b]					
65–69	3,225 (31.0)	43,043 (25.3)	3,216 (31.0)	2,883 (27.7)	0.0705
70–74	3,486 (33.5)	52,207 (30.7)	3,479 (33.5)	3,251 (31.3)	0.0468
75– 79	2,003 (19.2)	32,763 (19.3)	2,003 (19.3)	1,995 (19.3)	0.0017
80 and older	1,694 (16.3)	42,048 (24.7)	1,694 (16.3)	2,263 (21.8)	0.1397
Gender (% Male) [a,b]	5,863 (56.3)	65,978 (38.8)	5,850 (56.3)	6,162 (59.3)	0.0608
Race (%)[a,b]					
Caucasian	9,000 (86.5)	140,757 (82.8)	8,989 (86.5)	8,756 (84.3)	0.0629
Black	815 (7.8)	12,063 (7.1)	812 (7.8)	1,013 (9.8)	0.0680
Others	593 (5.7)	17,241 (10.1)	591 (5.7)	623 (6.0)	0.0127
NCI Comorbidity Index Score (mean, SD)[a,b]	0.5 (1.0)	0.9 (1.4)	0.9 (1.3)	1.0 (1.4)	0.0582
NCI Comorbidity Index Score categories[a,b]					
0	5,469 (52.6)	11,9240 (70.1)	5,468 (52.6)	5,283 (50.8)	0.0358
1–2	3,685 (35.4)	41,956 (24.7)	3,682 (35.4)	3,725 (35.8)	0.0086
3 or more	1,254 (12.1)	8,865 (5.2)	1,242 (11.9)	1,384 (13.3)	0.0413
Urban/rural (%)					
Big metro	5,295 (50.9)	87,713 (51.6)	5,289 (50.9)	4,856 (46.7)	0.0830
Metro	3,161 (30.4)	51,905 (30.5)	3,153 (30.4)	3,289 (31.6)	0.0280
Urban	683 (6.6)	10,902 (6.4)	682 (6.6)	822 (7.9)	0.0520
Less urban	1,018 (9.8)	15,834 (9.3)	1,017 (9.8)	1,172 (11.3)	0.0483
Rural	251 (2.4)	3,707 (2.2)	251 (2.4)	253 (2.4)	0.0013
SEER region[a]					
North East	2,042 (19.6)	33,885 (19.9)	2,040 (19.6)	2,076 (20.0)	0.0087
South	2,823 (27.1)	40,345 (23.7)	2,818 (27.1)	2,743 (26.4)	0.0163
North Central	1,246 (12.0)	19,078 (11.2)	1,245 (12.0)	1,242 (12.0)	0.0001
West	4,297 (41.3)	76,753 (45.1)	4,289 (41.3)	4,331 (41.7)	0.0082
Phase of Care					
Initial phase	1,779 (17.1)	24,580 (14.5)	1,778 (17.1)	1,777 (17.1)	NA
Continuing Phase	7,806 (75.0)	138,112 (81.2)	7,794 (75.0)	7,794 (75.0)	
Late phase	823 (7.9)	7,369 (4.3)	820 (7.9)	821 (7.9)	
Cancer stage					
Stage I	6,720 (64.6)	NA	6,710 (64.6)	NA	NA
Stage II	784 (7.5)		782 (7.5)		
Stage III	1554 (14.9)		1,551 (14.9)		
Stage IV	756 (7.3)		755 (7.3)		
Unknown	594 (5.7)		594 (5.7)		
Histology					
Clear cell	8,455 (81.2)	NA	8,443 (81.3)	NA	NA
Nonclear cell	1,953 (18.8)		1,949 (18.8)		

NA = not applicable; NCI = National Cancer Institute; RCC = renal cell carcinoma; SEER = Surveillance Epidemiology and End Results.
[a] Difference was statistically significant ($P < 0.05$) before matching.
[b] Difference was statistically significant after matching.

2.4. Statistical analysis

We compared patient characteristics between unmatched RCC and control groups using descriptive statistics. Incremental costs between treatment and control groups were calculated using generalized linear models (GLMs) controlling for demographics, NCI Comorbidity Score, and length of the time spent in each phase of care. The choice of distribution and link for GLMs was based on model fitting tests such as modified Park tests and Pregibon link tests. In cost categories with excess zeros (defined as ≥ 20%), 2-part models were used. Upon examination of the distribution of THC, we excluded observations with THC > $400,000 (above the 99.9th percentile) as outliers. Confidence intervals for mean costs were calculated using a nonparametric bootstrapping method with 1,000 replications.

The total economic burden was calculated by multiplying the average incremental THC with the estimated number of older RCC patients. We also calculated weighted economic burden based on incremental costs by stage at diagnosis and estimated prevalence of RCC by stage at diagnosis. (Appendix 1). The most recent year for which RCC prevalence estimates could be calculated using NCI's Projected Prevalence software at the time of analysis was

Table 2
Annual total healthcare cost associated with renal cell carcinoma by phase of care.

Phase of care	RCC (US $) (mean, 95% CI)	Matched noncancer (US $)(mean, 95% CI)	Incremental cost (US $) (mean, 95% CI)
Any stage (n = 20,784)	(n = 10,392)	(n = 10,392)	
All phases	23,489 (22,805–24,174)	16,070 (15,507–16,633)	7,419 (6,553–8,285)[a]
Initial	32,669 (31,109–34,229)	9,917 (8,911–10,923)	22,752 (20,875–24,629)[a]
Continuing	18,939 (18,226– 19,652)	14,078 (13,525–14,631)	4,860 (3,965–5,756)[a]
Late	54,983 (51,790–58,176)	41,750 (38,737–44,764)	13,232 (9,015–17,450)[a]

CI = confidence interval; RCC = renal cell carcinoma.
[a] Statistically significant difference (P value < 0.05). Regression models controlled for age, sex, race, SEER region, NCI comorbidty index and length of time spent in each phase.

2015. The costs were inflated to 2015 USD using the Consumer Price Index for medical care services and medical care comorbidities so that costs and prevalence estimates were from the same year [31]. Several sensitivity analyses were undertaken to assess the impact of outliers and GLM specifications on our main findings. All statistical analyses were conducted at an alpha level of 0.05 using SAS v.9.4 (SAS Institute Inc., Cary, NC), and STATA (version 13.0, StataCorp, College Station, TX).

3. Results

3.1. Sample characteristics

The final study sample, after PSM, included 10,392 each of RCC and control patients. The average age was 74 years for RCC and 75 years for controls. Both groups had a similar proportion of males (56% vs. 59%), Caucasians (87% vs. 84%) and patients with zero NCI Comorbidity Score (53% vs. 51%). Most standardized differences between matched groups were < 10%, which indicated a good match between the 2 groups (Table 1).

3.2. Total healthcare cost per patient

The THC per patient was $23,489 for RCC and $16,070 for the matched control group. The incremental THC per patient was the $7,419 for all phases combined, $22,752 for the initial phase, $4,860 for the continuing phase, and $13,232 for the late phase (Table 2). When analyzed by stage at diagnosis, we found that the average THC for patients diagnosed at stage IV was about 6 to 7 times higher than for patients diagnosed at stages I and II. Patients diagnosed at stage I had costs of $4,584 vs. costs of $9,331 for those diagnosed at stage III and $31,637 at stage IV. Phase-based costs for patients diagnosed at various stages of RCC can be found in Table 3.

3.3. Total economic burden of RCC on medicare

Based on the SEER Stat analysis, there were 18,121 older RCC patients alive in areas covered by SEER registries in 2015. The projected count of older RCC patients in the United States calculated using Projected Prevalence was 204,256. Multiplying the incremental cost of RCC by the projected number of RCC patients resulted in the total economic burden of $1.52 billion (unweighted for stage). To calculate economic burden by stage at diagnosis, we first calculated the number of RCC patients at each stage by assuming a distribution similar to SEER data. The total economic burden was estimated to be $524 million for stage I, $68 million for stage II, $267 million for stage III, $1.0 billion for stage IV, and $166 million for the unknown stage. Weighted total economic burden of RCC was found to be $2.1 billion (Appendix 1).

3.4. Healthcare costs by types of services used

RCC patients had significantly higher costs than controls for all types of resources used except for durable medical equipment and skilled nursing facility (SNF). For patients diagnosed at stage I, costs associated with hospital use, outpatient services, and physician provided care were the top 3 drivers of THC. A similar pattern was observed for stage II and stage III patients. For mRCC patients, prescription drug cost was the largest component of THC. Unlike patients from earlier stages, stage IV patients had significantly (P<0.05) higher home health and HS care costs than control group patients (Table 4).

3.5. Sensitivity analyses

The average THC changed by only a small magnitude for a majority of the sensitivity analyses. However, when the NCI Comorbidity Score was excluded from the propensity score model, the incremental cost per patient increased by 45% (Table 6).

4. Discussion

This study assessed the economic burden of RCC from Medicare's perspective. We used the most recent SEER-Medicare data to reflect the economic burden in the later part of the targeted therapy era (2009–2013). This was also

Table 3
Annual total healthcare cost associated with renal cell carcinoma by phase of care and by stage at which cancer was diagnosed.

Cancer stage at diagnosis & phase of care	RCC (US $) (mean, 95% CI)	Noncancer (US $) (mean, 95% CI)	Incremental cost (US $) (mean, 95% CI)
Stage I (*n* = 17,102)	(*n* = 6,710)	(*n* = 10,392)	
All phases	20,528 (19,749–21,306)	15,944 (15,385–16,504)	4,584 (3,652–5,515)[a]
Initial	29,073 (27,113–31,033)	9,942 (8,925–10,959)	19,131 (16,905–21,356)[a]
Continuing	17,210 (16,408–18,012)	14,150 (13,574–14,725)	3,060 (2,044–4,077)[a]
Late	52,314 (46,565–58,063)	43,006 (39,798–46,214)	9,307 (2,755–15,860)[a]
Stage II (*n* = 11,174)	(*n* = 782)	(*n* = 10,392)	
All phases	20,671 (18,407–22,936)	15,944 (15,385–16,504)	4,727 (2,418–7,037)[a]
Initial	33,417 (26,976–39,859)	9,926 (8,922–10,930)	23,491 (17,112–29,870)[a]
Continuing	16,403 (14,107–18,699)	14,226 (13,660–14,793)	2,177 (−208 to 4,561)
Late	52,068 (37,575–66,560)	43,196 (39,847– 46,545)	6,398 (−6,125 to 23,868)
Stage III (*n* = 11,943)	(*n* = 1,551)	(*n* = 10,392)	
All phases	25,275 (23,524–27,027)	15,944 (15,385–16,504)	9,331 (7,505–11,157)[a]
Initial	36,489 (31,738–41,241)	9,879 (8,874–10,884)	26,610 (21,756–31,464)[a]
Continuing	20,946 (19,038–22,854)	14,190 (13,624–14,756)	6,756 (4,783–8,729)[a]
Late	57,923 (50,237–65,610)	42,966 (39,752–46,181)	14,957 (6,701–23,213)[a]
Stage IV (*n* = 11,147)	(*n* = 755)	(*n* = 10,392)	
All phases	47,581 (44,217–50,946)	15,944 (15,385–16,504)	31,637 (28,220–35,054)[a]
Initial	50,805 (44,477–57,133)	9,862 (8,892–10,832)	40,943 (34,530–45,357)[a]
Continuing	46,546 (40,344–52,749)	14,250 (13,678–14,823)	32,296 (26,064–38,528)[a]
Late	62,008 (55,880–68,135)	41,647 (38,500–44,795)	20,360 (13,571–27,150)[a]
Stage unknown (*n* = 10,986)	(*n* = 594)	(*n* = 10,392)	
All phases	27,579 (24,562–30,597)	15,944 (15,385–16,504)	11,635 (8,559–14,712)[a]
Initial	35,026 (26,059–43,992)	10,014 (8,953–11,076)	25,011 (15,908–34,115)[a]
Continuing	22,971 (19,534–26,408)	14,258 (13,691–14,825)	8,713 (5,229–12,198)[a]
Late	59,415 (46,816–72,013)	42,398 (39,238–45,557)	17,017 (4,309–29,725)[a]

CI = confidence interval; RCC = renal cell carcinoma.
[a] Statistically significant difference (*P* value < 0.05).
Note: Patients from each stage were compared to noncancer controls. Regression models controlled for age, sex, race, SEER region and NCI Comorbidty Index.

the first study among older adults, in this era, to assess drivers of healthcare costs for patients diagnosed at different stages. The average THC associated with RCC was $7,419 while the total economic burden was estimated to be $2.1 billion. Although only 15% of patients were diagnosed at stage IV, they contributed 50% of the total economic burden. This suggested that the unmet need is much higher among stage IV patients compared to patients diagnosed at earlier stages, as the survival rate is lowest but the economic burden is highest in this patient group.

The average THC estimate from our study was slightly lower than the estimate of $11,169 from a study by Shih et al. Some methodological differences may explain the slightly lower costs in our study. Shih et al.

Table 4
Healthcare cost by types of resources used among RCC and control patients.

	RCC (mean, 95% CI)	Matched noncancer controls (mean, 95% CI)	Incremental cost (mean, 95% CI)
Any Stage (*n* = 20,784)	(*n* = 10,392)	(*n* = 10,392)	
Total	23,489 (23,141–24,511)	16,070 (15,178–16,289)	7,419 (6,553–8,285)[a]
Hospital	4,830 (4,564–5,095)	2,548 (2,320–2,776)	2,282 (1,929–2,634)[a]
ED	4,709 (4,455–4,964)	3,899 (3,648–4,150)	811 (461–1,161)[a]
Skilled nursing facility	1,503 (1,372–1,634)	1,405 (1,278–1,532)	98 (−80 to 276)
Outpatient services	3,053 (2,902–3,204)	1,556 (1,469–1,644)	1,497 (1,327–1,666)[a]
Physician services	4,419 (4,288–4,551)	2,875 (2,801–2,976)	1,544 (1,385–1,704)*
Prescription drugs	3,817 (3,538–4,097)	2,169 (2,067–2,272)	1,648 (1,352–1,944)[a]
DME	232 (215–250)	247 (225–268)	-14 (−38 to 10)
Hospice care	723 (627–818)	551 (469–634)	172 (51–292)[a]
Home health	818 (771–866)	691 (645–737)	127 (63–192)[a]

CI = confidence interval; DME = Durable medical equipment; ED = Emergency department; RCC = renal cell carcinoma.
[a] Statistically significant differences, *P* < 0.05. Regression models controlled for age, sex, race, SEER region and NCI Comorbidty Index.

Table 5
Healthcare cost by types of resources used by stage at RCC diagnosis.

	RCC (mean, 95% CI)	Noncancer (mean, 95% CI)	Incremental cost (mean, 95% CI)
Stage I (*n* = 17,102)	(*n* = 6,710)	(*n* = 10,392)	
Total	20,528 (19,749−21,306)	15,944 (15,385−16,504)	4,584 (3,652−5,515)[a]
Hospital	4,417 (4,096−4,738)	2,543 (2,316−2,770)	1,917 (1,532−2,301)[a]
ED	4,204 (3,892−4,516)	3,855 (3,607−4,103)	350 (−33 to 732)
Skilled nursing facility	1,356 (1,202−1,510)	1,411 (1,284−1,538)	-55 (−251 to 142)
Outpatient services	2,710 (2,535−2,885)	1,561 (1,473−1,649)	1,149 (955−1,343)[a]
Physician services	3,987 (3,849−4,125)	2,873 (2,786−2,961)	1,114 (949−1,278)[a]
Prescription drugs	2,458 (2,299−2,617)	2,279 (2,160−2,398)	179 (−19 to 377)
DME	223 (205−242)	246 (225−268)	-23 (−49 to 3)
Hospice care	393 (309−477)	580 (493−667)	-187 (−304, −69)[a]
Home health	746 (690−803)	695 (648−741)	52 (−20 to 123)
Stage II (*n* = 11,174)	(*n* = 782)	(*n* = 10,392)	
Total	20,671 (18,407−22,936)	15,944 (15,385−16,504)	4,727 (2,418−7,037)[a]
Hospital	4,128 (3,313−4,943)	2,543(2,316−2,770)	1,585 (747−2,424)[a]
ED	4,390 (3,304−5,478)	3,855 (3,607−4,103)	536 (−573 to 1,646)
Skilled nursing facility	1,267 (827−1,707)	1,411 (1,284−1,538)	-144 (−600 to 313)
Outpatient services	2,394 (1,950−2,838)	1,561 (1,473−1,649)	833 (381−1,825)[a]
Physician services	3,830 (3,409−4,252)	2,873 (2,786−2,961)	957 (492−1,360)[a]
Prescription drugs	3,522 (2,456−4,588)	2,279 (2,160−2,398)	1,243 (183−2,304)
DME	256 (167−343)	246 (225−268)	9 (−81 to 99)
Hospice care	701 (350−1052)	580 (493−667)	121 (−238 to 480)
Home health	763 (602−8923)	695 (648−741)	68 (−98 to 234)
Stage III (*n* = 11,943)	(*n* = 1,551)	(*n* = 10,392)	
Total	25,275 (23,524−27,027)	15,944 (15,385−16,504)	9,331 (7,505−11,157)[a]
Hospital	5,896 (5,141−6,652)	2,543 (2,316−2,770)	3,353 (2,564−4,142)[a]
ED	4,733 (4,099−5,364)	3,855 (3,607−4,103)	878 (183−1,574)[a]
Skilled nursing facility	1,323 (1,036−1,610)	1,411 (1,284−1,538)	-88 (−405 to 229)
Outpatient services	3,387 (2,991−3,784)	1,561 (1,473−1,649)	1,826 (1,424−2,228)[a]
Physician services	4,982 (4,568−5,396)	2,873 (2,786−2,961)	2,109 (1,686−2,532)[a]
Prescription drugs	4,330 (3,503−5,158)	2,279 (2,160−2,398)	2,052 (1,218−2,886)[a]
DME	213 (176−249)	246 (225−268)	-34 (−73 to 5)
Hospice care	821 (552−1,089)	580 (493−667)	241 (−38 to 519)
Home health	909 (782−1,036)	695 (648−741)	215 (80−349)[a]
Stage IV (*n* = 11,147)	(*n* = 755)	(*n* = 10,392)	
Total	47,581 (44,217−50,946)	15,944 (15,385−16,504)	31,637 (28,220−35,054)[a]
Hospital	5,574 (4,586−6,562)	2,543 (2,316−2,770)	3,031 (2,009−4,053)[a]
ED	7,532 (6,490−8,574)	3,855 (3,607−4,103)	3,677 (2,591−4,764)[a]
Skilled nursing facility	2,266 (1,689−2,842)	1,411 (1,284−1,538)	855 (274−1,435)[a]
Outpatient services	6,685 (5,840−7,530)	1,561 (1,473−1,649)	5,124 (4,280−5,968)[a]
Physician services	8,061 (7,306−8,816)	2,873 (2,786−2,961)	5,188 (4,422−5,953)[a]
Prescription drugs	14,026 (11,530−16,522)	2,279 (2,160−2,398)	11,747 (9,258−14,237)[a]

(*continued on next page*)

Table 5 (***Continued***)

	RCC (mean, 95% CI)	Noncancer (mean, 95% CI)	Incremental cost (mean, 95% CI)
DME	279 (200−357)	246 (225−268)	32 (−46 to 111)
Hospice care	2,457 (1,877−3,036)	580 (493−667)	1,877 (1,298−2,455)[a]
Home health	1,374 (990−1,387)	695 (648−741)	680 (448−912)[a]
Stage unknown (*n* = 10,986)	(*n* = 594)	(*n* = 10,392)	
Total	27,579 (24,562−30,597)	15,944 (15,385−16,504)	11,635 (8,559−14,712)[a]
Hospital	4,259 (3,172−5,347)	2,543(2,316−2,770)	1,716 (598−2,835)[a]
ED	6,323 (5,237−7,409)	3,855 (3,607−4,103)	2,468 (1,352−3,585)[a]
Skilled nursing facility	2,614 (1,936−3,291)	1,411 (1,284−1,538)	1,203 (514−1,892)[a]
Outpatient services	3,002 (2,470−3,534)	1,561 (1,473−1,649)	1,441 (903−1,979)[a]
Physician services	4,506 (4,046−4,967)	2,873 (2,786−2,961)	1,633 (1,165−1,984)[a]
Prescription drugs	3,865 (2,573−5,157)	2,279 (2,160−2,398)	1,586 (278−2,895)[a]
DME	301 (217−384)	246 (225−268)	54 (−32 to 140)
Hospice care	1,337 (834−1,839)	580 (493−667)	757 (251−1,262)[a]
Home health	849 (661−1,037)	695 (648−741)	155 (−-41 to 350)

CI = confidence interval; DME = Durable medical equipment; ED = Emergency department; RCC = renal cell carcinoma.

[a] Statistically significant differences, $P < 0.05$; DME = Durable medical equipment; ED = Emergency department. Regression models controlled for age, sex, race, SEER region and NCI Comorbidty Index.

Table 6
Results from sensitivity analyses.

	Incremental cost per patient (US $)				Total economic burden (US $)			
	Any stage	Change from base case	Stage IV	Change from base case	Any stage	Change from base case	Stage IV	Change from base case
Base case	**7,419**	**NA**	**31,637**	**NA**	**1.51 billion**	**NA**	**1.03 billion**	**NA**
Including potential outliers	7,330	−1.20%	31,458	−0.6%	1.50 billion	−1.20%	1.03 billion	−0.6%
Excluding NCI comorbidity index score from matching	10,770	+45.17%	34,880	+10.25%	2.20 billion	+45%	1.14 billion	+10.25%
Excluding covariates from the regression after matching	7,274	−1.95%	31,013	−1.97%	1.49 billion	−1.95%	1.01 billion	−1.97%
GLM with log link and Gamma distribution	7,739	+4.31%	31,235	−1.27%	1.58 billion	+4.31%	1.02 billion	−1.27%

GLM = generalized linear model; NA = not applicable; NCI = National Cancer Institute.

used frequency matching on demographics; we used propensity scores calculated using patient demographics and the NCI Comorbidity Index. In a sensitivity analysis, matching only on demographics resulted in a cost estimate ($10,770) similar to that from Shih et al. [18]. In addition, while approval of targeted therapies may have resulted in an increase in THC for stage IV patients, uptake of less invasive surgical procedures and active surveillance among early stage patients could have resulted in lower healthcare costs.

The pattern of THC by phases of care suggested that THC was higher in the initial and late phases of care than in the continuing phase. During the initial phase patients often undergo screening and monitoring and begin cancer-related treatment; while during the late phase they may receive aggressive treatment or palliative care. THC was lowest in the continuing phase, a phase where patients often have remission and require minimal follow-up care [18,23].

In our study, the costs among mRCC patients were about 6-7 times higher than patients diagnosed at stages I and II. Additionally, the average cost for stage IV patients was approximately $28,000 more than for early stage patients. In contrast, during the cytokine era, 1-year cost among patients with distant metastasis was only $4,482 higher (2 times higher) than the cost for patients with localized disease [3]. Thus, our findings suggest higher costs for stage IV patients in the targeted therapy era. For patients diagnosed at stage I to III, hospital cost was the largest component (~40%) of THC. Higher costs related to hospital use may indicate the use of nephrectomy and local therapies which are primarily used to treat early stage, localized tumors, and may require hospitalization. Services provided by physicians in hospitals and noninstitutional offices were the next largest components of THC. THC among stage III patients was about 2 times higher than costs for stages I and II, which could be due to advanced disease and aggressive treatment. In contrast to patients diagnosed at stage I and II, prescription drug costs among those diagnosed at stage III were significantly higher than control patients. This could be due to the use of systemic therapy in patients with recurrent disease or adjuvant use after nephrectomy. For stage IV patients, prescription drug costs accounted for 36% of THC, which suggest the use of high-cost targeted therapies and medications given to control complications arising at the site of metastasis. In addition to prescription drugs, costs associated with ED, HS care, and SNF use were much higher for mRCC patients than patients with earlier stages, which suggests the extensive use of these services among stage IV patients due to their severe form of disease.

This study has several limitations. We used PSM to make RCC and control groups similar in patient characteristics. However, we could not match or control for performance status, comorbidities not included in the NCI Comorbidity Index and lifestyle factors as they were not observed in SEER-Medicare database. Therefore, some differences between the RCC and control group may still persist, which may result in overestimation of incremental costs. It is possible, for example, that the controls were less likely to receive specialty and hospital care as a result of these differences. Second, while projecting the economic burden to Medicare, we assumed that patients on managed care plans have the same costs as patients from fee-for-service plans. While it was necessary to exclude patients from managed care plans due to unavailability of their Part A and Part B claims in the SEER-Medicare data, average costs among managed care patients may differ from those of patients on fee-for-service plans. This may result in under or over-estimation of the total economic burden. Due to unavailability of the data after 2013, the study did not include newer targeted therapies such as cabozantinib, approved in 2016. The SEER data measures cancer stage only at the time of first cancer diagnosis. Hence, the prevalence of RCC by stage was calculated based on the initial staging information, which may not be the most recent staging information. It is therefore possible that we underestimated prevalence and total economic burden of mRCC. Last, the use of administrative claims and registry data are subject to miscoding errors.

This study did not focus on out of pocket costs and financial problems faced by patients and their family members, which can be substantial among RCC patients. Several studies have reported negative consequences of cancer-related financial burden on health-related quality of life and psychological wellbeing [32–34]. Future studies could assess these issues in RCC population especially in the era of high-cost targeted and immunotherapies. Despite these limitations, this study provided important information on the economic burden of RCC and drivers of THC for patients diagnosed at various stages. Findings from this study may help in resource allocation by Medicare. Further, several targeted and immunotherapies have been approved recently to treat RCC. This study provides a baseline that can be used to evaluate the value of emerging therapies among older RCC patients.

Conflict of interest statement

Authors have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.016.

References

[1] American Cancer Society. Cancer Facts & Figures. 2017 https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf.

[2] American Cancer Society *Cancer Facts & Figures 2016*. Atlanta, GA:2016 Accessed December 1, 2016.
[3] Hollenbeak CS, Nikkel LE, Schaefer EW, Alemao E, Ghahramani N, Raman JD. Determinants of medicare all-cause costs among elderly patients with renal cell carcinoma. J Manag Care Pharm 2011;17:610–20.
[4] NCCN Clinical Practice Guidelines in Oncology- Kidney Cancer. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed December 5, 2016.
[5] Banegas MP, Harlan LC, Mann B, Yabroff KR. Toward greater adoption of minimally invasive and nephron-sparing surgical techniques for renal cell cancer in the United States. Urol Oncol 2016;34(433):e9433.
[6] Hutson TE, Quinn DI. Cytokine therapy: a standard of care for metastatic renal cell carcinoma. Clin Genitourin Cancer 2005;4:181–6.
[7] Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289–96.
[8] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
[9] Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449–56.
[10] Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–81.
[11] Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061–8.
[12] Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. J Clin Oncol 2017;35:591–7.
[13] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803–13.
[14] Hammers HJ, Plimack ER, Sternberg C, McDermott DF, Larkin JMG, Ravaud A, et al. CheckMate 214: a phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol Suppl 2015:Available from https://meetinglibrary.asco.org/record/115193/abstract. Accessed March 26, 2018.
[15] Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008;34:193–205.
[16] Lang K, Danchenko N, Gondek K, Schwartz B, Thompson D. The burden of illness associated with renal cell carcinoma in the United States. Urol Oncol 2007;25:368–75.
[17] Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 2011;103:117–28.
[18] Shih YC, Chien CR, Xu Y, Pan IW, Smith GL, Buchholz TA. Economic burden of renal cell carcinoma in the US: Part II−an updated analysis. Pharmacoeconomics 2011;29:331–41.
[19] Shih YC, Chien CR, Xu Y, Pan IW, Smith GL, Buchholz TA. Economic burden of renal cell carcinoma: part I−an updated review. Pharmacoeconomics 2011;29:315–29.
[20] Geynisman DM, Hu JC, Liu L, Tina Shih YC. Treatment patterns and costs for metastatic renal cell carcinoma patients with private insurance in the United States. Clin Genitourin Cancer 2015;13:e93–100.
[21] SEER-Medicare: SEER program & Data. Available at: https://healthcaredelivery.cancer.gov/seermedicare/aboutdata/program.html. Accessed December 14, 2016.
[22] SEER Fact Sheets and Brochure. Available at: https://seer.cancer.gov/about/factsheets/SEER_brochure.pdf. Accessed December 15, 2016.
[23] Mariotto AB, Robin Yabroff K, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010−2020. J Natl Cancer Inst 2011;103:117–28.
[24] Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst 2008;100:630–41.
[25] Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques *SUGI 26 proceedings*. 2001:Paper 214-26. Available from: http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed November 1, 2017.
[26] Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Med Decis Making 2009;29:661–77.
[27] Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J 2011;32:1704–8.
[28] Adjusted AJCC 6th ed. T, N, M and Stage criteria. Available at: https://seer.cancer.gov/seerstat/variables/seer/ajcc-stage/6th/. Accessed December 15, 2016.
[29] Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.4.
[30] ProjPrev, Version 1.0.4. June 2017; Data Modeling Branch, National Cancer Institute.
[31] Archived Consumer Price Index Detailed Reports. Available at: https://www.bls.gov/cpi/tables/detailed-reports/home.htm#. Accessed December 10, 2017.
[32] Kale HP, Carroll NV. Self−reported financial burden of cancer care and its effect on physical and mental health−related quality of life among US cancer survivors. Cancer 2016;122:283–9. https://doi.org/10.1002/cncr.29808.
[33] Park J, Look KA. Relationship between objective financial burden and the health-related quality of life and mental health of patients with cancer. J Oncol Pract 2018;14(2):e113–21 https://doi.org/10.1200/JOP.2017.027136.
[34] Casilla-Lennon M, Choi S, Deal A, et al. Financial toxicity among patients with bladder cancer: reasons for delay in care and effect on quality of life. J Urol 2018;199(5):1166–73.