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HEALTH OUTCOMES AND UTILIZATION ASSOCIATED WITH RENAL DISEASES IN PATIENTS WITH CANCER IN THE UNITED STATES

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HEALTH OUTCOMES AND UTILIZATION ASSOCIATED WITH RENAL DISEASES IN PATIENTS WITH CANCER IN THE UNITED STATES

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DEDICATION

This research is dedicated to Mom, Dad and my brother Krishi. Thank you for encouraging me to go on every adventure, especially this one.

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LIST OF ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
AKI	Acute kidney injury
ARF	Acute Renal Failure
CI	Confidence Intervals
CKD	Chronic kidney disease
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage renal disease
FPL	Federal poverty line
HRQoL	Health related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
KDQOL	The Kidney Disease Quality of Life survey
MCS	Mental component summary score
MEPS	Medical Expenditure Panel Survey
OR	Odds Ratio
PCS	Physical component summary score
RD	Renal Dialysis
RI	Renal Impairment
SF-12v2	Short Form Health Survey-12 version two

ABSTRACT

Background: Adverse events and impairments associated with cancer and its treatments causes worse outcomes. Increased incidence of renal diseases among cancer patients is of particular concern. **Objective:** To determine the risk factors for renal disease in cancer patients and compare healthcare costs, utilization and health-related quality of life (HRQoL) of cancer patients with a renal disease and cancer patients without renal diseases. **Methods:** Medical Expenditure Panel Survey files from 2009 – 2018 for cancer patients was used for this study. Multiple logistic regression, generalized linear model, Poisson regression and multiple linear regression for analyses after adjusting for demographic, socioeconomic and clinical factors. Healthcare costs and utilization were determined in propensity score matched cohorts. **Results:** Renal disease was present in 16% of cancer patients in United States. Cancer patients with renal disease had higher adjusted mean healthcare expenditure from all sources of payments for office-based visits to a provider ($7,881 vs $5.683), prescription medicines ($11,068 vs $6,764), total medical cost ($37,283 vs $22,403) as compared to cancer patients without renal diseases. Cancer patients with renal disease had higher median prescriptions filled (89 vs 57) and office-based visits to a physician (31 vs 21), higher PCS scores (40.52 vs 45.25) and MCS scores (50.31 vs 51.37). **Conclusion:** Cancer patients with renal disease had higher healthcare expenditure, resource utilization and worse health-related quality of life than cancer patients without renal disease, emphasizing the need of targeted care towards cancer patients with renal disease to have better health outcomes.

Chapter 1: BACKGROUND

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States.[1] In 2018, 21% of the deaths recorded in the United States were attributed to cancer.[2] In 2021, it is estimated that prostate, lung and colorectal cancers will account for 46% of all incident cases in men, with prostate cancer alone accounting for 26% of diagnoses. For women, breast cancer, lung, and colorectal cancers will account for 50% of all new diagnoses, with breast cancer alone accounting for 30% of female cancers.[2] Cancer survivors are projected to increase from 16.9 million people in 2019, to 22.2 million people in 2030.[3] The 5-year survival rates from 2010 to 2016 was highest for prostate cancer (98%), melanoma of the skin (93%), and female breast cancer (90%) and lowest for cancers of the pancreas (10%), liver (20%), esophagus (20%), and lung (21%).[4] The 5-year survival of cancer patients has increased from 35% in 1950-1954 to 67.4% in 2010-2016.[4] The increase in survival rate can be attributed to factors like early detection practices, advances in curative therapy, increased life expectancy and growth of an aging population.[2] The consequences of increased survival include increasing complications associated with the disease process.[5]

The economic burden of adverse events and complications in cancer patients is substantial.[6-10] The Agency for Healthcare Research and Quality's (AHRQ) Medical Expenditure Panel Survey estimated that for 2017, the direct medical costs for cancer, including all health care expenditures, were $105.5 billion, of which 52% was spent on hospital outpatient or office-based provider visits, 23.2% on inpatient hospital stays, and 19.6% on prescription medications.[11] Financial hardship can lead to lower quality of life, increased pain and greater symptom burden.[12-13] Due to treatment or disease burden, cancer patients have lower quality of life due

to physical symptoms like fatigue, pain, and nausea and vomiting, psychological symptoms like anxiety and depression, and limitations and difficulty in performing daily activities.[14]

Cancer treatments include systemic therapies such as chemotherapy, targeted therapy and immunotherapies. These therapies are used alone or in combination with localized therapies such as surgeries, radiation, heat or chemical ablation. Cancer therapies are effective but long-term cancer treatments can cause adverse effects and complications like anemia, nausea, vomiting, neurotoxicity, nephrotoxicity.[15,16] Management of adverse events and impairments associated with cancer and its treatment is important because they influence adherence to cancer therapies and quality of life.[17] Increased incidence of kidney diseases among patients with cancer is of particular concern because a decrease in renal function often requires dose adjustment which may include decreasing the dose or stopping the use of certain chemotherapeutic agents. This may delay or reduce the overall effectiveness of the cancer treatment. Several mechanisms may underlie the high rate of renal disease in cancer patients including drugs required to treat the malignancy and the nature of underlying disease causes cancer patients to more likely to have renal diseases.[18-22,]

1.1 DRUG-INDUCED NEPHROPATHY

Kidneys are the main site of drug elimination for metabolites of systemic therapies. Hence, they are exposed to high concentrations of metabolites of systemic therapies. Systemic therapeutic agents such as ifosamide, tyrosine kinase inhibitors, premetrexed, cisplatin have been associated with tubular toxicity.[23] Nephrotoxicity of cisplatin, gemcitabine, mitomycin and bevacizumab manifests as a glomerular disease in cancer patients as thrombotic micoangiopathy.[24-26] Immune checkpoint inhibitors like pembrolizumab and nivolumab causes

acute injury.[83] Electrolyte abnormalities are caused by cetuximab, panitumumab, imatinib[27-30] supportive care drugs like pain medications, antibiotics, antihistamines, antivirals, antacids, bisphosphonates have been established to have some degree of nephrotoxicity.[18] Chemotherapeutic drugs also cause nausea, vomiting, diarrhea and poor oral intake. These adverse events cause volume depletion.[19]

1.2 LOCALIZED THERAPY ASSOCIATED KIDNEY DISEASE

Radiotherapy is often used in adjuvant to systemic therapies. Radiation has been associated with renal injury. However due to long latency for radiotherapy induced kidney injury and high prevalence of confounding factors, the magnitude of the effect of radiotherapy is unclear.[31] Obstruction of the urinary tract by malignancy can occur due in patients with genitourinary cancer. Renal cell carcinoma is a common genitourinary malignancy. Patients are commonly recommended for a partial and radical nephrectomy. Evidence suggests that these surgeries increase the risk of AKI in short term and chronic kidney disease (CKD) both in long term.[32]

1.3 INDIRECT CAUSES OF RENAL DISEASE

Antitumor activities of novel target therapies increase the risk of patients experiencing tumor lysis syndrome. Tumor lysis syndrome leads to formation of uric acid crystals which causes renal damage.[20] Apart from this, tumor lysis syndrome also causes an imbalance of acid-base and electrolytes in the bloodstream which affects kidneys. Patients with cancer are at a higher risk for infections due to alterations in innate and adaptive immunity from the malignancy and aggressive cancer therapies. 2.3 million hospital bed days and $3 billion were attributed to infections in cancer patients and it is estimated to increase to 3.4 million hospital bed days and

$4.5 million expenditure.[33] Cancer patients are 10 times more likely to develop sepsis compared to the general population.[34] 20% of ICU admissions are cancer patients with sepsis being the leading reason of admission. These complications increase the length of stay and overall costs. Evidence suggests that AKI occurs in 19% of patients with moderate sepsis, 23% with severe sepsis and 51% with septic shock.[35–37] Previous literature has also suggested a link between cardiovascular and renal disease where both have common risk factors. Patients with CKD have a high prevalence of hypertension.[21] Hepatorenal syndrome is another risk factor which causes pre-renal AKI. [22]

Common renal diseases in cancer patients include acute kidney injury and chronic renal disease. Membranous Nephropathy is the most common type of renal disease associated with solid tumors.[38] IgA nephropathy, membranoproliferative glomerulonephritis and extra capillary glomerulonephritis have also been reported, in case studies although less commonly than other renal diseases mentioned previously.

With newer therapies which improve the overall survival of cancer patients, long-term management of patients who develop renal diseases from their cancer treatment is essential. Decrease in renal function often requires a dose adjustment which may include decreasing the dose or stopping the use of certain chemotherapeutic agents which may delay or reduce the overall effectiveness of the cancer treatment. This emphasizes the need for early detection and intervention to alleviate the cause of renal disease. Studies in non-cancer patients with renal diseases have shown longer hospitalization, increased hospital costs and lower quality of life.[39] Cancer and CKD are the costliest conditions for Part B Medicare beneficiaries and evidence suggests that presence of renal disease in cancer patients increases length of stay, and

mortality.[40-42] We hypothesize in our study that cancer patients with renal disease would also have higher healthcare utilization, expenditure and lower quality of life than cancer patients who do not have renal disease.

Chapter 2: LITERATURE REVIEW

A literature review was conducted to identify research articles which assesses the economic burden and quality of life associated with renal disease in cancer patients. The review and search were carried out in May 2020 in PubMed and CINAHL with a combination of keywords and MeSH terms. The search query used was a combination of: “Kidney Diseases” [Mesh], “Nephrotoxic*”, “Kidney toxic*”, “Renal toxic*”, "Observational Studies as Topic"[Mesh] “Cohort Studies” [Mesh], “Observational Study” [Publication Type], “Neoplasms” [Mesh], “Cancer*”, “malignan*”, “carcinoma*”, “metastat*” and “tumour*”. Titles and abstracts were screened. The following inclusion and exclusion criteria were applied:

Inclusion Criteria:

1) Studies conducted in cancer patients over 18 years of age
2) Studies with specific renal outcomes

Exclusion Criteria:

1) Case reports and reviews
2) Studies where renal disease is a post-surgery complication
3) Studies which built and validated predictive models
4) Studies which tested interventions to treat renal diseases
5) Studies not conducted in United States

1,148 articles were retrieved from the database and their titles and abstracts were read and 1,131 articles were excluded based on the exclusion criteria. The full-texts of remaining articles were accessed and read for including only eligible articles in the review. After reading the full texts, 7 articles were excluded based on the exclusion criteria and 10 articles were selected for

the final review.[43-52] These 10 articles are summarized in Table 1 which includes 7 articles with the objective of estimating risk factors associated with renal diseases and 3 articles which aim at estimating healthcare utilization and expenditure associated with renal diseases.

Figure 1: PRISMA flowchart for Literature Review

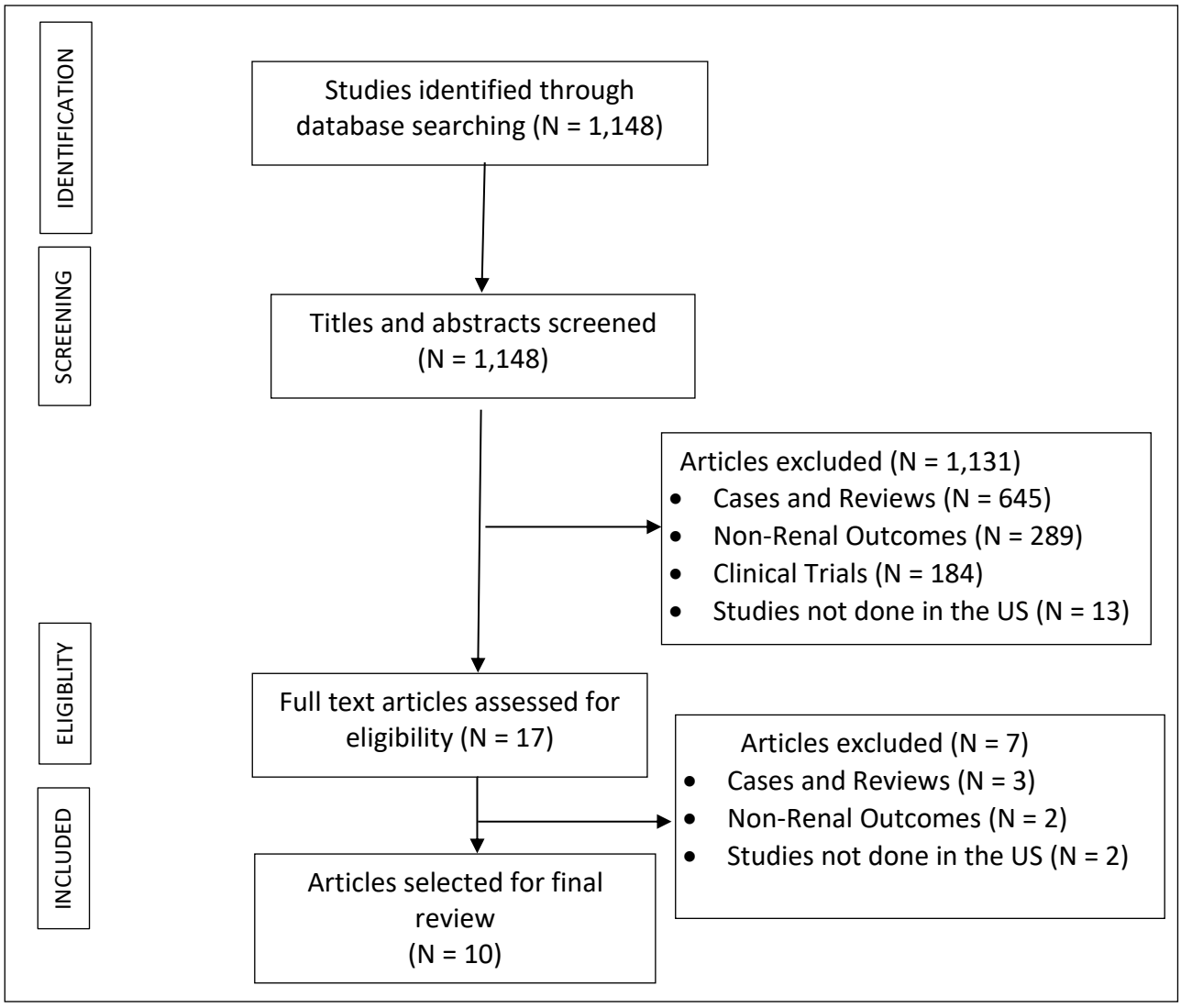


Table 1: Literature from PUBMED and CINAHL summarized

SR. NO	AUTHORS	OBJECTIVE	SAMPLE POPULATION	RESULTS
STUDIES ASSESSING RISK AND PREVALENCE				
1	Li et al. [43]	To examine the association between adjuvant chemotherapy and acute kidney injury (AKI)	Elderly Medicare enrollees with newly diagnosed early-stage breast cancer	Chemotherapy treated patients are 2.73 times more likely to have AKI than untreated patients. Incidence of AKI: Taxane > Other > Anthracycline > Cyclophosphamide/Methotrexate/5-Fluorouracil
2	Lahoti et al.[44]	To estimate the incidence of AKI and to evaluate therisk factors for AKI	Patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome(HR-MDS) undergoing induction chemotherapy	no AKI – 64%; Risk – 15%; Injury – 10%; Failure – 11%
3	Arellano et al.[45]	To estimate the prevalence of renal impairment and chronic kidney disease (CKD)	Patients with bone metastases from solid tumors	5-year prevalence of RI - 43%. 46% CKD patients received intravenous bisphosphonates in the 12 months following their confirming eGFR. 13% of these patients received at least one other nephrotoxic agent during that period
4	Huang et al.[46]	To assess kidney function outcomes	Patients undergoing surgery for renal cortical tumor in cancer center	Patients who underwent radical nephrectomy had a higher risk (3.82 times) of CKD than those who underwent partial nephrectomy
5	Qian et al. [47]	To estimate the prevalence of renal impairment and chronic kidney disease	Patients with multiple myeloma	6-month prevalence after multiple myeloma diagnosis: RI – 47%, CKD – 27% 12 months after multiple myeloma diagnosis: RI – 54%, CKD – 39%
6	Salahudeen et	To determine incidence rate,	Hospitalized patients with cancer	12% of the admitted patients had AKI; Risk – 68%, Injury – 21%, Failure – 11%. Length

	al.[48]	clinical correlates, and outcomes of AKI		of stay (100%), cost (106%) and odds of mortality(4.7-fold) was significantly greater
7	Lahoti et al.[49]	To estimate the incidence, outcomes, and costs associated with AKI	Hospitalized patients with cancer	AKI – 12.6%; risk – 6%; injury – 3%; failure – 4%; Each percent increase in serum creatinine was associated with a 0.16% increase in cost
STUDIES ASSESSING HEALTHCARE UTILIZATION AND EXPENDITURE				
8	Qian et al.[50]	To estimate healthcare resource use and costs associated with RI	Patients with bone metastases from solid tumors	Outpatient services (38.4 vs 26.7); Emergency dept visits (6.8 vs 3.9); Hospital admission ($72,557 vs $27,858); Total healthcare cost ($142,267 vs $88,839)
9	Bhowmik et al.[51]	To estimate healthcare resource use and costs associated with CKD	Patients with multiple myeloma	No. of patients with an admission (57.1% vs 32.1%); Frequency of prescription fills (90.2 vs 66.9); Office visits (35.7 vs 30.1); Frequency of Laboratory services (96.9 vs 66.4); Total healthcare cost ($106,634 vs $71,880);
10.	Candrilli et al.[52]	To compare inpatient length of stay and costs	Hospitalized patients with hematologic malignancies	ARF and RD - $44,619; ARF and no RD - $25,638; no ARF and no RD - $13,947

ARF – Acute Renal Failure; RD – Renal Dialysis; AKI – Acute Kidney Injury; CKD – Chronic Kidney Disease; RI – Renal Impairment; eGFR – estimated Glomerular Filtration Rate;

STUDIES ASSESSING RISK AND PREVALENCE

A study by Li et al. examined the association between adjuvant chemotherapy and acute kidney injury in elderly Medicare enrollees who were newly diagnosed with early-stage breast cancer.[43] They used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare

database and found that after adjusting for baseline characteristics, adjuvant chemotherapy increased the risk of AKI by almost 3 times (HR = 2.69). They also found that AKI risk was highest for patients who received only taxane-based chemotherapy (which included docetaxel or paclitaxel) with a 6-month cumulative incidence of AKI of 2%. The risk was lower in patients who received only anthracycline-based chemotherapy (0.7%) (included doxorubicin and epirubicin) and only CMF regimen (0.5%) (included cyclophosphamide, methotrexate, and 5-fluorouracil).

The study by Lahoti et al. was done for patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome who had developed AKI.[44] They found that 36% of patients had developed AKI (defined as >100% increase in serum creatinine).

The study by Arellano et al. in patients who had solid tumor metastasized to bones.[45] They found that 43% of the patients developed renal impairment (defined as at least one eGFR value <60 mL/min per 1.73 m^2). CKD prevalence (defined as at least 2 eGFR values <60 mL/min per 1.73 m^2, at least 90 days apart) was found to be 35% in this patient population. Pamidronic and zoledronic acids are intravenously administered bisphosphonates used to prevent bone complications which are also nephrotoxic. They also found that 46% of the CKD patients had received these intravenously administered bisphosphonates in the 12 months following their confirming eGFR.

In patients with renal cancer, one of the common treatment options is nephrectomy. Huang et al. found that the 3-year probability of not having a CKD (defined as GFR lower than 60 mL/min per 1·73 m^2) was 80% after partial nephrectomy and 35% after radical nephrectomy.[46]

Qian et al suggests that 47% of patients developed renal impairment and 27% of patients

developed chronic kidney disease, 6 months after multiple myeloma diagnosis.[47] 54% of patients developed renal impairment and 39% of patients developed chronic kidney disease 12 months after multiple myeloma diagnosis.

Salahudeen et al. examined cancer patients admitted to the hospital.[48] They found that 12% of cancer patients had AKI (defined as a two-fold increase in serum creatinine or >50% decrease of eGFR). Diabetes, chemotherapy, hyponatremia, antibiotic therapy, intravenous contrast and transfer to the ICU were found to be significant predictors of developing AKI in hospitalized patients. The median length of hospital stay was 10 days for patients with AKI and 5 days for patients with AKI. Similarly, the hospital bill was significantly higher in patients with AKI ($82,835) than patients without AKI ($40,164).

Another study by Lahoti et al. in hospitalized cancer patients found the incidence rate of AKI (defined as a two-fold increase in serum creatinine or >50% decrease of eGFR) in cancer patients admitted to the ICU to be 12.6% for AKI where 6% were at risk, 3% with injury and 4% with failure.[49] They also found that each percent increase in serum creatinine was associated with a 0.16% increase in cost.

STUDIES ASSESSING HEALTHCARE UTILIZATION AND EXPENDITURE

Qian et al. estimated the healthcare resource use and cost associated with renal impairment (RI) in patients with bone metastases from primary tumor using an administrative claims database.[50] They found that total healthcare cost was $142,267 in patients with RI vs $88,839 in patients without RI. Frequency of outpatient services used in patients with RI was 38.4 as compared to 26.7 in patients without RI. Frequency of other service (emergency department

visits, hospital admissions) used was also greater in the cohort with RI.

Similar results were found by Bhowmik et al. who looked at healthcare resource use and cost for CKD in multiple myeloma patients using an administrative claims database.[51] They found overall the healthcare resource use (including number of patients with an admission, frequency of prescription fills, frequency of office visits and laboratory services) and cost (total, hospital, outpatient cost) was significantly higher in patients with CKD than patients without CKD.

The study by Candiril et al, was done in cancer patients with hematological malignancy hospitalized with acute renal failure (ARF).[52] They suggested that patients with hematologic malignancy and ARF who require renal dialysis had the highest mean total cost ($44,619) compared to patients with hematologic malignancy with ARF who do not require renal dialysis ($25,638) and patients with hematologic malignancy who have no renal complications or do not require renal dialysis ($13,947). Similarly, mean length of stay was highest for patients with hematologic malignancy who had ARF and required renal dialysis (17.6 days) compared to patients with hematologic malignancy who had ARF and did not require renal dialysis (12.2 days) and patients with hematologic malignancy who have no renal complications or do not require renal dialysis (7.4 days).

Chapter 3: GAPS IN LITERATURE

Six out of ten studies reviewed have been done in a single cancer center or a hospital with electronic health records.[44-49,52] The results of these studies could not be generalizable to the US population. The healthcare utilization studies done by Bhowmik et al. and Qian et al. were done with an administrative claims database.[50,51] The results of these studies could not be generalizable to individuals who are uninsured or individuals with only Medicare or Medicaid. The healthcare utilization study done by Lahoti et al. was limited to one cancer center and did not document utilization and expenditure well.[49] The study by Li et al. was done at a population level however it was limited to women above 65 years who were enrolled with Medicare and had an early-stage breast cancer diagnosis.[43] None of the studies evaluated the socioeconomic and clinical risk factors of renal disease in cancer patients which are not limited to a single cancer type.

Another gap is that none of the prior studies assessed health-related quality of life of this patient population. Cancer patients with renal disease are vulnerable to adverse effects of cancer therapies and this cohort of patients are usually excluded from clinical trials.[53] Hence there is a need to assess the health-related quality of life in this patient population.

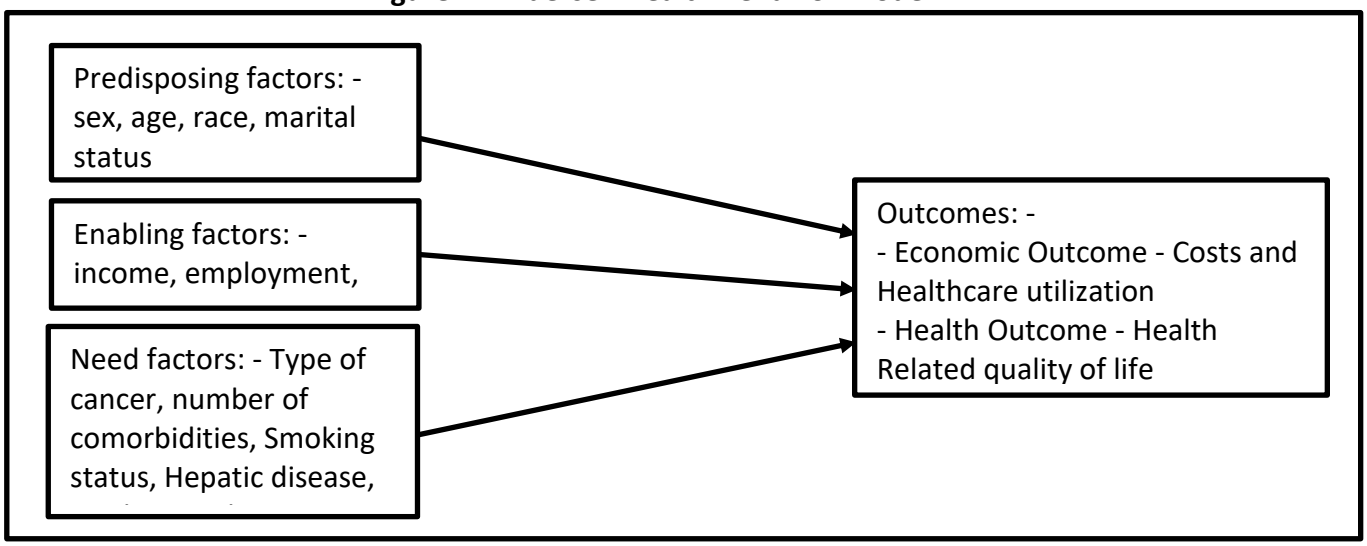
Chapter 4: RATIONALE

Except Li et al., none of the previous studies calculates the propensity to have a renal disease in cancer patients at a population level.[43] The study by Li et al. was limited to older women with breast cancer patients at population level. This would be the first study at population level which controlled for sociodemographic, economic and clinical factors. The results of this study could be used by clinicians to incorporate care for individuals who have a higher propensity to develop renal diseases. There have been studies assessing the expenditures and utilization associated with renal disease in cancer patients in the US, however they were limited to one cancer center or to patients who were commercially insured.[49-51] Our study would address this limitation by including patients with all types of insurance and uninsured individuals. Our study would also include individuals with all cancer types, thus increasing generalizability. There have been no studies which assess the health-related quality of life in cancer patients with comorbid renal diseases. Previous studies have shown that patients with renal diseases have worse health related quality of life, however this has not been proven in cancer patients. [54,55] Our study uses a nationally representative database which is generalizable to the US population to assess the health-related quality of life while controlling for sociodemographic, economic and clinical factors.

Chapter 5: CONCEPTUAL FRAMEWORK

We used the Andersen Health Behavioral Model which is widely accepted as a reliable tool for the study of health services utilization.[56] According to the Andersen model, as shown in Figure 2, health service utilization is a sequential and conditional function of three sets of factors: predisposing (demographic and social) factors, enabling (economic) factors, and need (clinical) factors. Predisposing factors like age, race etc. reflects an individuals' likelihood to use health services. Enabling factors like income, employment and education are the resources that facilitate access to services and need factors represent perceived and actual needs of health service use, such as self-perceived health status and comorbid chronic conditions.

Figure 2: Andersen Health Behavior Model



Chapter 6: SPECIFIC AIMS

AIM 1: To characterize the sociodemographic, economic and clinical characteristics of cancer patients with renal diseases in the US civilian non-institutionalized population

AIM 2: To compare healthcare costs and utilization of cancer patients with renal diseases and cancer patients without renal diseases in the US civilian non-institutionalized population

AIM 3: To compare health-related quality of life (HRQoL) of cancer patients with renal diseases and cancer patients without renal diseases in the US civilian non-institutionalized population

Chapter 7: SPECIFIC AIM 1

The first aim of our study was to examine the prevalence and predictors of renal disease in cancer patients. We studied sociodemographic, economic and clinical characteristics of cancer patients with renal diseases in the U.S. civilian non-institutionalized population. We hypothesized that certain characteristics would differ significantly between the group of cancer patients with renal disease and the group of cancer patients without renal disease. We also hypothesized that certain characteristics would be significantly associated with likelihood of having a renal disease in cancer patients.

7.1 METHODS

STUDY DESIGN

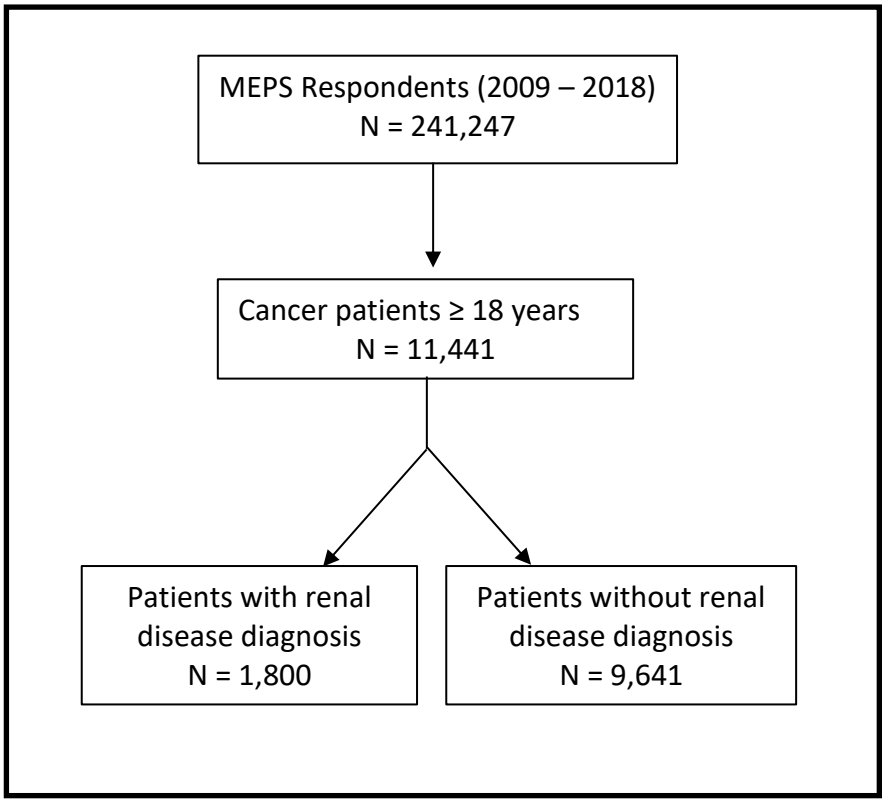
This study was designed as a retrospective, cross-sectional study using Medical Expenditure Panel Survey (MEPS).[57] A sample of families and individuals across the United States were interviewed for five rounds that covers two years. The data from the interviews was collected and compiled into a publicly available dataset. We used data from the interviews conducted from January 2009 to December 2018 for our study. We used the Household Component (HC) of MEPS which provides data about demographics, health services, charges and expenditures, etc. The files were downloaded and merged for this study to improve the sample size.

STUDY SAMPLE

We identified individuals for our sample using the Medical Conditions files of MEPS. Cancer patients from 2016 to 2018 were identified from ICD-10 codes (Table 1 of Appendix) and patients were identified from 2009 to 2015 from ICD-9 codes (Table 2 of Appendix).[58,59] Renal disease diagnosis was identified from the Medical conditions files of 2016 to 2018 using ICD-10 codes from "N00" to "N39" (Table 3 of Appendix).[60] ICD-9 codes from "580" to "599" (Table 4 of Appendix) was used for renal disease diagnosis from the Medical Conditions files of 2009 to 2015.[61] The Medical Condition files are event level files and hence after identifying the medical conditions associated with renal disease or cancer, the files were transposed to person-level files in SAS using PROC TRANSPOSE. After transposing, each person was identified as a patient with either renal disease or cancer or both or none. Figure 3 shows the sample selection process. There were 241,247 individuals who responded to MEPS from 2009 to 2018 of which 11,441 patients were

patients with cancer who were above the age of 18. Out of 11,441 cancer patients, 1,800 reported a diagnosis of renal disease and 9,641 did not report a diagnosis of renal disease.

Figure 3: Flow chart of sample size after inclusion and exclusion criteria for cancer patients using Medical Expenditure Panel Survey (2009 – 2018)



VARIABLES

Sociodemographic, economic information including sex, age, race, education, income, employment, marital status and census region were obtained from the full year consolidated files. Sex was directly used from MEPS which was coded as "Male" and "Female". Age was a continuous variable which was categorized as 18-44 years, 45 – 65 years, and above 65 years which was consistent with previous study.[75] Race was recoded as a new variable which indicated "White", "Black" and "Other races". Other races included individuals who identified as American

Indian, Asian, Native Hawaiian, Pacific Islander and Multiple Races. Marital status was recoded into 3 categories as “Married”, “Never Married” and “Widowed/Divorced/Separated”. Education was recoded to a new variable which indicated “No School or less than High School”, “High School” and “College and above”. Census region was used without recoding and labelled as “Northeast”, “Midwest”, “South” and “West”. Income was a continuous variable in MEPS and was recoded into more meaningful categories as “Low Income”, “Middle Income” and “High Income”. The income variable was recoded based on a previous study where low income was defined as 100% below the Federal Poverty Line (FPL). In 2021, the FPL for a single person was $12,880 and hence low income was defined as an income less than $12,880.[62] Middle income was defined as an income between 100-400% of FPL, i.e., between $12,880 and $51,520 and high income was defined an income above 400% of FPL, i.e., $51,520 and above. Insurance was used without change and labelled as “Private”, “Public” and “Uninsured”. Employment was recoded into a new variable which represented 2 categories “Employed” and “Unemployed”. Smoking status was recoded into a new variable which represented “Smoker” and “Non-smoker”. Perceived health status was recoded into a new variable which represented “Excellent”, “Very Good”, “Good”, “Fair” and “Poor”. A new categorical variable was created to indicate the number of comorbidities a cancer patient would have. Several chronic conditions such as diabetes, asthma, arthritis, hypertension, hypercholesterolemia have been causally associated with an increased risk of cancer and hence they were used to count the number of comorbidities.[63-67] Categorical variables which depicted whether a patient had a cardiovascular disease and hepatic disease were also used in the analyses. These variables were created from ICD-9 and ICD-10 codes of the Medical Condition files.

Apart from the covariates, complex survey variables were also used in selected analyses to have unbiased estimates which would account for the survey design and survey non-response.[68] Complex survey variables included a pooled person-level weight, variance estimation primary sampling unit and a sampling stratum required for variance estimation. Since this study spans over 10 years, the pooled person-level weight was calculated by dividing the person-level weight by 10.

The outcome variable for this aim was created from the medical conditions file as a categorical variable which indicated whether the cancer patient had a renal disease diagnosis or did not have a renal disease diagnosis.

STATISTICAL ANALYSES

A preliminary chi-square test was done in SAS using PROC SURVEYFREQ to assess the significance of the sociodemographic, economic and clinical characteristics in cancer patients. The chi square test was weighted using complex survey variables. The sample was summarized using means and frequencies. A multivariable binomial logistic regression model using PROC SURVEYLOGISTIC was used to estimate the likelihood of cancer patients to have a renal disease and hence characterize the significant factors associated with the presence of renal disease in the study sample. The model for multivariate binomial logistic regression was:

$y = \beta_0 + \beta_1 Age + \beta_2 Sex + \beta_3 Race + \beta_4 Marital\ Status + \beta_5 Census\ Region + \beta_6 Income + \beta_7 Insurance\ Status + \beta_8 Employment\ Status + \beta_9 Smoking\ Status + \beta_{10} Health\ Status + \beta_{11} Number\ of\ comorbidities + \beta_{12} Hepatic\ disease\ indicator + \beta_{13} Cardiovascular\ disease\ indicator + \varepsilon_0$

y = Renal Disease Indicator

The probability of having a renal disease was modelled. The variables were considered statistically significant based on Type 3 analysis of effects. Results of the logistic regression was summarized in Table 3 using odds ratio. The complex sampling design of the MEPS dataset was considered by using variables which account for variance estimation strata, person level weights and primary sampling unit. A significance level of 0.05 was used. SAS v9.4 was used for statistical analyses and MS Excel was used for data visualization.

7.2 RESULTS

The inclusion and exclusion criteria resulted in 11,441 cancer patients (weighted frequency = 13,858,510). Out of this, 1,800 patients had a renal disease diagnosis (weighted frequency = 2,183,534). Table 2 shows the distribution of sociodemographic, economic and clinical characteristics of these cancer patients.

Figure 4: Prevalence of renal disease in cancer patients in non-institutionalized US population from 2009 - 2018

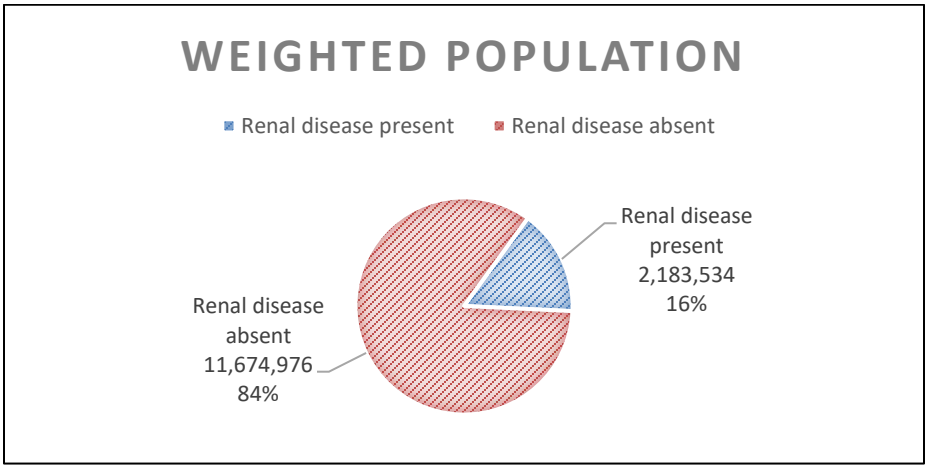


Table 2: Distribution of sociodemographic, economic and clinical factors in cancer patients in the US from 2009 - 2018

Sociodemographic, Economic and Clinical Factors	Cancer patients with Renal disease Freq (%)	Cancer patients without Renal disease Freq (%)	**p-value***
Overall, n (%)	1800 (15.73)	9641 (84.27)	
Age[a] (years) mean (S.D)			**< 0.0001**
	66.20 (14.76)	61.05 (15.85)	
Age groups			**< 0.001**
18 - 44 years	182 (10.11)	1588 (16.47)	
45 – 64 years	510 (28.33)	3554 (36.86)	
65+ years	1108 (61.56)	4499 (46.67)	
Missing	0	0	
Sex			**0.0049**
Male	697 (38.72)	4198 (43.54)	
Female	1103 (61.28)	5443 (56.46)	
Missing	0	0	

Race			**0.0411**
White	1506 (83.67)	7828 (81.19)	
Black	212 (11.78)	1282 (13.30)	
Others	82 (4.56)	531 (5.51)	
Missing	0	0	
Marital Status			**< 0.0001**
Married	951 (52.83)	5584 (57.91)	
Widowed/Divorced/ Separated	678 (37.67)	2845 (29.51)	
Never Married	171 (9.50)	1212 (12.57)	
Missing	0	0	
Education			0.2239
No School or less than HS	286 (15.89)	1358 (14.09)	
High School	697 (38.72)	3746 (38.85)	
College or above	804 (44.67)	4461 (46.27)	
Missing	13 (0.72)	76 (0.79)	
Census Region			**0.0031**
Northeast	270 (15.00)	1737 (18.02)	
Midwest	408 (22.67)	2107 (21.85)	
South	721 (40.06)	3502 (36.32)	
West	400 (22.22)	2284 (23.69)	
Missing	1 (0.06)	11 (0.11)	
Income[a] (USD) mean			**< 0.0001**
	39952.07	46530.11	
Income[b]			**< 0.0001**
Low	362 (20.11)	1544 (16.01)	
Middle	899 (49.94)	4736 (49.12)	
High	478 (26.56)	2943 (30.53)	
Missing	61 (3.39)	418 (4.34)	
Insurance			**< 0.0001**
Private	1067 (59.28)	6222 (64.54)	
Public	688 (38.22)	3012 (31.24)	
Uninsured	45 (2.50)	407 (4.22)	
Missing	0	0	
Employment status			**< 0.0001**
Employed	557 (30.94)	4477 (46.44)	
Unemployed	1243 (69.06)	5097 (52.87)	
Missing	0	67 (0.69)	
Smoking status			**0.0028**
Smoker	202 (11.22)	1305 (13.54)	
Non-smoker	1229 (68.28)	6199 (64.30)	
Missing	369 (20.50)	2137 (22.17)	
Health Status			**< 0.0001**
Excellent	292 (16.22)	2322 (24.08)	
Very Good	491 (27.28)	3054 (31.68)	
Good	528 (29.33)	2604 (27.01)	

Fair	336 (18.67)	1027 (12.52)	
Poor	153 (8.50)	408 (4.23)	
Missing	0	46 (0.48)	
Number of comorbidities			**< 0.0001**
0	191 (10.67)	1953 (20.26)	
1	279 (15.50)	2175 (22.56)	
2	454 (25.22)	2352 (24.40)	
3	474 (26.33)	2021 (20.96)	
4+	402 (22.28)	1140 (11.82)	
Missing	0	0	
Hepatic Disease			**< 0.0001**
Absent	1762 (97.89)	9555 (99.11)	
Present	38 (2.11)	86 (0.89)	
Missing	0	0	
Cardiovascular Disease			**< 0.0001**
Absent	533 (29.61)	4493 (46.60)	
Present	1267 (70.39)	5148 (53.40)	
Missing	0	0	

P-values are obtained from chi-square test
a - p-values obtained from Satterthwaite test
b - Income groups: Low income – less than $12,880; Middle income - between $12,880 and $51,520; High income – above $51,520
HS – High School

Almost 2/3rd of the patients with renal disease were older cancer patients. Majority of the population identified as whites in both the groups. Nearly half of the population in both the groups were married. Majority of the cancer population in both the groups had a high school education. Almost half of the cancer population belonged to the middle-income category and more than half of the cancer population in both the groups had a private insurance. There were more unemployed cancer patients with renal disease than cancer patients without renal disease (69.06% vs 52.87%). Unadjusted analyses from the chi-square test and Satterthwaite test shown in Table 2 showed that at significance value of 0.05, all the variables differed significantly between the two groups except education (p = 0.2239).

The significant variables were included in the binomial logistic model to calculate the odds

ratio. The results from the binomial multivariate logistic regression are shown in Table 3 below. The results show that that in the presence of all other variables, only sex, census region, employment status, smoking status, health status, number of comorbid diseases, cardiovascular and hepatic diseases had significant odds ratio. We found that compared to females, males were 30% less likely to have renal diseases ($p<0.0001$). Overall census region significantly predicts likelihood of having a renal disease in cancer patients ($p=0.0062$). The odds of having a renal disease were 30% lower in cancer patients living in Northeast than cancer patients living in Midwest. We also found that compared to unemployed, cancer patients who were employed were almost 30% less likely to have renal diseases ($p=0.0010$). Smokers were almost 40% less likely to have renal disease than non-smokers ($p=0.0001$). Overall health status significantly predicts likelihood of having a renal disease in cancer patients ($p=0.0029$). Compared to cancer patients who reported having a poor health status, cancer patients who reported having an excellent health status were almost 40% less likely to have renal diseases. Overall number of comorbidities significantly predicts likelihood of having a renal disease in cancer patients ($p=0.0001$). Cancer patients with 4 or more comorbidities were almost 79% more likely to have a renal disease than cancer patients with no comorbidities. Cancer patients with hepatic disease were almost 3 times more likely to have a renal disease than cancer patients who did not have a hepatic disease ($p<0.0001$). Cancer patients with cardiovascular disease were 27% more likely to have a renal disease than cancer patients who did not have a CVD ($p=0.00231$).

Table 3: Sociodemographic, Economic and Clinical Factors associated with renal diseases in cancer patients in the United States from 2009 - 2018

Covariates	Odds Ratio	95% Confidence Intervals		P-value
		Upper limit	Lower limit	
	Age			0.0536
18-44 years	0.985	0.749	1.295	

45-64 years	0.817	0.673	0.991	
65+ years	REFERENCE	-	-	
	Sex**			< 0.0001
Male	0.692	0.587	0.817	
Female	REFERENCE		-	
	Race			0.2420
Black	0.856	0.712	1.029	
Others	1.025	0.736	1.427	
White	REFERENCE	-	-	
	Marital status			0.4083
Never married	0.973	0.744	1.272	
Widowed/Divorced/Separated	1.098	0.945	1.276	
Married	REFERENCE	-	-	
	Census Region**			0.0062
South	1.001	0.852	1.177	
West	0.836	0.690	1.012	
Northeast	0.712	0.570	0.889	
Midwest	REFERENCE	-	-	
	Income			0.6622
Low	0.905	0.704	1.163	
Middle	0.929	0.785	1.099	
High	REFERENCE	-	-	
	Insurance			0.9024
Uninsured	0.827	0.468	1.459	
Public	0.974	0.821	1.155	
Private	REFERENCE	-	-	
	Employment status**			0.0010
Employed	0.680	0.560	0.824	
Unemployed	REFERENCE	-	-	
	Smoking status**			<0.0001
Smoker	0.634	0.504	0.797	
Non-smoker	REFERENCE	-	-	
	Health Status**			0.0029
Excellent	0.593	0.413	0.851	
Very Good	0.644	0.467	0.889	
Good	0.72	0.527	0.984	
Fair	0.866	0.6	1.25	
Poor	REFERENCE	-	-	
	Number of comorbidities**			0.0001
1	0.978	0.737	1.299	
2	1.276	0.916	1.777	
3	1.437	1.025	2.015	
4+	1.786	1.254	2.543	
0	REFERENCE	-	-	
	Hepatic Disease**			< 0.0001
Present	2.974	1.727	5.12	

Absent	REFERENCE	-	-	
Cardiovascular Disease**				0.00231
Present	1.277	1.034		
Absent	REFERENCE	-		

** statistically significant at p=0.05 based on Type 3 test

7.3 DISCUSSIONS

Our study examined the characteristics associated with renal disease in cancer patients. To our knowledge, this is the first population-based study in cancer patients which was not limited to one cancer type. We found that certain characteristics were significantly associated with renal disease. One of our findings was that males were less likely to have renal disease than females. This could be because pregnancy is a risk factor for renal disease.[31] Women are also more likely to have a urinary tract infection which is a risk factor for renal disease. [69-70] We found that cancer patients who are older (65+ years) are more likely to have a renal disease than cancer patients who are between 18 – 44 years and 45 - 64 years, although this finding was not statistically significant (p = 0.0536). These were similar to the results reported in the study by Lahoti et al. in patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (OR = 1.8, p = 0.012).[44]

Lifestyle risk factors such as smoking have been associated with a risk of CKD and up to 9-fold increased risk of cancer.[71,72] However our study found smoking as a protective factor where cancer patients who were smokers were 40% less likely to have a renal disease than cancer patients who were non-smokers. As shown in Table 2, almost 20-22% of the data for smoking status was missing and hence this association could be biased. This association could be studied further in a longitudinal data where causal relationship is established. A meta-analysis in general population found that individuals with liver disease were almost twice more likely to have CKD (OR = 2.12).[73] In our study, cancer patients with liver diseases were almost 3 times more likely to have a renal disease (OR = 2.974). Our study also confirmed the association of renal disease and CVD in cancer patients (OR = 1.277). This association has been observed in the general population

by Foley et al.[74] This might be due to shared risk factors such as age between renal disease and CVD.

There are several limitations in this study. Firstly, this study is a cross sectional study and hence causality cannot be inferred. The associations that have been found between the predictors and outcomes could not be proven true over a longitudinal duration. Secondly, since MEPS is a patient reported survey, there may be some self-reporting bias, where individuals tend to report inaccurate or false information.[75] Thirdly there may also be recall bias where participants do not remember previous events or experiences accurately or omit details.[75] Fourthly, the design of data collection is such that one member of the household answers the survey for all the other members of the household which may lead to errors.[75] We could not exclude individuals with a prior renal diagnosis because of missing data for age of diagnosis of cancer and renal disease. We have assumed that all the patients who were diagnosed with renal disease were treated for it. We did not establish an association of cancer therapies and adjuvant drugs to renal disease in cancer patients and this could be a potential hypothesis for further research. Finally, the prevalence of individuals diagnosed with renal disease and cancer is depicted in the study and could not account for individuals who have cancer and renal disease but are undiagnosed.

Despite the limitations mentioned above, our study still has some implications. Our study determines the risk factors associated with renal disease in cancer patients in a nationally representative sample. Using a nationally representative sample increases generalizability of our results. Our study found that certain factors such as being female, being older, or having a comorbid cardiovascular disease or hepatic diseases increases the propensity to develop renal

disease in cancer patients. Our study also proves the association of renal disease and cancer development. Given the link between renal disease and cancer development, the aim of this study highlights the importance of multidisciplinary collaboration between oncologist and nephrologist to predict and prevent renal diseases. The results of our study could also inform clinicians to incorporate care and heighten monitoring for patients who have more propensity to develop renal disease.

Chapter 8: SPECIFIC AIM 2

The second aim of our study was to compare healthcare expenditure and utilization of cancer patients with renal diseases and cancer patients without renal diseases in the U.S. civilian non-institutionalized population. We hypothesized that cancer patients with renal diseases had significantly higher healthcare expenditure and utilization than cancer patients without renal diseases.

8.1 METHODS

STUDY DESIGN

This study was designed as a retrospective, cross-sectional study using Medical Expenditure Panel Survey (MEPS).[57] A sample of families and individuals across the United States were interviewed for five rounds that covers two years. The data from the interviews was collected and compiled into a publicly available dataset. We used data from the interviews conducted from January 2009 to December 2018 for our study. We used the Household Component (HC) of MEPS which provides data about demographics, health services, charges and expenditures, etc. The files were downloaded and merged for this study to improve the sample size.

STUDY SAMPLE

We identified individuals for our sample using the Medical Conditions files of MEPS. Cancer patients from 2016 to 2018 were identified from ICD-10 codes (Table 1 of Appendix) and patients were identified from 2009 to 2015 from ICD-9 codes (Table 2 of Appendix).[58,59] Renal disease diagnosis was identified from the Medical conditions files of 2016 to 2018 using ICD-10 codes from “N00” to “N39” (Table 3 of Appendix).[60] ICD-9 codes from “580” to “599” (Table 4 of

Appendix) was used for renal disease diagnosis from the Medical Conditions files of 2009 to 2015.[61] The Medical Condition files are event level files and hence after identifying the medical conditions associated with renal disease or cancer, the files were transposed to person-level files in SAS using PROC TRANSPOSE. After transposing, each person was identified as a patient with either renal disease or cancer or both or none. There were 241,247 individuals who responded to MEPS from 2009 to 2018 of which 11,441 were patients with cancer who were above the age of 18. Out of 11,441 cancer patients, 1,800 reported a diagnosis of renal disease ("Renal disease group") and 9,641 did not report renal disease diagnosis ("Control group"). To reduce selection bias, the "Renal disease" group was matched in a 1:1 ratio with the Control group using propensity score matching (PSM). Propensity score matching is a 2-step process where the first step is to calculate the probability of a cancer patient being diagnosed with renal disease. A propensity score was calculated using multiple logistic regression with renal disease indicator, sex, age, region, income, race and marital status as matching variables, where income and age were used as continuous variables. In the second step the Renal disease group and the Control group were matched using a greedy matching technique with replacement. The quality of match was assessed using standardized differences, where a standardized difference of less than 0.1 was considered a good match. Variance ratio, the ratio of treatment variance and control variance was also used to compare the quality of match. A ratio closer to 1 was considered a good match.

VARIABLES

Sociodemographic, economic information including sex, age, race, education, income, employment, marital status and census region were obtained from the full year consolidated files. Sex was directly used from MEPS which was coded as "Male" and "Female". Age was a

continuous variable which was categorized as 18-44 years, 45 – 65 years, and above 65 years which was consistent with previous study.[75] Race was recoded as a new variable which indicated "White", "Black" and "Other races". Other races included individuals who identified as American Indian, Asian, Native Hawaiian, Pacific Islander and Multiple Races. Marital status was recoded into 3 categories as "Married", "Never Married" and "Widowed/Divorced/Separated". Education was recoded to a new variable which indicated "No School or less than High School", "High School" and "College and above". Census region was used without recoding and labelled as "Northeast", "Midwest", "South" and "West". Income was a continuous variable in MEPS and was recoded into more meaningful categories as "Low Income", "Middle Income" and "High Income". The income variable was recoded based on a previous study where low income was defined as 100% below the Federal Poverty Line (FPL). In 2021, the FPL for a single person was $12,880 and hence low income was defined as an income less than $12,880.[62] Middle income was defined as an income between 100-400% of FPL, i.e., between $12,880 and $51,520 and high income was defined an income above 400% of FPL, i.e., $51,520 and above. Insurance was used without change and labelled as "Private", "Public" and "Uninsured". Employment was recoded into a new variable which represented 2 categories "Employed" and "Unemployed". Smoking status was recoded into a new variable which represented "Smoker" and "Non-smoker". Perceived health status was recoded into a new variable which represented "Excellent", "Very Good", "Good", "Fair" and "Poor". A new categorical variable was created to indicate the number of comorbidities a cancer patient would have. Several chronic conditions such as diabetes, asthma, arthritis, hypertension, hypercholesterolemia have been causally associated with an increased risk of cancer and hence they were used to count the number of comorbidities.[63-67] Categorical

variables which depicted whether a patient had a cardiovascular disease and hepatic disease were also used in the analyses. These variables were created from ICD-9 and ICD-10 codes of the Medical Condition files. A categorical variable was created which indicated whether the cancer patient had a renal disease diagnosis or did not have a renal disease diagnosiswas used as the main independent variable.

The outcome variables included healthcare utilization variables and cost variables. The utilization variable included the number of office-based visits to the physician and number of prescribed medicines which included refills. The healthcare expenditure variables included out-of-pocket cost associated with the office-based visits to the physician, amount paid for an office-based visit to the physician from all the sources of payments, out-of-pocket cost associated with prescribed medicines including refills and amount paid for prescribed medicines including refills from all sources of payments. We also included total out of pocket expenditure which was calculated as a sum of out-of-pocket cost associated with inpatient visits, outpatient visits, emergency visits, office-based visits to a physician, and out-of-pocket associated with prescribed medicines (including refills). Total expenditure from all sources of payment was calculated as a sum of expenditure associated with inpatient visits, outpatient visits, emergency visits, office-based visits to a physician, and expenditure associatedwith prescribed medicines (including refills). All sources of payment included payments from out of pocket, Medicare, Medicaid, private insurance, Veteran's administration, TRICARE, other federal sources, other state and local sources, workers' compensation, other private, other public, and other unclassified sources.

STATISTICAL ANALYSES

The unadjusted mean expenditure for both groups were compared using t-tests.

Statistical differences for count outcomes between cancer patients with renal disease and without renal disease were analyzed using the Wilcoxon Rank Sum Test. Due to skewed data, traditional ordinary least squares (OLS) was not used for modelling the cost outcome. Even though the log-transformed OLS would account for the skewed data, the interpretation of estimates would be difficult. Therefore, we used a generalized linear model using the log link function to model cost outcomes. We used the traditional Poisson regression for modelling the count outcomes and assumed that the means and variances are equal. The model was built using PROC GLM as following:

$y = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{Sex} + \beta_3 \text{Race} + \beta_4 \text{Marital Status} + \beta_5 \text{Census Region} + \beta_6 \text{Income} + \beta_7 \text{Insurance Status} + \beta_8 \text{Employment Status} + \beta_9 \text{Smoking Status} + \beta_{10} \text{Health Status} + \beta_{11} \text{Number of comorbidities} + \beta_{12} \text{Renal Disease Indicator} + \beta_{13} \text{Hepatic disease indicator} + \beta_{14} \text{Cardiovascular disease indicator} + \varepsilon_0$

y = # of office-based visits / # of prescribed medicines including refills / out-of-pocket cost associated with office-based visits / out-of-pocket cost associated with prescribed medicines (including refills) / out-of-pocket cost associated with total medical costs / amount paid by all sources of payment associated with office-based visits / amount paid by all sources of payment associated with prescribed medicines (including refills) / amount paid by all sources of payment associated with total medical costs

A significance level of 0.05 was used and SAS v9.4 was used for statistical analyses. MS Excel was used to plot the graphs.

8.3 RESULTS

There were 1,736 patients in the treatment group (patients with renal disease) and 9,221 patients in the control group (patients without renal disease) before matching. The sample characteristics before matching and after matching are compared in Table 6 and the distribution of propensity score before and after matching is shown below in Figure 5 and 6. Before matching, the mean age for renal disease group was 66.20 years and 61.05 years for control group. The renal disease group had a higher proportion of individuals who identified as males (44% vs 39%), white (84% vs 81%), widowed/divorced/separated (38% vs 30%) and living in South (40% vs 36%) than control group. The mean income was lower in the renal disease group than the control group ($39,998 vs $46,610). After matching, there were 1,736 patients in the treatment group and 1,736 patients in the control group. The magnitude of the difference between the treatment and control group decreased after matching. The mean and standard deviation of the propensity scores of the two groups as shown in Table 4 were equal after matching indicating less variance and more balance between the two groups. As shown in Table 5, the absolute value of standardized difference of propensity scores and matching variables was closer to 0 after matching indicating less variance between the two groups. After matching, the ratio of variance of treatment group to control group (variance ratio) was closer to 1 indicating equal variance was achieved in both the groups after matching. After matching, the mean age of renal disease group was 66.60 years and 66.62 years for control group. The renal disease group had an almost equal proportion of individuals who identified as females (61% vs 61%), white (84% vs 84%), married (52% vs 53%) and living in South (40% vs 39%) than control group. The mean income was also almost equal ($40,039 vs $39,623) in both the groups.

Table 4: Distribution of propensity scores of both the groups before and after matching

	Treated (Renal = YES)		Control (Renal = NO)	
	Before Matching	After Matching	Before Matching	After Matching
Sample size	1736	1736	9221	1736
Mean	0.1774	0.1774	0.1549	0.1774
Standard Deviation	0.0544	0.0544	0.0553	0.0544
Minimum	0.0497	0.0497	0.0307	0.0495
Maximum	0.3483	0.3483	0.3627	0.3627

Table 5: Metrics to compare quality of match

Variable	Observations	Mean Difference	Standard Deviation	Standardized Difference	Variance Ratio
Propensity Score	Before Matching	0.18	0.42	0.43147	0.7936
	After Matching	-0.00		-0.00007	0.9997
Age	Before Matching	5.11	15.13	0.33772	0.8667
	After Matching	-0.02		-0.00141	1.0939
Income	Before Matching	-6578.16	39711.69	-0.16565	0.6772
	After Matching	416.66		0.01049	1.0677
Sex	Before Matching	0.05	0.49	0.10690	0.9648
	After Matching	-0.00		-0.00585	1.0027

Figure 5: Distribution of propensity scores of cancer patients with renal disease and without renal diseases before matching

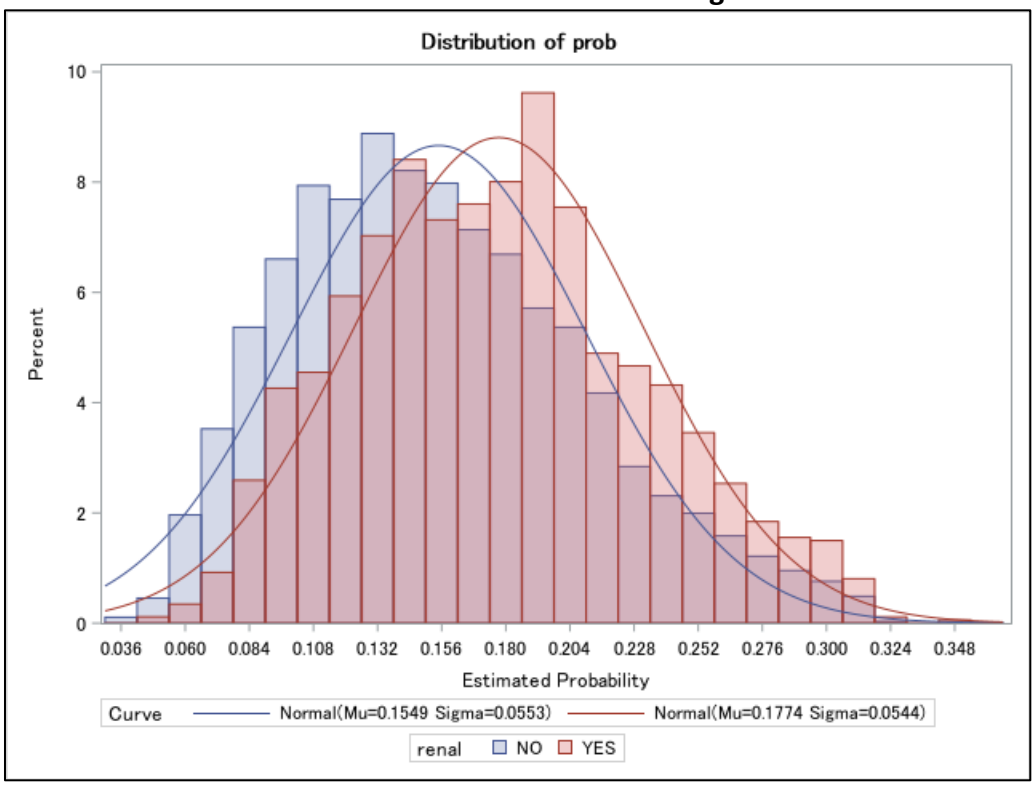


Figure 6: Distribution of propensity scores of cancer patients with renal disease and without renal diseases after matching

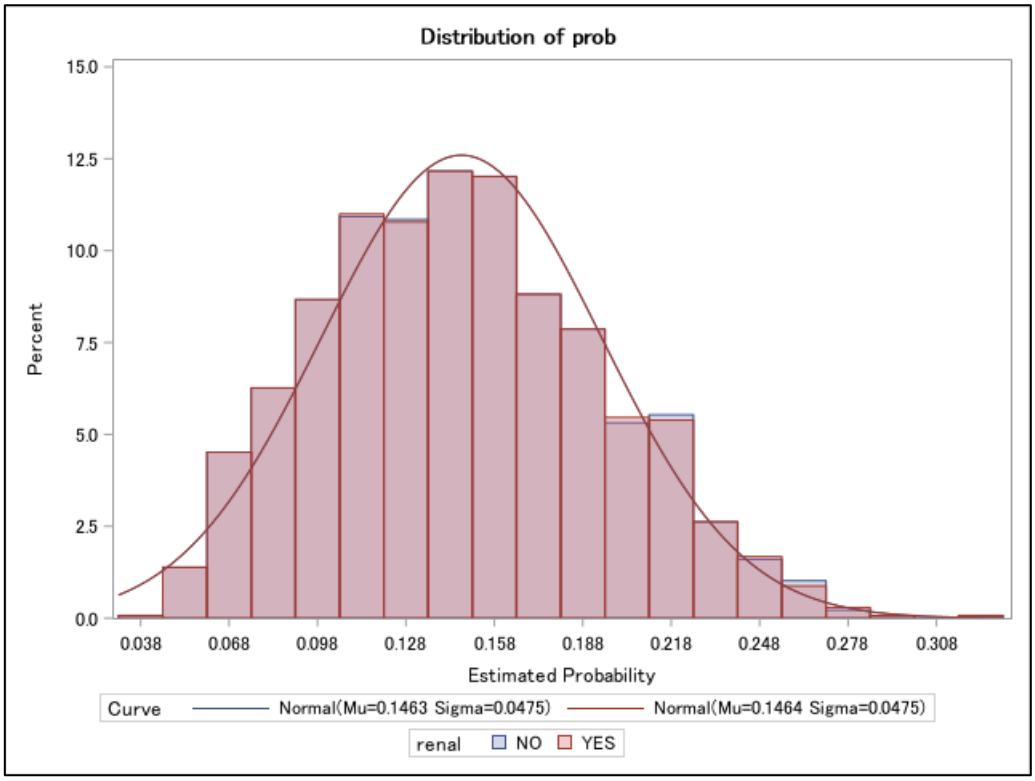


Table 6: Sample characteristics of cancer patients with renal disease and without renal disease before and after matching

Variables	Before Matching		After Matching	
RENAL DISEASE	PRESENT	ABSENT	PRESENT	ABSENT
Age (mean, SD)				
	66.20 (14.76)	61.05 (15.85)	66.60 (14.56)	66.62 (13.94)
Sex				
Male	697 (43.56)	4200 (38.72)	679 (39.11)	674 (38.82)
Female	5441 (56.44)	1103 (61.28)	1057 (60.89)	1062 (61.18)
Race				
White	1506 (83.67)	7828 (81.19)	1453 (83.70)	1466 (84.45)
Black	212 (11.78)	1282 (13.30)	203 (11.69)	199 (11.46)
Others	82 (4.55)	531 (5.52)	80 (4.61)	71 (4.09)
Income (Median, SD)				
	39998.01 (35671.33)	46610.82 (43362.73)	40039.35 (35686.30)	39622.69 (34536.24)
Marital Status				
Married	951 (52.83)	5584 (57.92)	911 (52.48)	928 (53.46)

Widowed/Divorced/Separated	678 (37.67)	2845 (29.51)	661 (38.08)	655 (37.73)
Never Married	171 (9.50)	1212 (12.57)	164 (9.45)	153 (8.81)
Region				
Northeast	269 (14.94)	1740 (18.05)	259 (14.92)	289 (16.65)
Midwest	407 (22.61)	2109 (21.88)	400 (23.04)	393 (22.64)
South	721 (40.06)	3506 (36.37)	690 (39.75)	676 (38.94)
West	399 (22.17)	2284 (23.69)	387 (22.29)	378 (21.77)

UNADJUSTED RESOURCE UTILIZATION AND COSTS

The sample included 1,736 patients in each group of patients with renal disease and without renal disease. As shown in Table 7, respondents with renal disease had higher unadjusted mean out-of-pocket cost associated with office-based provider visits ($507.02 vs $464.87, p=0.3963), prescribed medicines (including refills) ($1203.21 vs $867.28, p<0.0001) and total medical costs ($2041.37 vs $1695.56, p=0.0155) compared to patients without renal disease. Unadjusted mean cost from all sources of payment associated with office-based provider visits ($7069.39 vs $5165.08, p<0.0001), prescribed medicines (including refills) ($9554.65 vs $6007.22, p<0.0001) and total medical costs ($33185.46 vs $21133.39, p<0.0001) compared to patients without renal disease. Except for out-of-pocket costs associated with office-based provider visits (p=0.3963), cancer patients with renal disease had a significantly higher mean costs than cancer patients without renal disease. The results for unadjusted utilization measures for cancer patients are shown in Table 8. The results show a higher median office-based visits to provider (17 vs 12, p<0.0001) and higher median prescriptions filled (including refills) (53 vs 31, p<0.0001) for cancer patients with renal disease than cancer patients without renal disease.

Table 7: Unadjusted mean cost estimates for cancer patients with renal disease and without renal disease in propensity matched groups from MEPS (2009 – 2018)

Expenditure measure ($)		Cancer Patients with renal disease			Patients without renal disease			P -value
		Mean ($)	SD	95% CI	Mean ($)	SD	95% CI	
Office-based visits	Out-of-pocket	507.02	1153.04	452.75 -561.30	464.87	1718.52	383.99 – 545.78	0.3963
	All sources of payment**	7069.39	11909.30	6508.78 – 7630.00	5165.08	13475.27	4530.75 – 5799.41	<0.0001
Prescribed medicines	Out-of-pocket**	1203.21	2431.66	1088.74 - 1317.68	867.28	2535.92	747.91- 986.66	<0.0001
	All sources of payment**	9554.65	21788.23	8529.00 – 10580.30	6007.22	20690.31	5033.26 – 6981.19	<0.0001
Total medical costs	Out-of-pocket**	2041.37	3234.82	1889.10 - 2193.65	1695.56	4994.07	1460.47 – 1930.65	0.0155
	All sources of payment**	33185.46	50679.29	30799.81 – 35571.11	21133.39	44021.41	19061.15 – 3205.63	<0.0001

Abbreviation used: SD = Standard deviation; CI = Confidence interval; **significant at p = 0.05

Table 8: Unadjusted utilization estimates for cancer patients with renal disease and without renal disease in propensity matched groups from MEPS (2009 – 2018)

Utilization measure (#)	Renal disease	Median	Range	Mean	SD	95% CI	P-value
Office based visits to provider	Present	17.00	0.00 – 354.00	26.56	29.43	25.18 – 27.95	< 0.0001
	Absent	12.00	0.00 – 326.00	17.48	21.10	16.48 – 18.47	
Prescription fills including refills	Present	53.00	0.00 – 836.00	85.45	100.72	80.71 – 90.19	< 0.0001
	Absent	31.00	0.00 – 720.00	55.01	72.11	51.62 – 58.40	

Abbreviation used: SD = Standard deviation; CI = Confidence interval; p-value obtained from Wilcoxon signed rank sum test

ADJUSTED RESOURCE UTILIZATION AND COSTS

The sample for adjusted analyses included 1,385 cancer patients with renal disease and 1,342 cancer patients without renal disease. The results of the generalized linear model, after including only non-zero costs in matched groups and adjusting for covariates are shown in Table 9. Similar to unadjusted results, individuals with renal disease had higher costs associated with office-based provider visits, prescribed medicines (including refills) and total medical costs compared to patients without renal disease. As shown in Table 10, respondents with renal disease had higher adjusted mean out-of-pocket cost associated with office-based provider visits ($711.79 vs $670.70, p<0.0001), prescribed medicines (including refills) ($1370.24 vs $1022.66, p<0.0001) and total medical costs ($2274.67 vs $1907.74, p<0.0001) compared to patients without renal disease. Adjusted mean cost from all sources of payment associated with office-based provider visits ($7881.35 vs $5683.24, p<0.0001), prescribed medicines (including refills)

($11068.02 vs $6764.57, p<0.0001) and total medical costs ($37283.40 vs $22402.58, p<0.0001) compared to patients without renal disease. The results for adjusted utilization measures for cancer patients are shown in Table 9. The results show a higher mean office-based visits to provider (29.60 vs 19.94, p<0.0001) and higher mean prescriptions filled (including refills) (96.75 vs 63.32, p< 0.0001) for cancer patients with renal disease than cancer patients without renal disease. Median office-based visits to provider was higher for cancer patients with renal disease than cancer patients without renal disease (30.50 vs 20.61); this difference represents a 50% increase (p < 0.0001). Similarly, median prescriptions filled including refill was increased by almost 57% for cancer patients with renal disease than cancer patients without renal disease. Similar to unadjusted results, we see a patten of higher mean and median visits to office-based provider and prescription fills for patients with renal disease compared to patients without renal disease.

Table 9: Adjusted utilization estimates for cancer patients with renal disease and without renal disease in propensity matched groups from MEPS (2009 – 2018)

Utilization measure (#)	Renal disease	Median	Range	Mean	SD	95% CI	P-value
Office based visits to provider	Present	30.50	7.89 – 77.12	29.60	10.38	29.05 – 30.15	< 0.0001
	Absent	20.61	5.99 – 37.51	19.94	7.03	19.57 – 20.32	
Prescription fills including refills	Present	88.83	15.96 – 412.25	96.75	56.76	93.76 – 99.75	< 0.0001
	Absent	56.74	12.68 – 198.41	63.32	38.40	61.27 – 65.38	

Abbreviation used: SD = Standard deviation; CI = Confidence interval;

Figure 7: Adjusted number of prescriptions filled including refills for cancer patients with renal disease and without renal disease in propensity matched groups from MEPS (2009 – 2018)

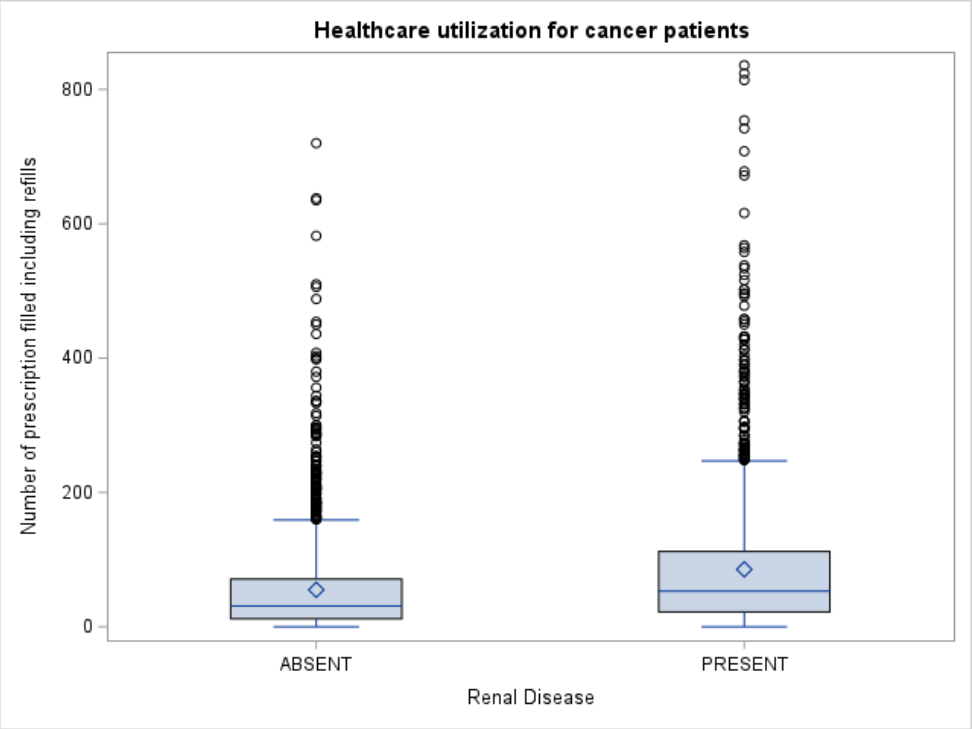


Figure 8: Adjusted number of office-based visits to a physician for cancer patients with renal disease and without renal disease in propensity matched groups from MEPS (2009 – 2018)

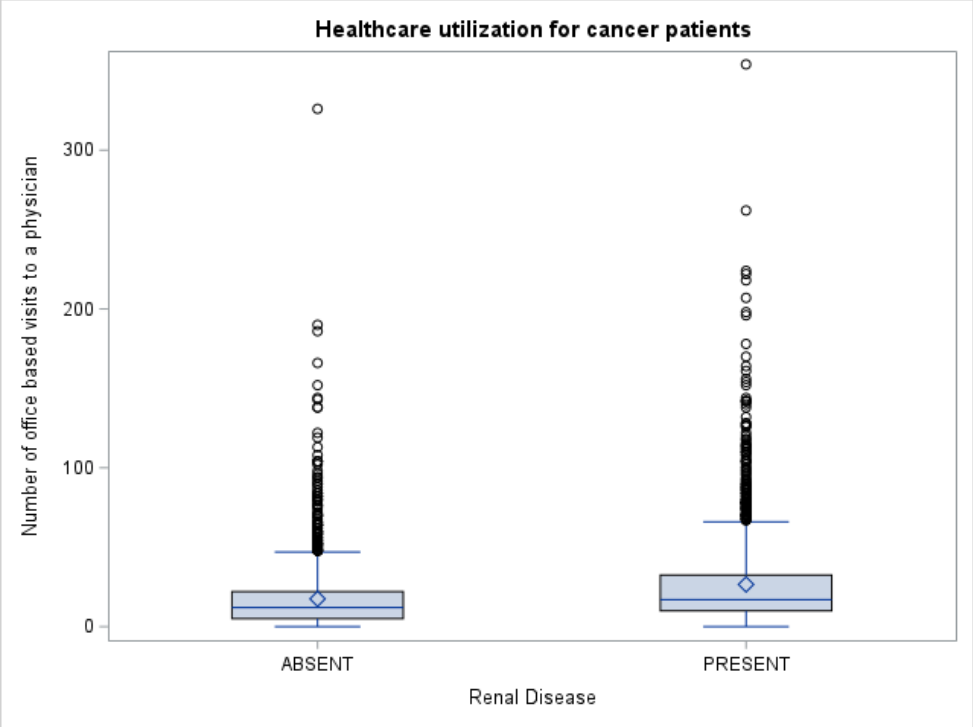


Table 10: Adjusted mean cost estimates for cancer patients with renal disease and without renal disease in propensity matched groups from MEPS (2009 – 2018)

Expenditure measure ($)		Patients with renal disease			Patients without renal disease			P-value
		Mean ($)	SD	95% CI	Mean ($)	SD	95% CI	
Office-based visits	Out-of-pocket	711.79	204.83	700.98 – 722.60	670.70	184.07	660.85 – 680.56	<0.0001
	All sources of payment	7881.35	2728.287	7737.38 – 8025.32	5683.24	1996.12	5576.34 – 5790.13	<0.0001
Prescribed medicines	Out-of-pocket	1370.24	645.57	1336.17 – 1404.30	1022.66	506.92	995.52 – 1049.81	<0.0001
	All sources of payment	11068.02	7766.29	10658.21 – 11477.84	6764.57	4161.37	6541.72 – 6987.41	<0.0001
Total medical costs	Out-of-pocket	2274.67	720.16	2236.67 – 2312.67	1907.74	608.18	1875.17 – 1940.31	<0.0001
	All sources of payment	37283.40	17482.95	36360.85 – 38205.95	22402.58	10642.39	21832.67-22972.48	<0.0001

Abbreviation used: SD = Standard deviation; CI = Confidence interval;

8.4 DISSCUSSION

The major finding of this aim was that mean unadjusted costs and utilization were higher for cancer patients with renal disease than cancer patients without renal disease. The sample used in this aim were MEPS respondents who were diagnosed with cancer and above the age of 18. Previous studies have shown that kidney damage represented by an increase in serum creatinine level has been correlated with increased hospital cost in cancer patients admitted to the ICU.[49] Our study showed similar results, kidney damage in cancer patients was associated with higher mean out-of-pocket cost for office-based visits ($41), prescribed medicines ($348) and total medical cost ($366.93). Apart from out-of-pocket costs, kidney damage was also associated with higher costs from all sources of payment for office-based visits ($2,188), prescribed medicines ($4,303) and total medical costs ($14,881). Similar results were found by Bhowmik et al. in patients with multiple myeloma using claims database.[51] They found that patients with CKD had higher frequency of physician office visits (1.2 vs 0.5), prescription fills (74.6 vs 57.9) than patients without CKD. A study by Qian et al. had similar results in patients with bone metastases from solid tumor.[50] They found that patients with renal impairment had higher physician's visits (22.9 vs 18.8), outpatient pharmacy visits (49.2 vs 40.8) and outpatient pharmacy costs ($10,315 vs $7,718).

There were many limitations for this study. Firstly, to account for the shape of the cost and utilization outcomes, we used generalized linear model and Poisson regression model. These models could not account for complex sampling weights which are used to produce estimates of nationally representative samples. Hence the results of this aim are generalizable only to the participants of MEPS and not the US population. Secondly, we assumed that the mean and

variances of the utilization variables are equal. Hence, we could not control for overdispersion in the Poisson regression. Thirdly, we did a propensity score matching to account for selection bias and confounding; however, differences between the cohorts might still exist for unobservable characteristics (e.g., stages of cancer, patient preferences). Indirect costs such as loss of productivity for the patient or the caregiver was not accounted for and thus the economic burden estimated might be underestimated.

Despite the limitations mentioned above, our study still has some implications. This study was the first in cancer patients which was not limited to one cancer type. Unlike the previous studies by Bhowmik et al. and Qian et al., the expenditure was accounted for individuals with public and private insurance as well as uninsured.[50,51] Our study estimates the mean expenditure for cancer patients with renal disease. This could be used by payers to estimate savings that can potentially accrue if care and preventive measures are incorporated in cancer patients who have a propensity to develop renal disease.

CHAPTER 9: SPECIFIC AIM 3

The third aim of our study was to compare health-related quality of life (HRQoL) of cancer patients with renal diseases and cancer patients without renal diseases in the U.S. civilian non-institutionalized population. We hypothesized that the cancer patients with renal disease will have lower mean PCS and MCS scores than cancer patients without renal disease. A lower score indicates worse HRQoL.

9.1 METHODS

STUDY DESIGN

This study was designed as a retrospective, cross-sectional study using Medical Expenditure Panel Survey (MEPS).[57] A sample of families and individuals across the United States were interviewed for five rounds that covers two years. The data from the interviews was collected and compiled into a publicly available dataset. We used data from the interviews conducted from January 2009 to December 2018 for our study. We used the Household Component (HC) of MEPS which provides data about demographics, health services, charges and expenditures, etc. The files were downloaded and merged for this study to improve the sample size.

STUDY SAMPLE

We identified individuals for our sample using the Medical Conditions files of MEPS. Cancer patients from 2016 to 2018 were identified from ICD-10 codes (Table 1 of Appendix) and patients were identified from 2009 to 2015 from ICD-9 codes (Table 2 of Appendix).[58,59] Renal disease diagnosis was identified from the Medical conditions files of 2016 to 2018 using ICD-10 codes from "N00" to "N39" (Table 3 of Appendix).[60] ICD-9 codes from "580" to "599" (Table 4 of

Appendix) was used for renal disease diagnosis from the Medical Conditions files of 2009 to 2015.[61] The Medical Condition files are event level files and hence after identifying the medical conditions associated with renal disease or cancer, the files were transposed to person-level files in SAS using PROC TRANSPOSE. After transposing, each person was identified as a patient with either renal disease or cancer or both or none. Figure 3 shows the sample selection process. There were 241,247 individuals who responded to MEPS from 2009 to 2018 of which 11,441 patients were patients with cancer who were above the age of 18. Out of 11,441 cancer patients, 1,800 reported a diagnosis of renal disease and 9,641 did not report a diagnosis of renal disease.

VARIABLES

Sociodemographic, economic information including sex, age, race, education, income, employment, marital status and census region were obtained from the full year consolidated files. Sex was directly used from MEPS which was coded as "Male" and "Female". Age was a continuous variable which was categorized as 18-44 years, 45 – 65 years, and above 65 years which was consistent with previous study.[75] Race was recoded as a new variable which indicated "White", "Black" and "Other races". Other races included individuals who identified as American Indian, Asian, Native Hawaiian, Pacific Islander and Multiple Races. Marital status was recoded into 3 categories as "Married", "Never Married" and "Widowed/Divorced/Separated". Education was recoded to a new variable which indicated "No School or less than High School", "High School" and "College and above". Census region was used without recoding and labelled as "Northeast", "Midwest", "South" and "West". Income was a continuous variable in MEPS and was recoded into more meaningful categories as "Low Income", "Middle Income" and "High Income". The income variable was recoded based on a previous study where low income was defined as 100%

below the Federal Poverty Line (FPL). In 2021, the FPL for a single person was $12,880 and hence low income was defined as an income less than $12,880.[62] Middle income was defined as an income between 100-400% of FPL, i.e., between $12,880 and $51,520 and high income was defined an income above 400% of FPL, i.e., $51,520 and above. Insurance was used without change and labelled as "Private", "Public" and "Uninsured". Employment was recoded into a new variable which represented 2 categories "Employed" and "Unemployed". Smoking status was recoded into a new variable which represented "Smoker" and "Non-smoker". Perceived health status was recoded into a new variable which represented "Excellent", "Very Good", "Good", "Fair" and "Poor". A new categorical variable was created to indicate the number of comorbidities a cancer patient would have. Several chronic conditions such as diabetes, asthma, arthritis, hypertension, hypercholesterolemia have been causally associated with an increased risk of cancer and hence they were used to count the number of comorbidities.[63-67] Categorical variables which depicted whether a patient had a cardiovascular disease and hepatic disease were also used in the analyses. These variables were created from ICD-9 and ICD-10 codes of the Medical Condition files. A categorical variable was created which indicated whether the cancer patient had a renal disease diagnosis or did not have a renal disease diagnosis and was used as the main independent variable. Apart from the covariates, complex survey variables were also used in selected analyses to have unbiased estimates which would account for the survey design and survey non-response.[68] Complex survey variables included a pooled person-level weight, variance estimation primary sampling unit and a sampling stratum required for variance estimation. Since this study spans over 10 years, the pooled person-level weight was calculated by dividing the person-level weight by 10.

Health related quality of life (HRQoL) is measured in MEPS using Short Form Health Survey-12 version two (SF-12v2) measured in rounds 2 and 4 of a panel. The SF-12v2 measures the following eight concepts: physical functioning, role limitations resulting from physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitation resulting from emotional problems, and mental health with 12 questions including "How often physical health or emotional problems interfered with social activities", "Whether they accomplished less than they would like at work or other regular activity as a result of their physical health".[76] Responses to these questions are combined to form two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). PCS is presented as a continuous variable which ranges from 4.48 to 70.51 and MCS is presented as a continuous variable which ranges from 3.71 to 75.6. A higher score is indicative of a better HRQoL. The reliability of SF-12 instrument was high (Cronbach's alpha of 0.89 for PCS and 0.88 for MCS) in the cancer patients in US.[77] PCS and MCS are the patient reported outcomes which were the dependent variables in this study. PCS and MCS scores were measured in rounds 2 and 4 of the survey and hence each individual had 2 scores of PCS and MCS scores. Hence average PCS and average MCS score were used as the outcome variables for this aim.

STATISTICAL ANALYSES

Test for normality for PCS scores ($p < 0.01$) and MCS scores ($p < 0.01$) showed that the outcome variables were fairly normally distributed and hence parametric tests were used for analyses. Unadjusted analyses were done using SAS procedure PROC SURVEYMEANS. A multiple linear regression model was built to determine the mean PCS and MCS in both groups while controlling for the independent variables mentioned above. Means of PCS and MCS were

compared using PROC SURVEYREG. The difference between the means of 2 groups were tested using T-test and SAS procedure PROC SURVEYREG. The model for multivariate linear regression was:

$y = \beta_0 + \beta_1 Age + \beta_2 Sex + \beta_3 Race + \beta_4 Marital\ Status + \beta_5 Census\ Region + \beta_6 Income + \beta_7 Insurance\ Status + \beta_8 Employment\ Status + \beta_9 Smoking\ Status + \beta_{10} Health\ Status + \beta_{11} Number\ of\ comorbidities + \beta_{12} Hepatic\ disease\ indicator + \beta_{13} Cardiovascular\ disease\ indicator + \beta_{13} Renal\ disease\ indicator + \varepsilon_0$

y = PCS / MCS score

The complex sampling design of the MEPS dataset was considered by using variables which account for variance estimation strata, person level weights and primary sampling unit. A significance level of 0.05 was used. SAS v9.4 was used for statistical analyses and MS Excel was used for data visualization.

9.2 RESULTS

Health-related quality of life was calculated using mean PCS and MCS scores in both the groups of patients i.e., patients with renal disease and without renal disease. The mean unadjusted scores are summarized below in Table 11. Unadjusted analyses showed that patients with renal disease had a lower mean PCS (40.57 vs 45.38) and MCS scores (50.39 vs 51.47). We did a multivariate analysis by adjusting for sociodemographic, economic and clinical characteristics. The results are summarized in Table 12. The results of adjusted analyses were similar results to unadjusted analyses. Patients without renal disease had a higher PCS score by 4.73 points than a patient with renal disease while controlling for other factors. The difference in scores was statistically significant ($p < 0.0001$). On average, patients without renal disease had a higher MCS score by 1.06 points than a patient with renal disease while controlling for other factors and this difference in scores was also statistically significant ($p < 0.0001$).

Table 11: Unadjusted mean HRQoL scores in cancer patients with renal disease and without renal disease in non-institutionalized US population

HRQoL measure	Renal Disease	Sample size	Mean	Std. Error of Mean	95% CI for Mean	
PCS	Present	1800	40.57	0.3238	39.93	41.21
	Absent	9641	45.38	0.1796	45.03	45.74
MCS	Present	1800	50.39	0.3154	49.77	51.01
	Absent	9641	51.47	0.1333	51.21	51.73

Table 12: Adjusted mean HRQoL scores in cancer patients with renal disease and without renal disease in non-institutionalized US population

HRQoL measure	Renal Disease	Sample size	Mean	Std. Error of Mean	95% CI for Mean	
PCS	Present	1786	40.52	0.2213	40.08	40.95
	Absent	9431	45.25	0.1494	44.96	45.55
MCS	Present	1786	50.31	0.1324	50.05	50.57
	Absent	9431	51.37	0.0746	51.22	51.52

9.3 DISCUSSION

To our knowledge, this analysis is the first to quantify HRQoL of noninstitutionalized cancer patients at the national level. It provides vital information to assess the impact of renal diseases in cancer patient in the US from a new perspective: quality of life. Previous studies have shown that renal diseases have an impact on mortality.[78] Our study shows that renal diseases also have an impact on quality of life of cancer patients, specifically 4.73 points decrease in PCS score and 1.06 points decrease in MC-12S score. A previous study has suggested that increase in HRQoL scores is associated in decrease in healthcare expenditure in cancer patients.[84] A one-point increase in MCS score was associated with 2% decrease in medical expenditures in all types of cancer. The association of MCS and medical expenditure was not varied by cancer type. There was no significant association between MCS and frequency of healthcare utilization. A one-point increase in PCS score was associated with 6% decrease in medical expenditures in prostate cancer, 4% decrease in medical expenditures in skin cancer and 1% decrease in medical expenditure on other types of cancer. A one-point increase in PCS score was associated with 1% decrease in frequency of healthcare utilization in all types of cancer patients and this association did not differ by cancer type.

A comparison of the PCS and MCS scores for the different populations is shown in the Table 13 below. The results were similar to what was reported by Abdel-Kader et al. which estimated HRQoL in patients with end stage renal diseases (ESRD) and chronic kidney disease (CKD)[55]. They found that patients with ESRD had a mean PCS score of 36.6 and mean MCS score of 44.6. Patients with CKD had mean PCS score of 39.3 and mean MCS score of 44.0. Similar to patients with ESRD and CKD in the Abdel-Kader et al study, cancer patients in our study reported

worse physical health than mental health status. In our study which included cancer patients, the PCS and MCS score was higher than that reported for adults with CKD only or ESRD only in the study by Abdel-Kader et al.[55] These findings indicate that cancer patients with and without comorbid renal diseases report better HRQoL than adults with only CKD or ESRD. These findings are similar to the study by Naylor et al. which indicate that patients on CKD have worse outcomes than cancer patients.[79]

Our study had some limitations. Firstly, this study is a cross sectional study and hence causality cannot be inferred. The associations that have been found between the predictors and outcomes could not be proven true over a longitudinal duration. Secondly, since MEPS is a patient reported survey, there may be some self-reporting bias, where individuals tend to report inaccurate or false information.[75]

Table 13: Comparison of PCS and MCS Scores across different population based on previous literature

Population	General population[80]	Cancer patients without renal disease	Cancer patients with renal disease	General population with CKD[55]	General population with ESRD[55]
Mean PCS Scores	50.04	45.25	40.52	39.3	36.6
Mean MCS Scores	51.50	51.37	50.31	44.0	44.6

Thirdly there may also be recall bias where participants do not remember previous events or experiences accurately or omit details.[75] Fourthly, the design of data collection is such that one member of the household answers the survey for all the other members of the household which may lead to errors.[75] We could not exclude individuals with a prior renal diagnosis because of missing data for age of diagnosis of cancer and renal disease. We have assumed that all the

patients who were diagnosed with renal disease were treated for it. The study could not establish an association of cancer therapies and adjuvant drugs to renal disease in cancer patients. Finally, we could not account for disease severity. It is intuitive that individuals with severe disease would have worse outcomes. The quality of life could be associated with only cancer and not renal disease. Our study did not assess the HRQoL using disease-specific questionnaire like The Kidney Disease Quality of Life survey (KDQOL) which would have given a more responsive and clinically useful than generic quality of life scale like SF-12 v2.[81] In 2018, the SF-12v2 was replaced by the Veteran's RAND 12-item (VR-12) and was administered to individuals who identified as Veterans in Round 1 of the interviews. The stage of cancer and type of cancer could also have some effect on the quality of life of cancer patients and we could not control for that in our study.

Despite these limitations, our study had some strong implications. None of the studies have evaluated HRQoL associated with renal diseases in cancer patients. Previous studies have shown that incorporating of early palliative care the patient's increase quality of life.[54,82] Thus, we encourage clinicians and other stakeholders to integrate early palliative care to relieve symptom burden which would improve quality of life.

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APPENDIX

Table 1: International Classification of Diseases, Tenth Revision (ICD-10) Codes to identify cancer patients

C00-C14	Malignant neoplasms of lip, oral cavity and pharynx	C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C15-C26	Malignant neoplasms of digestive organs	C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs	C7A	Malignant neuroendocrine tumors
C40-C41	Malignant neoplasms of bone and articular cartilage	C7B	Secondary neuroendocrine tumors
C43-C44	Melanoma and other malignant neoplasms of skin	C81-C96	Malignant neoplasms of lymphoid, hematopoietic and related tissue
C45-C49	Malignant neoplasms of mesothelial and soft tissue	D00-D09	In situ neoplasms
C50-	Malignant neoplasms of breast	D10-D36	Benign neoplasms, except benign neuroendocrine tumors
C51-C58	Malignant neoplasms of female genital organs	D37-D48	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
C60-C63	Malignant neoplasms of male genital organs	D3A	Benign neuroendocrine tumors
C64-C68	Malignant neoplasms of urinary tract	D49	Neoplasms of unspecified behavior
C69-C72	Malignant neoplasms of eye, brainand other parts of central nervous system		

Table 2: International Classification of Diseases, Ninth Revision (ICD-9) Codes to identify cancer patients

140-149	Malignant neoplasms of lip, oral cavity and pharynx	200-209	Malignant neoplasms of lymphatic and hematopoietic tissue
150-159	Malignant neoplasms of digestive organs and peritoneum	210-229	Benign neoplasms
160-165	Malignant neoplasms of respiratoryand intrathoracic	230-234	Carcinoma in situ

	organs		
170-176	Malignant neoplasms of bone, connective tissue, skin and breast	235-238	Neoplasms of uncertain behavior
179-189	Malignant neoplasms of genitourinary organs	239	Neoplasms of unspecified nature
190-199	Malignant neoplasms of other andunspecified sites		

N00-N08	Glomerular diseases	N20-N23	Urolithiasis
N10-N16	Renal tubulo-interstitial diseases	N25-N29	Other disorders of kidney and ureter
N17-N19	Acute kidney failure and chronic kidney disease	N30-N39	Other diseases of the urinary system

Table 4: International Classification of Diseases, Ninth Revision (ICD-9) Codes to identify renal diseases

580-589	Nephritis, Nephrotic Syndrome, and Nephrosis	590-599	Other diseases of urinary system

Table 5: Overview of covariates used in study

Variable name in study	Variable name in MEPS	Operationalization
Age	AGEyyX	18 – 44 years, 45 – 64 years, 65+ years
Sex	SEX	Male, Female
Race	RACEV1X, RACEX	White, Black, Other races
Marital status	MARRY31X	Married, Never married, Divorced / Widowed / Separated
Census region	REGIONyy	Northeast, Midwest, South, West
Income	TTLPyyX	Low, Middle, High
Insurance	INSCOVyy	Private, Public, Uninsured
Education	HIDEG, EDUYRYDG	No school or less than highschool, Highschool, College or above
Employment status	EMPST31	Employed, Unemployed
Health Status	RTHLTH31	Excellent, Very Good, Good, Fair, Poor
Smoking status	ADSMOK42, OFTSMK53	Smoker, Non-smoker
Number of comorbidities	Multiple variables	0, 1, 2, 3, 4+
Hepatic Disease	ICD10CDX, ICD9CODX	Present, Absent
Cardiovascular Disease	ICD10CDX, ICD9CODX	Present, Absent

yy – represents the year example AGE17X for age as of 2017