Health Care Resource Use and Cost Burden of Chronic Kidney Disease in Patients With Chronic Liver Disease: A Real-World Claims Analysis

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Chronic Liver Disease (CLD) is associated with an increased risk of chronic kidney disease (CKD). However, the health care burden of CKD in the CLD spectrum is unknown. We aimed to evaluate the health care use and cost burdens associated with CKD in patients with CLD in the United States by using real-world claims data. We analyzed data from the Truven Health MarketScan Commercial Claims database from 2010 to 2015. A total of 19,664 patients with CLD with or without comorbid CKD were identified using International Classification of Diseases, Ninth Revision, codes and matched 1:1 by sociodemographic characteristics and comorbidities using propensity scores. Total and service-specific unadjusted and adjusted health care parameters were analyzed for the 12 months following an index date selected at random to capture whole disease burdens. In CLD, comorbid CKD was associated with a higher annual number of claims per person (CKD vs. no CKD, 69 vs. 55) and higher total annual median health care costs (CKD vs. no CKD, $21,397 vs. $16,995). A subanalysis stratified by CKD category showed that health care use and cost burden in CLD increased with disease stage, with a peak 12-month median cost difference of $77,859 in patients on dialysis. The adjusted per person annual health care cost was higher for CKD cases compared to controls ($35,793 vs. $24,048, respectively; *P* < 0.0001). Stratified by the type of CLD, the highest between-group adjusted cost differences were for cirrhosis, viral hepatitis, hemochromatosis, and nonalcoholic fatty liver disease. *Conclusion:* CKD is a cost multiplier in CLD. The CKD health care burden in liver disease differs by the type of CLD. Improved CKD screening and proactive treatment interventions for at-risk patients can limit the excess burden associated with CKD in patients with CLD. (*Hepatology Communications* 2020;4:1404-1418).

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Chronic Liver Disease (CLD) currently affects an estimated 844 million individuals and accounts for 2 million deaths annually worldwide.[1] Cirrhosis alone is in the top 20 leading causes of disability-adjusted life years (1.6%) and years of life lost (2.1%).[1] In the United States, the prevalence and cost of CLD have steadily increased. Between 2012 and 2016, the rates of CLD-related hospitalizations in the United States increased by 22.9%.[2] A medical

Abbreviations: AFL, alcoholic fatty liver disease; aIRR, adjusted comorbidity-stratified incident rate ratio; AKI, acute kidney injury; CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; CLD, chronic liver disease; DCC, decompensated cirrhosis; ED, emergency department; ESRD, end-stage renal disease; GLM, generalized linear model; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; MI, myocardial infarction; MSCC, Truven Health MarketScan Commercial Claims; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

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expenditure panel survey analysis for 2004 to 2013 reported health care expenses of $19,390 in patients with CLD compared to $5,567 in those without CLD.[3] Between 2001 and 2011, the inpatient costs related to cirrhosis doubled in the United States.[4] In a study of common causes of CLD in the United States between 1988 and 2008, nonalcoholic fatty liver disease (NAFLD) was the only disorder with a rise in prevalence.[5] At present, NAFLD is estimated to affect a quarter of the U.S. adult population[6] and is associated with annual direct medical costs of approximately $103 billion.[7] The rising prevalence of NAFLD and CLD-related risk factors, including obesity, type 2 diabetes mellitus (T2DM), and other metabolic disorders, will continue to amplify these trends.[8]

Chronic kidney disease (CKD) is a disorder characterized as “kidney damage or glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause.”[9] The current prevalence of CKD in the United States is 14.8%, representing more than 30 million Americans.[10] As with CLD, rising rates of CKD and end-stage renal disease (ESRD) in the United States are primarily tied to an epidemic of risk factors, including obesity, T2DM, metabolic syndrome, smoking, and hypertension.[10,11]

CKD is a significant cause of health care spending in the United States. The total 2016 Medicare spending for both CKD and ESRD exceeded $114 billion, representing 23% of all Medicare fee-for-service spending that year.[10] A 2011 analysis of health care expenditures in the United States reported an annual per person cost of $37,649 for CKD, which denoted an excess of $17,472 for CKD relative to subjects without CKD.[12] The high medical costs for CKD are mainly explained by high rates and durations of comorbidity-driven hospitalization.[13,14] In 2016, the per patient year Medicare spending was $39,506 for patients with CKD with both T2DM and heart failure compared to $16,176 for those with CKD alone.[10] For this reason, CKD is considered to be a “cost multiplier” for its association with surging medical costs due to accompanying comorbidities and the disease itself.

Several reports have described an increased risk of CKD among specific CLD subgroups, including NAFLD,[15] hepatitis B virus (HBV), hepatitis C virus (HCV),[16] cirrhosis, and patients who undergo liver transplantation.[17] Nevertheless, there is a lack of available data on the importance of CKD as a cost multiplier in CLD, representing a critical literature gap given the rising prevalence of CLDs and especially NAFLD in the United States. With the cost of health care in the United States projected to reach 20% of the economy by 2024,[18] the availability of these data can facilitate the development of improved early screening, intervention strategies, and resource allocations by highlighting vulnerable patient subpopulations. Our main objective was to quantify the cost and health care burdens of CKD in the context of the overall CLD spectrum and various CLD subgroups using real-world claims data.

Materials and Methods

DATA SOURCE

This study was a case-control analysis of the Truven Health MarketScan Commercial Claims (MSCC) databases for the period January 1, 2010, to December 31, 2015. To account for the continuous enrollment requirements of 12 months before and after the index date, we defined an index period for both cases and controls between January 1, 2011, and December 31, 2014. The MSCC databases are composed of longitudinal individual-level data for health insurance claims

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across inpatient, outpatient, and prescription drug services from approximately 350 payers annually. The total cost of care provided in the MSCC represents the amount eligible for payment after applying pricing guidelines, such as fee schedules and discounts, and before applying coordination of benefits, deductibles, and copayments. The Internal Review Board of Rutgers Robert Wood Johnson Medical School approved the study protocol.

STUDY SAMPLE

Records from inpatient admissions and outpatient services were used to classify participants as either with or without CLD. CLD was defined as one inpatient admission or outpatient service diagnosis of an International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code for any CLD (Supporting Table S1). Patients were then classified by CLD status into one of 10 groups: liver transplant, liver cancer, decompensated cirrhosis (DCC), compensated cirrhosis, alcoholic fatty liver disease (AFL), HBV, HCV, hemochromatosis, NAFLD, and other CLDs. The "other CLDs" group included patients with autoimmune disease of the liver, hepatitis E virus, primary biliary cirrhosis, and primary sclerosing cholangitis. NAFLD was defined as ICD-9-CM code 571.8 in the absence of both any CLDs and a history of excessive alcohol use.

Patients with CKD were identified as those with at least two separate inpatient or outpatient records for CKD, using ICD-9-CM codes for CKD stages 3-5, unspecified CKD stage, dialysis, or kidney transplant (Supporting Table S1). The use of a minimum of two records to define CKD was enforced to avoid misclassifications. Patients were then classified by CKD status into one of six mutually exclusive groups: CKD stage 3, CKD stage 4, CKD stage 5, unspecified CKD stage, dialysis, and kidney transplant. CKD stage 5 was defined using ICD-9-CM codes for either CKD stage 5 or ESRD. In case a participant had different CKD stage classifications across multiple claims, the patient was grouped in the most severe CKD stage recorded.

The case cohort included patients with both CLD and CKD diagnoses (i.e., CKD cohort), whereas the control cohort included patients with only CLD (i.e., no CKD cohort). For patients who met the inclusion criteria, an index date was randomly selected from all eligible claims dates in order to capture the complete burden associated with the entire spectrums of both CKD and CLD. In the case group, the index date was selected from all claim records following the first date of the CKD diagnosis. Potential index dates in the control group included all claim records starting with the first date of CLD diagnosis. A baseline period was defined as the 12 months before the index date. The study follow-up period was defined as the 12 months after the index date. Only adult (18+ years) participants with at least 12 months of enrollment before and after the index date were eligible for inclusion in the study.

PATIENT CHARACTERISTICS AND COMORBIDITY PROFILES

Baseline demographics, including age, sex, the region of residence, and the type of health insurance plan, were obtained from index date records. Comorbidity profiles were quarried for each participant during the baseline period using ICD-9-CM codes obtained from inpatient admissions and outpatient services. The profile included a total Charlson Comorbidity Index (CCI) score,[19] T2DM, hypertension, obesity, history of smoking, myocardial infarction (MI), and heart failure.

MATCHING PROCEDURE

We used propensity score matching to ensure comparability in the distributions of the case and control groups on all observed baseline demographics and comorbidity profiles. We estimated a propensity score for each patient using a multivariate logistic regression model with CKD status as the outcome and age group, sex, region of residence, type of health insurance, CCI category (0, 1, 2, 3, or 4+), T2DM, and hypertension as covariates. The propensity scores were then used to match cases 1:1 to controls using the GREEDY algorithm with a caliper of 0.25, while matching exactly on age group, sex, and the type of CLD (Table 1).[20]

HEALTH CARE USE AND COSTS

All-cause health care use and cost parameters were aggregated for each participant over the 12 months following the index date. Measures of health care

TABLE 1. STUDY SAMPLE BASELINE CHARACTERISTICS FOR PATIENTS WITH CLD BY CKD STATUS BEFORE AND AFTER MATCHING

	Unmatched			Matched[†]		
	With CKD	Without CKD		With CKD	Without CKD	
Patient Characteristics *	(n = 9,869)	(n = 588,586)	Standardized Difference[‡]	(n = 9,832)	(n = 9,832)	Standardized Difference[‡]
Age, mean (SD)	54.17 (8.59)	48.53 (10.83)	0.577	54.17 (8.59)	54.14 (8.36)	0.004
Age group (years)			0.570			EM
18-34	374 (3.79)	71,979 (12.23)		370 (3.76)	370 (3.76)	
35-44	855 (8.66)	113,082 (19.21)		855 (8.70)	855 (8.70)	
45-54	2,702 (27.38)	191,950 (32.61)		2,690 (27.36)	2,690 (27.36)	
55+	5,938 (60.17)	211,575 (35.95)		5,917 (60.18)	5,917 (60.18)	
Sex			0.212			EM
Male	5,697 (57.73)	277,673 (47.18)		5,679 (57.76)	5,679 (57.76)	
Female	4,172 (42.27)	310,913 (52.82)		4,153 (42.24)	4,153 (42.24)	
Region of residence			0.033			0.012
Northeast	2,106 (21.34)	131,448 (22.33)		2,096 (21.32)	2,118 (21.54)	
North Central	1,805 (18.29)	105,089 (17.85)		1,798 (18.29)	1,781 (18.11)	
South	3,942 (39.94)	229,366 (38.97)		3,929 (39.96)	3,963 (40.31)	
West	1,826 (18.50)	112,259 (19.07)		1,819 (18.50)	1,783 (18.13)	
Unknown	190 (1.93)	10,424 (1.77)		190 (1.93)	187 (1.90)	
Type of health insurance			0.115			0.022
Unknown	308 (3.12)	20,210 (3.43)		307 (3.12)	294 (2.99)	
Comprehensive	464 (4.70)	15,950 (2.71)		460 (4.68)	457 (4.65)	
Exclusive provider organization	160 (1.62)	10,053 (1.71)		160 (1.63)	151 (1.54)	
Health maintenance organization	1,274 (12.91)	75,205 (12.78)		1,271 (12.93)	1,293 (13.15)	
Noncapitated point-of-service	821 (8.32)	44,983 (7.64)		817 (8.31)	819 (8.33)	
Preferred provider organization	5,869 (59.47)	361,076 (61.35)		5,846 (59.46)	5,877 (59.77)	
Point of service with capitation	46 (0.47)	2,541 (0.43)		46 (0.47)	36 (0.37)	
Consumer-driven health plan	642 (6.51)	38,499 (6.54)		640 (6.51)	620 (6.31)	
High-deductible health plan	285 (2.89)	20,069 (3.41)		285 (2.90)	285 (2.90)	
Comorbidities profile[§]						
CCI, mean (SD)	5.46 (2.98)	1.27 (1.87)	1.685	5.45 (2.98)	4.77 (2.47)	0.249
CCI group		2.271		0.004		

TABLE 1. *Continued*

	Unmatched			Matched†		
	With CKD	Without CKD		With CKD	Without CKD	
Patient Characteristics *	(n = 9,869)	(n = 588,586)	Standardized Difference‡	(n = 9,832)	(n = 9,832)	Standardized Difference‡
0	113 (1.14)	268,823 (45.67)		113 (1.15)	114 (1.16)	
1	145 (1.47)	151,400 (25.72)		145 (1.47)	144 (1.46)	
2	1,265 (12.82)	68,689 (11.67)		1,265 (12.87)	1,254 (12.75)	
3	1,448 (14.67)	44,928 (7.63)		1,448 (14.73)	1,447 (14.72)	
4+	6,898 (69.90)	54,746 (9.30)		6,861 (69.78)	6,873 (69.90)	
Diabetes	5,344 (54.15)	147,334 (25.03)	0.624	5,322 (54.13)	5,273 (53.63)	0.010
Hypertension	8,907 (90.25)	305,348 (51.88)	0.934	8,870 (90.22)	8,857 (90.08)	0.004
CLDs						
Liver transplant	860 (8.71)	2,766 (0.47)	0.402	825 (8.39)	825 (8.39)	EM
Liver cancer	139 (1.41)	4,420 (0.75)	0.064	139 (1.41)	139 (1.41)	EM
DCC	2,682 (27.18)	69,340 (11.78)	0.396	2,682 (27.28)	2,682 (27.28)	EM
Compensated cirrhosis	504 (5.11)	21,905 (3.72)	0.068	504 (5.13)	504 (5.13)	EM
AFL	186 (1.88)	10,532 (1.79)	0.007	186 (1.89)	186 (1.89)	EM
HCV	842 (8.53)	56,825 (9.65)	0.039	842 (8.56)	842 (8.56)	EM
HBV	177 (1.79)	17,997 (3.06)	0.082	177 (1.80)	177 (1.80)	EM
Hemochromatosis	457 (4.63)	41,304 (7.02)	0.102	455 (4.63)	455 (4.63)	EM
Nonalcoholic fatty liver‖	3,863 (39.14)	352,753 (59.93)	0.425	3,863 (39.29)	3,863 (39.29)	EM
Other CLD¶	159 (1.61)	10,744 (1.83)	0.017	159 (1.62)	159 (1.62)	EM

All data represent the number (%) unless otherwise noted.
*Demographic data were obtained from index date records.
†Cases and controls were propensity score matched 1:1. The logistic regression model used to estimate propensity scores included age group, sex, region of residence, type of health insurance, CCI category (0, 1, 2, 3, and 4+), diabetes, and hypertension.
‡Difference in means or proportions divided by standard error. Smaller values indicate better balance.
§Estimated during the 12-month baseline period.
‖Defined as ICD-9-CM code 571.8 in the absence of any other CLD or any history of excessive alcohol use.
¶Autoimmune hepatitis, hepatitis E virus, primary biliary cirrhosis, or primary sclerosing cholangitis.
Abbreviation: EM, exact matching.

use included the average, median, and twenty-fifth/seventy-fifth percentiles of the annual number of claims per patient for emergency department (ED) visits, inpatient admissions, outpatient visits, and pharmaceutical prescriptions. Similarly, the mean, median, and twenty-fifth/seventy-fifth percentiles per person annual all-cause health care expenditures were estimated for overall and service-specific costs for cases versus controls. We also assessed the prevalence of having at least one inpatient admission, ED visit, and outpatient visit during the 12 months following the index date. Additionally, we calculated the prevalence of inpatient admissions within 30 days after the index date as well as the proportions of readmission within 30, 60, and 90 days after discharge, among patients who were admitted in the first 30 days following the index date.

In addition to the primary analyses, we examined the stage-specific CKD cost and use differences between matched cases and controls. In a subanalysis, health care cost differences between cases and controls were also stratified by age group (i.e., 18-34, 35-44, 45-54, and 55+ years). Finally, we conducted a comorbidity-specific analysis to determine the differences in all-cause health care costs between cases and controls in relation to the type of CLD, T2DM, hypertension, MI, and heart failure. All cost estimates were adjusted to 2017 US$ using the medical care commodities component of the Consumer Price Index.

STATISTICAL ANALYSIS

We compared baseline characteristics and comorbidity profiles between the case and control cohorts before and after matching by using standardized differences of means for continuous variables and standardized differences of proportions for categorical variables. Wald chi-square tests were used to test the associations between CKD status, categorical patient characteristics, and comorbidity profiles in the unmatched sample. Wilcoxon signed-rank tests were used to compare cases and controls on all continuous measures of health care cost and use, and McNemar tests were used to examine all dichotomous variables.

To ensure the robustness of our primary comorbidity-specific results, we conducted secondary multivariable regression analyses using generalized linear models (GLMs) with negative binomial distributions for health care use rates and gamma distributions for cost estimates. We used generalized estimation equations with an exchangeable structure to account for the correlation between matched cases and controls. All regression models were adjusted for age group, sex, region of residence, type of health insurance, index year, CCI category, history of smoking, and obesity. Results of the GLM analyses represented adjusted comorbidity-stratified incident rate ratios (aIRRs) for health care use comparisons between cases and controls. We also used the GLM models to estimate the adjusted comorbidity-specific annual per person all-cause health care costs for cases and controls. *P* values and 95% confidence intervals (CIs) were calculated for differences in means between cases and controls for all health care costs and use parameters. $P < 0.05$ was considered to be statistically significant. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Results

SAMPLE CHARACTERISTICS

The study sample included 598,455 patients with CLD in the MSCC databases who met the inclusion criteria, including 9,869 patients with CKD (CKD cohort) and 588,586 patients without CKD (no CKD cohort) (Fig. 1). Patients in the CKD cohort were generally older, more likely to be men, and had higher comorbidities compared to the no CKD cohort (CCI 4+, CKD vs. no CKD, 69.9% vs. 9.3%; $P < 0.0001$). An analysis of specific comorbidities highlighted the relative prevalence of T2DM (54.2% vs. 25.0%; $P < 0.0001$) and hypertension (90.3% vs. 51.9%; $P < 0.0001$) in the CKD group compared to the no CKD cohort. The CKD cohort also exhibited higher rates of liver transplant (8.7% vs. 0.5%; $P < 0.0001$), liver cancer (1.4% vs. 0.8%; $P < 0.0001$), DCC (27.2% vs. 11.8%; $P < 0.0001$), and compensated cirrhosis (5.1% vs. 3.7%; $P < 0.0001$) compared to the no CKD group, indicating a higher severity of liver disease (Table 1).

HEALTH CARE USE

Health care use for the 12 months after the index date was compared in the primary matched cohort and in subanalyses stratified by CKD category. In general, health care use was higher in the CKD group

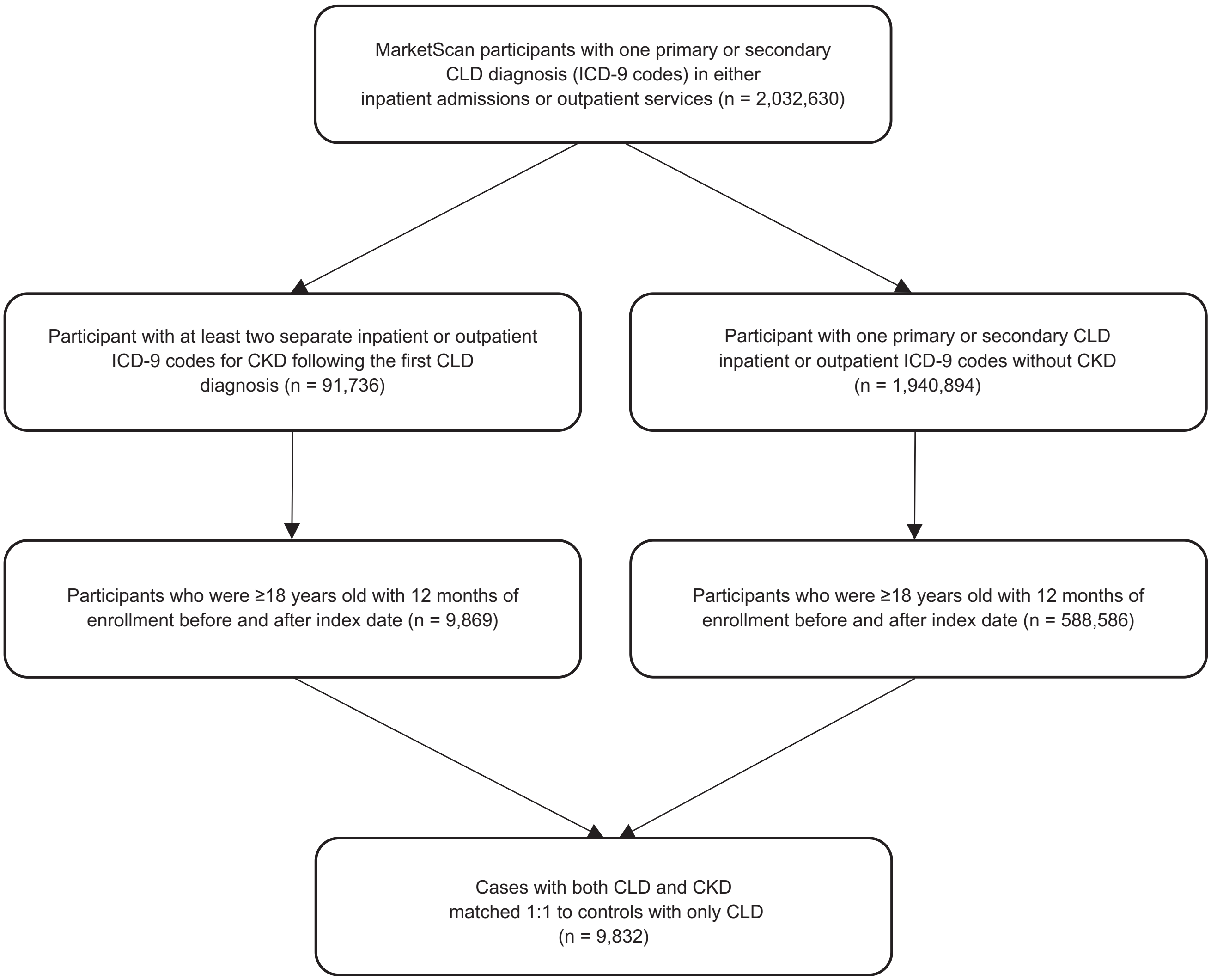


FIG. 1. Diagram for study sample selection.

compared to the no CKD group (mean total number of claims, 69.31 vs. 54.65, respectively; P < 0.0001), with this difference largely driven by outpatient visits (mean visits, 37.60 vs. 27.44; P < 0.0001) and to a lesser extent by inpatient visits (mean visits, 5.23 vs. 2.38; P < 0.0001), pharmaceutical claims (mean claims, 25.49 vs. 24.10; P < 0.0001), and ED visits (mean visits, 0.99 vs. 0.72; P < 0.0001). The mean per person length of hospital stay was significantly higher for cases versus controls (4.49 days vs. 2.11 days, respectively; P < 0.0001). Patients with CLD with CKD had a higher prevalence of having at least one inpatient admission and visits to ED when compared to those with CLD only (Table 2).

In the matched cohort, the prevalence of having at least one hospital admission within 30 days of the index date was significantly higher in the CKD group compared to the no CKD group (15.3% vs. 10.2%, respectively; P < 0.0001) (data not shown). Similarly, of those who were admitted within 30 days of the index date, inpatient readmission prevalence was significantly higher for patients with CKD versus those without CKD for 30 days readmission (27.5% vs. 18.1%, respectively; P < 0.0001), 60 days readmission (33.9% vs. 23.0%; P < 0.0001), and 90 days readmission (38.7% vs. 27.4%; P < 0.0001).

The subanalysis of health care use stratified by CKD category revealed that the mean difference in

TABLE 2. ANNUAL PER PERSON ALL-CAUSE HEALTH CARE RESOURCE USE FOR MATCHED PATIENTS WITH CLD WITH VERSUS WITHOUT CKD IN THE 12 MONTHS FOLLOWING THE INDEX DATE

Health Care Use Category	With CKD (n = 9,832)	Without CKD (n = 9,832)	*P* Value*
Total number of claims			
Mean (SD)	69.31 (59.67)	54.65 (39.88)	<0.0001
Median [25th, 75th percentile]	53 [29, 90]	46 [26, 73]	
Inpatient admissions			
Prevalence of at least one visit, n (%)	3,461 (35.2)	2,508 (25.5)	<0.0001
Number of admissions			
Mean (SD)	5.23 (15.89)	2.38 (8.57)	<0.0001
Median [25th, 75th percentile]	0 [0, 4]	0 [0, 1]	
Length of stay per patient (days)			
Mean (SD)	4.49 (15.14)	2.11 (9.04)	<0.0001
Median [25th, 75th percentile]	0 [0, 2]	0 [0, 0]	
ED visits			
Prevalence of at least one visit, n (%)	3,550 (36.1)	3,114 (31.7)	<0.0001
Number of visits			
Mean (SD)	0.99 (2.79)	0.72 (2.23)	<0.0001
Median [25th, 75th percentile]	0 [0, 1]	0 [0, 1]	
Outpatient visits			
Prevalence of at least one visit, n (%)	9,777 (99.4)	9,790 (99.6)	0.1883
Number of visits			
Mean (SD)	37.60 (41.73)	27.44 (23.82)	<0.0001
Median [25th, 75th percentile]	25 [13, 47]	21 [12, 36]	
Pharmaceutical claims			
Number of claims			
Mean (SD)	25.49 (23.02)	24.10 (20.40)	<0.0001
Median [25th, 75th percentile]	22 [5, 39]	21 [8, 36]	

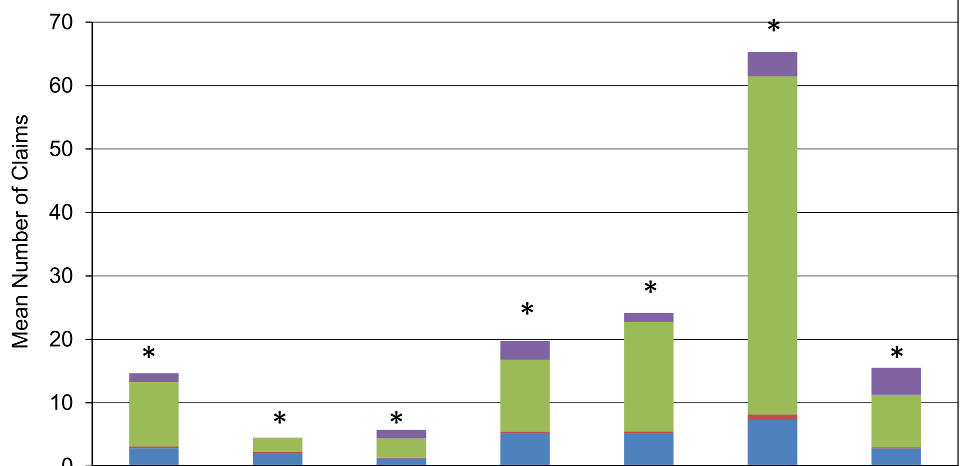
*For comparisons between cases and controls, all *P* values were obtained from Wilcoxon signed-rank tests for continuous variables and McNemar tests for binary variables.

use between the CKD and no CKD groups tended to increase with severity until dialysis, decreasing thereafter in patients with a kidney transplant. The mean difference in claims was 5.72 (95% CI, 3.84-7.61), 19.75 (95% CI, 14.13-25.37), 24.15 (95% CI, 19.53-28.77), 65.31 (95% CI, 59.28-71.33), and 15.53 (95% CI, 9.83-21.23) in the CKD stage 3, CKD stage 4, CKD stage 5, dialysis, and kidney transplant groups, respectively (Fig. 2). In all subgroups, differences in health care use were largely explained by outpatient visits (especially in the dialysis subgroup) followed by inpatient admissions. An exception was the dialysis group, in which health care use was foremost explained by outpatient visits and pharmaceutical claims.

HEALTH CARE COSTS

Health care costs during the 12 months following the index date were compared in the matched cohorts and subanalyses stratified by age and CKD category. In general, health care costs were higher in the CKD group compared to the no CKD group (median total cost, \$21,397 vs. \$16,995, respectively; $P < 0.0001$). Higher costs in the CKD group were largely explained by inpatient admission and outpatient visit costs (Table 3). When stratified by age group, the median cost of CKD tended to decrease as age increased, with median (twenty-fifth, seventy-fifth percentile) annual costs of \$29,986 (\$6,448, \$98,960), \$21,171 (\$5,855, \$80,511), \$20,333 (\$6,618, \$65,029), and \$21,625 (\$7,572, \$65,741) in the 18-34, 35-44, 45-54, and 55+ years age groups, respectively (Supporting Table S2). Similarly, differences between cases and controls in median annual health care costs decreased with age. Excess costs associated with CKD status were primarily driven by outpatient and inpatient costs in the 18-34, 35-44, and 45-54 years age groups and by inpatient and ED costs in the 55+ years age group.

Subanalysis of health care costs stratified by CKD category revealed that the median cost of CKD in CLD tended to increase with severity until dialysis, decreasing thereafter in patients with a kidney transplant. The median (twenty-fifth, seventy-fifth percentile) annual costs were \$16,379 (\$6,132, \$46,270), \$27,266 (\$9,800, \$86,270), \$32,741 (\$9,014, \$10,6405), \$96,249 (\$22,223, \$228,346), and \$33,487 (\$14,435, \$91,139) in the CKD stage 3, CKD stage 4, CKD stage 5, dialysis, and the kidney transplant groups, respectively (Fig. 3). In the CKD stage 3 group, the difference between cases and controls was primarily driven by inpatient admission costs, whereas in the CKD stages 4 and 5, differences were driven by inpatient admissions, outpatient visits, and ED visits; all service-specific costs drove the difference in total cost in the dialysis subgroup (data not shown).



	All	Stage Unspecified	Stage 3	Stage 4	Stage 5	Dialysis	Kidney Transplant
Pharmaceutical Claims	1.39	–0.13	1.31	2.95	1.37	3.85	4.26
Outpatient Visits	10.16	2.25	3.08	11.35	17.27	53.3	8.26
Emergency Room Visits	0.26	0.25	0.09	0.35	0.28	0.87	0.19
Inpatient Admissions	2.85	2.01	1.24	5.1	5.23	7.29	2.82

FIG. 2. Differences in annual per person all-cause health care use between cases (patients with both CLD and CKD) and matched controls (patients with only CLD) by CKD category. *$P < 0.05$, Wilcoxon signed-rank test for the difference in the total number of claims between cases and controls by CKD category.

Pharmaceutical claims as well as inpatient admissions and outpatient visits drove the cost difference in the liver transplant group. These findings were largely consistent with the pattern observed for health care use.

Subanalysis of health care costs stratified by CLD or other comorbidities in matched patients with and without CKD revealed that the median health care cost increased dramatically with comorbid CKD in several subgroups except for liver cancer, AFL, and other CLD (Supporting Table S3). Significant differences were observed for DCC (CKD vs. no CKD; median cost, \$37,542 vs. \$20,861; $P <$ 0001), compensated cirrhosis (median cost, \$25,993 vs. \$16,899; $P < 0.0001$), HBV (median cost, \$16,973 vs. \$12,778; $P = 0.006$), HCV (median cost, \$19,549 vs. \$15,269; $P < 0.0001$), and hemochromatosis (median cost, \$15,467 vs. \$11,077; $P < 0.0001$). Among those with NAFLD, patients with CKD had a median annual health care expenditure of \$14,020 compared to \$13,781 for those with NAFLD only. Notable significant differences were also observed for subgroups with T2DM and cardiovascular diseases, especially heart failure (median cost, \$41,397 vs. \$25,393, respectively; $P < 0.0001$).

ADJUSTED COMORBIDITY SUBANALYSIS

We next analyzed adjusted differences in health care use by comorbidity status in pairs of matched patients in the CKD and no CKD cohorts. Similar to our main findings, having CKD resulted in a significant increase in total adjusted per person annual health care use in all CLD and comorbidity groups except for participants with liver cancer, AFL, and other CLD (Fig. 4). Patients with both CKD and any CLD had aIRR 1.26 (95% CI, 1.23-1.29) times the total annual per person claims compared to those with CLD only. Among those with DCC, compensated cirrhosis, HCV, and NAFLD, CKD cases had 46%, 28%, 29%, and 12% higher aIRR, respectively, for the total annual per person claims compared to controls with only DCC, compensated cirrhosis, HCV, and NAFLD. Similarly, CKD was associated with higher

TABLE 3. ANNUAL PER PERSON ALL-CAUSE HEALTH CARE COSTS FOR MATCHED PATIENTS WITH CLD WITH VERSUS WITHOUT CKD DURING THE 12 MONTHS FOLLOWING THE INDEX DATE*

Health Care Cost Category	With CKD (n = 9,832)	Without CKD (n = 9,832)	*P* Value†
Total cost			
Mean (SD)	69,077 (138,724)	44,522 (87,664)	<0.0001
Median [25th, 75th percentile]	21,397 [7,079, 67,868]	16,995 [6,634, 45,508]	
Inpatient admissions			
Mean (SD)	25,139 (89,484)	12,933 (54,133)	<0.0001
Median [25th, 75th percentile]	0 [0, 12,582]	0 [0, 134]	
ED visits			
Mean (SD)	1,864 (6,099)	1,498 (5,563)	<0.0001
Median [25th, 75th percentile]	0 [0, 1,323]	0 [0, 900]	
Outpatient visits			
Mean (SD)	32,488 (80,620)	20,460 (46,520)	<0.0001
Median [25th, 75th percentile]	8,632 [3,043, 25,608]	7,452 [2,914, 18,382]	
Pharmaceutical claims			
Mean (SD)	9,586 (24,937)	9,631 (28,232)	0.0168
Median [25th, 75th percentile]	2,657 [154, 9,331]	2,522 [317, 8,138]	

*All costs were adjusted to 2017 US$ using the medical care component of the Consumer Price Index.
†Wilcoxon signed-rank tests for the difference in annual health care cost between cases and controls.

aIRR for health care use in T2DM, hypertension, heart failure, and MI.

The adjusted per person annual health care cost was higher for CKD cases compared to controls ($35,793 vs. $24,048, respectively; $P < 0.0001$) (Table 4). Similar to the results from the main analysis, CKD was associated with increases in per person annual cost among all CLD groups except for liver cancer and other CLD. In DCC, compensated cirrhosis, HCV, hemochromatosis, and NAFLD, CKD resulted in $25,462, $10,563, $15,891, $15,620, and $4,319 higher adjusted annual per person cost, respectively, compared to those with only DCC, compensated cirrhosis, HCV, hemochromatosis, and NAFLD. In CLD, CKD was also associated with $18,281, $12,941, $19,240, and $9,723 excesses in annual per person health care costs among those with T2DM, hypertension, heart failure, and MI, respectively.

Discussion

In this real-world data analysis, we investigated the excess health care burden and costs associated with CLD and comorbid CKD among a cohort of patients with CLD. Relative to those with CLD, our results show that patients with both CKD and CLD were older, had higher rates of comorbidities, used a significantly higher annual number of claims per person, and had higher annual health care costs. In our analyses, the incremental differences in health care cost between the CKD and no CKD cohorts were highest among younger patients. We also demonstrate that the differences between the CKD and no CKD cohorts increased with severity of stage and peaked among patients on dialysis. These findings help inform the role of CKD as a cost multiplier in CLD.

Our analysis characterized the group of patients with CLD and comorbid CKD as patients older in age with higher rates of comorbidities, including hypertension (90% vs. 52%; $P < 0.0001$) and T2DM (54% vs. 25%; $P < 0.0001$), compared to patients with CLD alone. These findings were partly expected given the role of cardiovascular and metabolic risk factors in both CKD and CLD. This result is consistent with a study by de Boccardo et al.[21] that examined the burden of CKD among long-term liver transplant recipients and similarly determined that patients with CKD tended to be older, were more likely to be hypertensive (59% vs. 38%), and have diabetes (43.3% vs. 19.3%). In this study, the CLD plus CKD group also tended to have more severe liver disease, as indicated by higher rates of liver transplants, DCC, and compensated cirrhosis.

The second primary finding of our analysis was an association of CKD with significant excess in cost

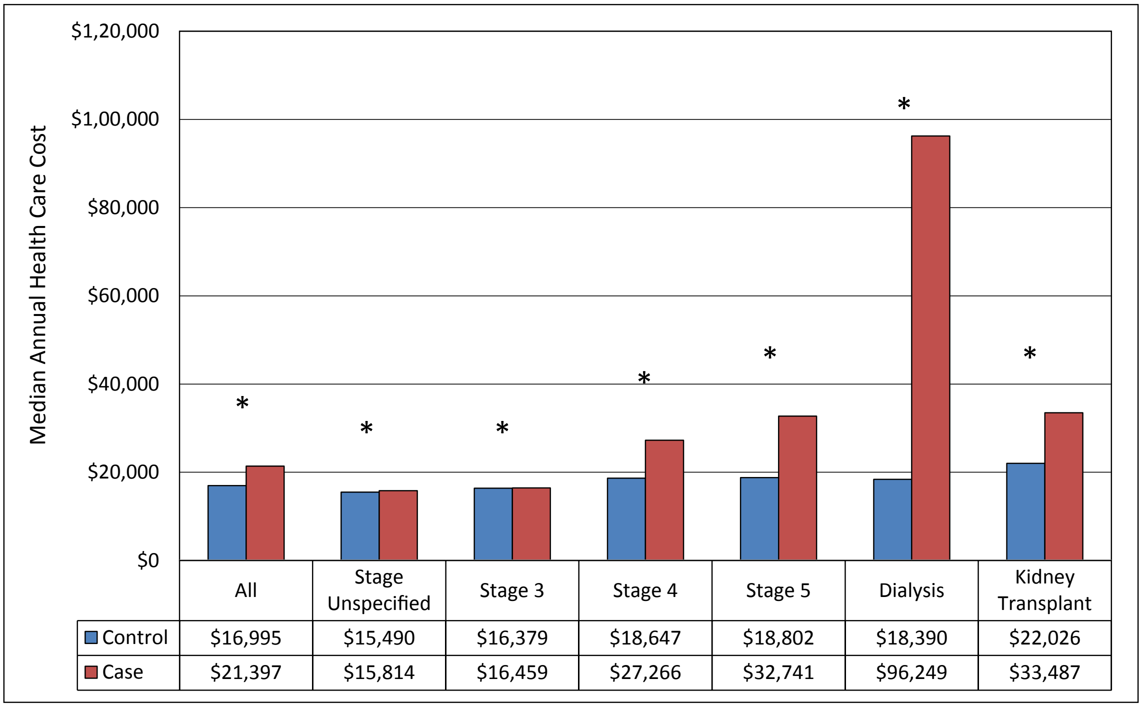


FIG. 3. Unadjusted median annual all-cause health care costs by CKD category for cases with both CLD and CKD versus matched controls with only CLD. *P < 0.05, Wilcoxon signed-rank tests for the total difference in annual health care cost between cases and controls by CKD category. All costs were adjusted to 2017 US$ using the medical care component of the Consumer Price Index.

burden and health care use over patients with CLD alone. Overall, there was an annual median total between-group per person cost difference of $4,402 and between-group per person claims difference of 14.66 during the 12-month study period. More outpatient visits and inpatient admissions mainly explained the total higher costs and use in the CKD plus CLD group versus patients with just CLD. In accord with our findings, another study using MarketScan found that total inpatient admissions and outpatient visits for patients with HCV and ESRD were significantly higher among patients with comorbid CKD and ESRD compared to those with HCV alone.[22] Health care costs were 1.7-fold and 2.5-fold higher in the non-ESRD CKD and ESRD groups, respectively, compared to the HCV-only group. Another study of the Optum databases found that patients with both HCV and CKD had significantly more comorbidities and higher health care costs ($5,481 vs. $1,922) than patients without CKD after HCV treatment.[23] While these studies represented CLD subgroups, our present findings confirm and extend previous observations to a broader context of CLD.

There are several potential explanations for higher health care use and cost burden in patients with both CKD and CLD compared to those with CLD alone. CKD itself is associated with high total and out-of-pocket health care expenditures, even in the early stages of disease.[24] Furthermore, several reports have described excess health care and cost burden attributable to comorbid CKD in various disease contexts, such as T2DM,[25] multiple myelomas,[26] and anemia.[27] CKD is associated with a progressive reduction in kidney function over time, resulting in higher stage progression and subsequently increased health care use and cost burdens.[28] The presence of uncontrolled risk factors or comorbidities, such as T2DM and hypertension, are significant cost drivers that can further accelerate rising costs in CKD.[14] As aforementioned, we observed a higher comorbidity burden alongside higher costs and use in the CLD plus CKD group in this study. These cost patterns suggest the need for timely medical intervention aimed at preventing CKD progression and controlling CKD risk factors and comorbidities.

The third main finding of our study regarded the relationship between age and health care burden in

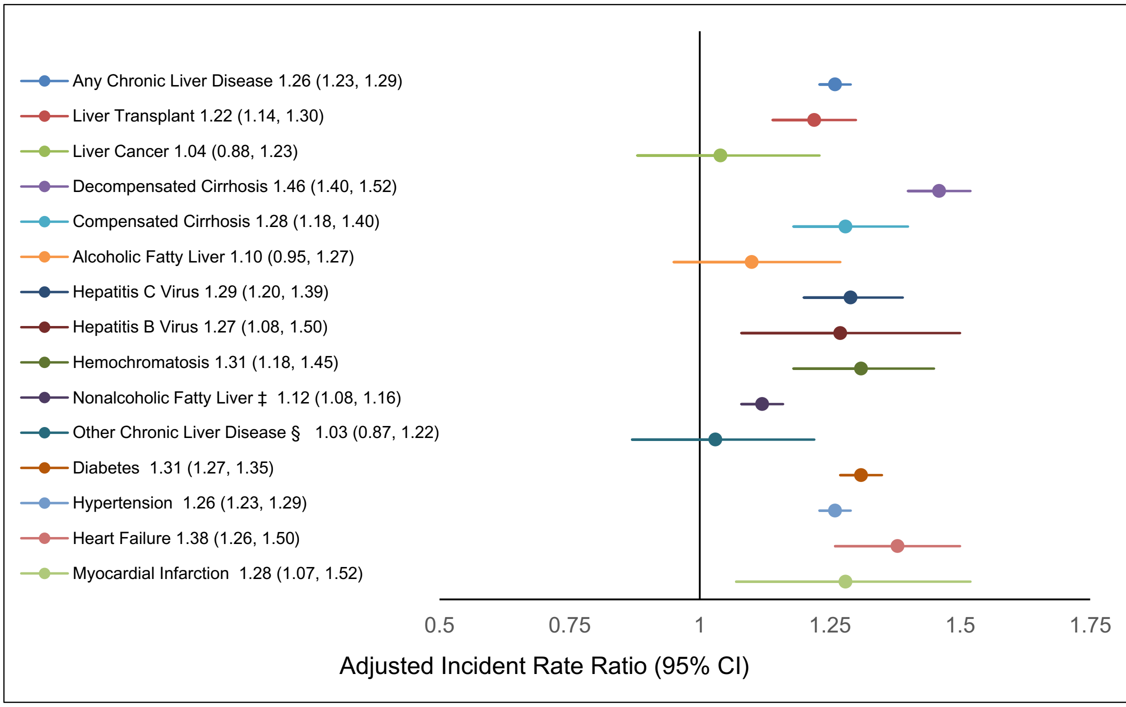


FIG. 4. Adjusted incident rate ratios for annual per person all-cause health care use by comorbidity status during the 12 months following the index date for matched patients with CLD versus without CKD. Data are adjusted for age group, sex, region of residence, type of health insurance, index year, CCI category (0, 1, 2, 3, and 4+), obesity, and smoking. ‡Defined as ICD-9-CM code 571.8 in the absence of any other CLD or any history of excessive alcohol use. §Autoimmune hepatitis, hepatitis E virus, primary biliary cirrhosis, and primary sclerosing cholangitis.

CLD with or without CKD. A subanalysis of health care costs by age group revealed that cost differences between the CKD and no CKD cohorts were highest among younger patients (i.e., ages 18-34 years), amounting to a median annual cost difference of $13,193 compared to a median cost difference of $4,066 in those 55+ years of age. The role of CKD as a cost multiplier in younger subjects with CLD may be in part related to the high costs of early stage disease diagnosis and management.[24] The main driver of cost differences in the 18-34 age group included inpatient admissions, outpatient visits, and pharmaceutical claims, while inpatient admissions and ED visits accounted for the cost differences in patients 55+ years old. Recent studies have documented rising rates of liver disease to related mortality in younger age groups,[29] raising concerns over increasing costs related to the additional burden of CKD in this youthful population.

The fourth finding of our analysis was that CKD burden varied by stage or status of liver disease. When health care cost and use were stratified by CKD stage, differences between the CKD and no CKD cohorts increased with disease severity and peaked among patients on dialysis. The mean difference in annual claims per person between patients with both CDK and CLD versus those with just CLD was 5.72, 19.75, and 24.15 in CKD stage 3, CKD stage 4, and CKD stage 5, respectively. Similarly, the median annual per person costs in nondialysis patients were $80, $8,619, and $13,939 higher in those with CLD in CKD stage 3, CKD stage 4, and CKD stage 5, respectively, compared with patients with CLD alone. These results are consistent with findings from a study of Medicare beneficiaries in which the direct cost of CKD increased as the disease severity worsened.[28]

Dialysis treatments amounted to case-control differences of 65.31 claims and $77,859 in CLD over the 12-month study period. This observation is consistent with previous literature documenting higher health care costs associated with CKD progression.[28] In contrast, the health care burden was generally

TABLE 4. ADJUSTED* ANNUAL PER PERSON ALL-CAUSE HEALTH CARE COSTS ($) BY COMORBIDITY STATUS DURING THE 12 MONTHS FOLLOWING THE INDEX DATE FOR MATCHED PATIENTS WITH CLD WITH AND WITHOUT CKD

Patient Subgroup	Number of Pairs	With CKD (95% CI)	Without CKD (95% CI)	*P* Value†
Any CLD	9,832	35,793 (32,323-39,637)	24,048 (21,709-24,048)	<0.0001
Liver transplant	825	49,231 (39,622-61.170)	38,080 (30,771-47,124)	0.0004
Liver cancer	139	65,997 (27,687-157,320)	71,283 (29,846-170,249)	0.6028
DCC	2,682	57,583 (46,512-71,290)	32,121 (25,650-40,225)	<0.0001
Compensated cirrhosis	504	28,205 (20,246-39,293)	17,642 (12,590-24,721)	<0.0001
AFL	186	21,079 (13,234-33,572)	15,333 (10,121-23,227)	0.0360
HCV	842	46,621 (34,327-63,320)	30,730 (22,643-41,707)	<0.0001
HBV	177	23,275 (15,271-35,474)	12,816 (9,076-18,099)	<0.0001
Hemochromatosis	455	39,668 (28,773-54,690)	24,048 (16,880-34,258)	<0.0001
Nonalcoholic fatty liver‡	3,863	22,531 (19,544-22,531)	18,212 (15,875-20,891)	<0.0001
Other CLD§	159	40,093 (27,781-57,859)	31,057 (24,174-39,900)	0.2265
Diabetes	5,192	43,536 (36,875-51,400)	25,255 (21,402-29,802)	<0.0001
Hypertension	8,807	37,122 (33,083-27,131)	24,181 (21,552-27,131)	<0.0001
Heart failure	534	40,903 (29,894-56,053)	21,663 (15,782-29,735)	<0.0001
MI	109	26,453 (14,030-49,874)	16,730 (9,104-29,433)	0.0058

*Adjusted for age group, sex, region of residence, type of health insurance, index year, CCI category (0, 1, 2, 3, and 4+), obesity, and smoking. All costs were converted to 2017 US$ using the medical care component of the Consumer Price Index.
†For the difference in annual health care cost between cases and controls of the same patient subgroup.
‡Defined as ICD-9-CM code 571.8 in the absence of any other CLD or any history of excessive alcohol use.
§Autoimmune hepatitis, hepatitis E virus, primary biliary cirrhosis, and primary sclerosing cholangitis.

lower among patients who had undergone kidney transplantation. This observation was also in line with the clinical preference for transplantation and studies establishing the cost effectiveness of transplantation compared to dialysis treatments.[30,31]

The fifth and perhaps most critical finding of our analysis informed the role of CKD as a cost multiplier in specific CLD contexts. In a study of 3.6 million inpatient admissions related to cirrhosis, the prevalence of acute kidney injury (AKI) in the United States doubled from 15% to 30% between 2004 and 2016. AKI was strongly associated with CKD development in patients with cirrhosis. In turn, the presence of AKI in cirrhosis resulted in an increase of $5,048 in median admission cost.[32] In a cohort study of 39,719 patients who underwent liver transplant, those with CKD pre-liver transplantation had a 16% higher mortality risk after the liver transplant relative to patients without CKD pre-liver transplantation.[33] A study of over 1 million CLD-related hospitalizations found the cost of inpatient admission in 2016 to be 18.6% higher in patients with CLD with CKD compared to CLD alone. [2]

Our study shows comorbid CKD was associated with an excess of unadjusted cost burden in various liver diseases, amounting to mean annual per person cost differences of $24,846 for liver transplant, $47,090 for DCC, $28,130 for compensated cirrhosis, $23,668 for HCV, $31,226 for HBV, and $10,062 for NAFLD. The results of our adjusted stratified cost analysis confirmed our initial results. These findings validate the importance of CKD as a cost multiplier in CLD and provide a foundation for future strategies to limit anticipated increases in cost and health care burdens associated with increasingly prevalent CLDs in the United States.

Although several liver diseases are associated with an increased risk of CKD, the overall burden of CLD in the United States is increasingly driven by the prevalence of NAFLD,[5] which at present is estimated to affect 25% of the population.[6] The rising prevalence of NAFLD is a significant global health problem given an epidemic of its risk factors, including obesity and T2DM.[34] Approximately 25% of patients with NAFLD progress to nonalcoholic steatohepatitis (NASH) and further to end-stage liver disease, hepatocellular carcinoma, and renal manifestations.[35] Costs associated with care for patients with NAFLD are high, independent of associated comorbidities, and especially at first diagnosis. In one study, the total annual cost of health care for privately insured patients with NAFLD was $7,804 for new diagnoses and $3,789 for long-term management.[4] Similarly, in 2017, the lifetime yearly cost for an estimated 232,000 incident NASH cases was $222.6 billion.[36] Collectively, these studies establish an important degree of cost and health care burden associated with both NAFLD and NASH and raise a further alarm for the additional burden imposed by CKD in this context.

The conclusions of the present study are bolstered by several essential design elements, including a stringent definition of CKD compared to similar studies (i.e., two separate diagnostic codes of CKD), the use of a randomized index date to capture whole disease burden, and a comprehensive analytic approach that stratified the case and control cohorts by age, disease staging, and comorbidity status. However, there are limitations. A principal limitation is the use of electronic health claims data, which do not always capture the complete clinical picture of a given disease context. Additionally, our analysis focused only on direct costs. The inclusion of indirect medical care costs may have further increased the estimated burden of CKD in CLD. Finally, patients included in our analysis were enrolled in private insurance; therefore, the results may not apply to patients with public health insurance.

Few other studies have examined incremental health care use and cost burden due to CKD in patients with the spectrum of CLD. The present findings indicate that CKD in CLD is associated with higher comorbidities as well as substantial excess health care and cost burden in the United States as determined from claims data for the period 2010-2015. Better screening practices for CKD in patients with existing CLD, additional efforts to promote timely lifestyle changes, and proactive treatment as well as comorbidity management are necessary to minimize the escalating burden of CKD in CLD.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1573/suppinfo.