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Outcomes, Mortality, and Cost Burden of Acute Kidney Injury and Hepatorenal Syndrome in Patients with Cirrhosis

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ABSTRACT

Background & Aims: Cirrhosis is associated with an increased risk of acute kidney injury (AKI) and hepatorenal syndrome (HRS). Healthcare utilization and cost burden of AKI and HRS in cirrhosis is unknown. We aimed to analyze the health care use and cost burden associated with AKI and HRS in patients with cirrhosis in the United States by using real-world claims data.

Methods: We conducted a case-control study using the Truven Health MarketScan Commercial Claims databases from 2007-2017. A total of 34,398 patients with cirrhosis with or without AKI and 4,364 patients with cirrhosis with or without HRS were identified using International Classification of Diseases, Ninth or Tenth Revision, codes and matched 1:1 by sociodemographic characteristics and comorbidities using propensity scores. Total and service-specific were quantified for the 12-months following versus the 12-months before the first date of AKI or HRS diagnosis and over 12-months following a randomly selected date for cirrhosis controls to capture entire disease burdens.

Results: The AKI and HRS group had a higher number of comorbidities and were associated with higher rates of readmission and mortality. The AKI and HRS groups had a significantly higher prevalence of ascites, spontaneous bacterial peritonitis (SBP), encephalopathy, gastrointestinal bleeding, septic shock, pulmonary edema, and respiratory failure. Compared to patients with cirrhosis only, AKI was associated with higher number of claims per person (AKI vs. cirrhosis only, 60.30 vs. 47.09; p<0.0001) and total annual median health care costs (AKI vs. cirrhosis only, $46,150 vs. $26,340; p<0.0001). Compared to patients with cirrhosis only, the HRS cohort was associated with a higher number of claims per person (HRS vs. cirrhosis only, 44.96 vs. 43.50; p<0.0009) and total annual median health care costs (HRS vs. cirrhosis only, $34,912 vs. $23,354; p<0.0001). Inpatient costs were higher than the control cohort for AKI (AKI vs. cirrhosis only, $72,720 vs. $29,111; p<0.0001) and HRS (HRS vs. cirrhosis only, $ 98,246 vs. $27,503; p<0.0001). Compared to the control cohort, AKI and HRS had a higher rate of inpatient admission, mean number of inpatient admissions, and mean total length of stay.

Conclusions: AKI and HRS are associated with higher health care utilization and cost burden compared to cirrhosis alone, highlighting the importance for improved screening and treatment modalities.

Key words: acute kidney injury – hepatorenal syndrome – cirrhosis – cost burden.

Abbreviations: AKI: acute kidney injury; ALD: alcoholic liver disease; ED: emergency department; HRS: hepatorenal syndrome; NAFLD: nonalcoholic fatty liver disease; NIS: National Inpatient Sample; SBP: spontaneous bacterial peritonitis.

INTRODUCTION

Cirrhosis is a leading cause of mortality and morbidity worldwide. It is the 11th leading cause of death and 15th leading cause of morbidity, accounting for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide in 2016 [1]. In the US, increasing prevalence of cirrhosis and chronic liver disease is shifting more towards alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) due to improvements in the management of viral hepatitis [2-4]. Cirrhosis has led to more hospitalizations, readmissions, longer stays, and poorer outcomes compared to other prevalent chronic diseases [5]. One study estimates the burden of cirrhosis and chronic liver disease in the United States (US) to be in the range of $2.5 billion with indirect costs

up to $10.6 billion [6]. Between 2008 and 2014, hospitalization costs in patients with cirrhosis increased by 30.2% to $7.37 billion, driven by increasing number of admissions, length of stay, procedural interventions, and complications [7].

Acute kidney injury (AKI) is a very common diagnosis and is becoming increasingly prevalent, particularly in hospitalized patients. A large systematic review found that AKI occurred in one in five adults hospitalized with an acute illness [8]. Using the National Inpatient Sample (NIS) database, a study showed that total number of hospitalizations with AKI increased from 953,926 in 2000 to 1,823,054 in 2006 and 3,959,560 in 2014 [9].

Hepatorenal syndrome (HRS), or HRS-AKI, and AKI are prevalent in patients with cirrhosis and are associated with poorer outcomes. The incidence of AKI in hospitalized patients with cirrhosis varies from 25-50% [10]. Several studies have reported incidence rates of HRS-AKI between 27% and 53% in patients who are hospitalized for complications of cirrhosis [10-13]. Renal dysfunction, including HRS-AKI and non-HRS-AKI, is associated with increased mortality and morbidity. One study showed that 26% of patients with AKI and cirrhosis die before discharge [14]. Another study showed that patients with AKI and cirrhosis have a very high mortality rate of 58% and 63% in 1 and 12 months, respectively [15]. Patients who are discharged are more prone to developing complications of cirrhosis, such as ascites and hepatic encephalopathy [16, 17]. Similarly, patients with HRS have as high as 80% mortality rate within 2 weeks of detection and 90% mortality rate within 3 months [18].

Acute kidney injury is associated with increased health care utilization and costs. In a US study, patients with a KDIGO stage 2 AKI had a 6.5-fold increased adjusted odds ratio for death, prolonged hospital stay (defined as > 3.5 days), and an additional USD$9,000 in hospital costs compared to hospitalized patients who did not develop AKI [19]. Patients with HRS have been shown to have higher hospital costs driven by longer hospitalizations, and a higher rate of readmissions [20]. However, a direct comparison and data regarding the magnitude of health care utilization and cost burden linked to AKI and HRS in patients with cirrhosis is lacking. Using real world claims data from the US, we aimed to assess the health care utilization and cost burdens of AKI and HRS in patients with cirrhosis by conducting a propensity-score matched case-control analysis using commercial insurance data.

METHODS

Data Source

Our study is a case-control study using the Truven Health MarketScan® Commercial Claims (MSCC) database from January 1, 2007, to December 31, 2017. The claims data represent health care records from government and public organizations, large employers, and health plans from approximately 350 payers annually. The MSCC database includes longitudinal individual-level data for health insurance claims including inpatient, outpatient, and prescription drugs. The MSCC provides the total gross cost of care which is 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 MSCC database contains de-identified data that is compliant with all United States patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. The Internal Review Board (IRB) of Rutgers Robert Wood Johnson Medical School approved the protocol of this study.

Study Sample

The study sample was created with inpatient admissions and outpatient records from January 1st, 2007 to December 31st 2017 and included adult (≥18+) patients with cirrhosis. Cirrhosis, AKI, and HRS diagnoses were defined as one inpatient admission or outpatient service diagnosis using International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) or Tenth revision (ICD-10-CM) code (Table I).

Table I. ICD9/ICD10 codes for AKI, HRS, Cirrhosis

Name	ICD-9 Codes	ICD-10 Codes
AKI	584.9	N17.9
HRS	572.4	K76.7
Cirrhosis	571.5, 571.2, 456.1, 456.21, 456.0, 456.20, 572.4, 567.0, 567.2x, 567.8x, 567.9, 789.5,789.50,789.59, 572.3, 572.2	K74.6, K74.60, K74.69, K70.3, K70.30, K70.31, I85.00, I85.10, I85.01, I85.11, K76.7, K65.0, K65.1, K65.2, K65.8, K65.9, R18.8, K71.51, K76.6, K72.91

ICD: International Classification of Disease; AKI: acute kidney injury; HRS: hepatorenal syndrome.

The case cohort included patients with both cirrhosis and a diagnosis of AKI or HRS whereas the control cohort included patients with only cirrhosis. We defined an index date for each participant as either the earliest date of AKI or HRS diagnoses for potential cases, or a randomly selected claim date for cirrhosis controls without AKI/HRS. A baseline period of 12 months prior to their respective index date was defined for all participants. The study follow-up period represented the 12 months following each participant's index date. Eligible subjects had at least 12 months of continuous enrollment before and after their defined index date.

Study Variables

Index date records were used to obtain demographics, including age, gender, region of residence, and healthcare insurance plan. A medical history comorbidity profile was acquired from each participant during the baseline period using ICD-9-CM/ICD-10-CM codes collected from inpatient admissions and outpatient services. The comorbidity profile included ascites, spontaneous bacterial peritonitis (SBP), encephalopathy, variceal bleeding, gastrointestinal bleeding, rectal bleeding, sepsis, shock, respiratory failure, pulmonary edema, ventilator dependence, dialysis, and kidney transplant. Medications, such as the use of midodrine or octreotide, and a history of smoking and alcohol use were captured from records before the index date. In addition, the total weighted Charlson Comorbidity Index (CCI) score was calculated for each participant using the baseline period records [21]. Inpatient admission and mortality at 30, 90, 180-days were

captured after index. Healthcare utilization and cost in terms of a total number of claims, inpatient admissions, emergency department visits, outpatient visits, and pharmaceutical claims were captured during the 12-month post-index date.

Matching Procedure

We used propensity score matching to ensure the comparability between the distrubtion of all observed baseline demographics and comorbidity profiles. A propensity score was estimated for each patient using a multivariate logistic regression model with AKI/HRS as the outcome and age group, gender, region of residence, type of health insurance, CCI category (0, 1, 2, 3, 4+), T2DM, and HTN as covariates. The estimated propensity scores were then used to match cases 1:1 to controls using the GREEDY algorithm while matching exactly on age group and gender.

Healthcare Utilization and Costs

Healthcare utilization parameters included the number of claims per patient for inpatient admission, Emergency Department (ED) visits, outpatient visits, pharmaceutical claims/prescriptions, and the sum or total number of claims. The cost burden associated with a new AKI/HRS diagnosis was assessed by aggregating health care use and cost parameters over the 12 months before and after the first diagnosis of AKI and HRS. We quantified all use and cost parameters over the 12 months following a randomly selected index date for cirrhosis controls, to compare the burden of AKI and HRS with that of matched patients with cirrhosis patients.

Health care utilization was measured with the mean, median, and $25^{th}/75^{th}$ percentiles of the number of claims per patient for inpatient admissions, ED visits, outpatient visits, and pharmaceutical claims/prescriptions. Similarly, the mean, median, and $25^{th}/75^{th}$ percentile per person healthcare expenses were estimated for both overall and service-specific costs in the 12 months following the index date. The prevalence of having at least 1 inpatient admission, ED visit, and outpatient visit was estimated. Furthermore, the mean, median, and $25^{th}/75^{th}$ percentile of the total length of stay was also estimated for the 12 months following the index date. All cost estimates were adjusted to the 2017 US$ using the medical care commodities component of the Consumer Price Index.

Statistical Analysis

We compared the groups‘ baseline characteristics and comorbidity profiles between the case and control cohorts before and after matching using standardized differences of means for continuous variables and standardized differences of proportions for categorized variables. We used standardized difference cutoffs of 0.2, 0.5, and 0.8 to indicate small, medium, and significant differences between the means and proportions of the compared groups [22, 23]. Wald Chi-square tests were performed to test associations between AKI/HRS status, categorical patient characteristics, and comorbidity profiles in the unmatched samples. Wilcoxon signed-ranked tests were used to compare cases and controls on all continuous measures of healthcare cost and utilization. McNemar tests were used to examine all dichotomous parameters of healthcare utilization. A p-value of < 0.05 was considered statistically significant. The study analysis was performed using the SAS 9.4 software (SAS Institute, NC, USA).

RESULTS

Sample Characteristics and Comorbidity Profiles

The study sample included 446,582 patients with cirrhosis who met the inclusion criteria of age ≥18 and continuous enrollment for 12 months before and after the index date (Fig. 1). Of the 446,582 who met the inclusion criteria, 68,782 patients with AKI, 4,913 with HRS, and 372,887 with cirrhosis only. Patients were only included in the statistical analysis if the diagnosis date of AKI or HRS was not earlier than the date of their cirrhosis diagnosis. Therefore, 34,398 and 4,364 patients were included where the diagnosis of AKI and HRS, respectively, followed the first diagnosis date of cirrhosis. Both cohorts were matched 1:1 using propensity scores to the control cohort (only cirrhosis).

Between-group differences in the unmatched and matched samples are summarized in Table II. Comparing the AKI and HRS cohorts with the control (cirrhosis only) cohort, patients in the AKI and HRS cohort were generally older (53.34 vs 53.06 vs. 47.81; $p<0.0001$), male (54.04% vs 61.32% vs. 40.68%; $p<0.0001$), and had higher comorbidities compared to the cirrhosis only cohort (CCI 4+, AKI vs. HRS vs. cirrhosis only, 18.96% vs 12.42% vs. 3.41%; $p<0.0001$). An analysis of specific comorbidities emphasized the relative prevalence of diabetes mellitus (39.29% vs 32.17% vs. 21.14%; $p<0.0001$). The AKI and HRS cohorts also exhibited higher prevalence of smoking, alcohol use, and were more likely taking midodrine compared to the control cohort (Table II).

Comparison of Outcomes among the AKI, HRS, and Control Cohort

The prevalence of complications, readmissions, and mortality in the unmatched and matched samples are represented in Table III. The AKI and HRS cohorts demonstrated higher rates of ascites, SBP, encephalopathy, variceal bleeding, gastrointestinal bleeding, and septic shock (Table III). In the unmatched and matched samples, patients were more often administered midodrine in the AKI and HRS cohorts compared to the cirrhosis only cohort. In a comparison among unmatched samples, patients in the AKI and HRS cohorts had a higher rate of requiring dialysis and kidney transplant compared to patients in the control cohort. Following propensity matching, patients in the AKI and HRS cohort had a higher prevalence of requiring dialysis compared to the control. In the unmatched and matched samples, patients in the AKI and HRS cohort had a higher prevalence of respiratory complications, including pulmonary edema, respiratory failure, and ventilator dependence compared to patients with cirrhosis only. Readmission rates in 30, 90, and 180 days were analyzed among the groups. The AKI and HRS cohorts had higher rates of readmission in 30, 90, and 180 days compared to the control. Furthermore, patients in the AKI and HRS cohort had a higher rate of mortality within 7, 30, 90, 180, and 365 days compared to patients with cirrhosis only. The prevalence of readmission and mortality remained statistically significant following propensity matching.

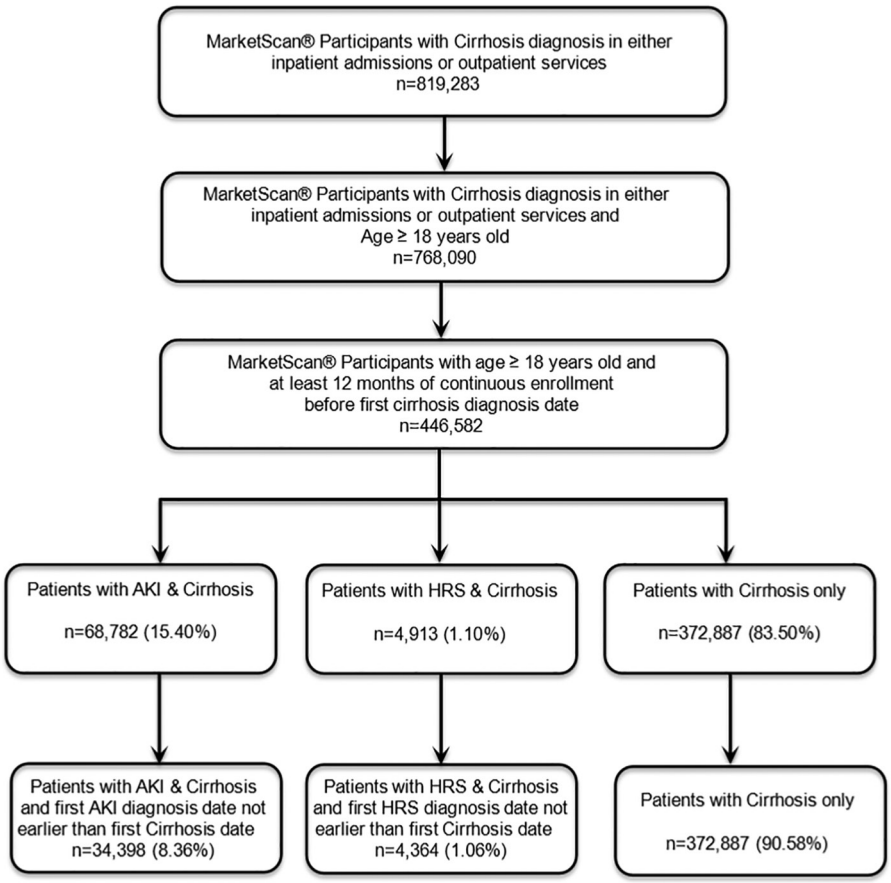

Fig. 1. Diagram for study sample selection

Comparison of Outcomes between the AKI and HRS Cohorts

Subgroup analysis and a comparison of outcomes between the AKI and HRS cohorts are shown in Table III. The AKI cohort had a higher prevalence of ascites, sepsis, septic shock, respiratory failure, and ventilator dependence compared to the HRS cohort. Furthermore, the AKI cohort had a higher rate of 30-, 90-, and 180-day inpatient readmissions compared to the HRS cohort. On the other hand, the HRS cohort was more likely to be affected by spontaneous bacterial peritonitis, encephalopathy, variceal bleeding, and GI bleeding compared to the AKI cohort. There was a significantly higher utilization of midodrine in HRS compared to AKI cohort, but no significant difference in the use of octreotide. The HRS cohort had a higher rate of mortality, including within 7, 30, 90, 180, and 365 days, compared to the AKI cohort.

Cost Burden of AKI in Patients with Cirrhosis

Healthcare utilization and cost was compared between patients with a diagnosis of an AKI and cirrhosis and cirrhosis without AKI during the 12-month post-index date (Table IV). The total number of claims was significantly higher in the 12-month period after AKI diagnosis compared to the baseline period (mean total number of claims, 60.30 vs. 47.09, p<0.0001), representing an increase of 13.21 (95%CI: 12.44-13.99) claims after diagnosis. The increase in total claims is driven by inpatient admissions (mean visits, 16.84 vs 6.68; p<0.0001) and outpatient visits (mean visits, 28.16 vs. 25.59; p<0.0001). The prevalence of at least one inpatient admission was significantly higher in the AKI cohort compared to the control cohort during the index period (91.36% vs. 59.35%; p<0.0001). The average length of the inpatient stay in the AKI cohort was significantly higher compared to the control cohort (mean total length of stay, 12.50 vs 5.51, p<0.0001), representing an increase of 6.99 (95% CI: 6.71, 7.27) days in the 12-month period following index date.

Health care costs in the 12 months following the index date were compared and analyzed between the matched AKI and cirrhosis control cohort (Table V). The per-patient total costs of health care services within 12 months after the index was in the AKI cohort compared to the no AKI, or control, cohort (median total cost, $46,150 vs $26,340, respectively; p<0.0001). Higher costs in the AKI cohort can be attributed to inpatient admissions (median total cost, $24,470 vs $4,732; p<0.0001).

Cost Burden of HRS in Patients with Cirrhosis

Health care use was compared between matched HRS cases and cirrhosis only controls (Table VI). The total number of claims in the 12 months following the index date was significantly higher in the HRS cohort compared to the control cohort (mean total number of claims, 44.96 vs 43.50; p<0.0009). The increase in total number of claims can be attributed to inpatient admissions (mean visits, 15.49 vs 5.91; p<0.0001).

Table II. Baseline characteristics of the study sample of patients by group

	Unmatched (n=411,649)			P-Value			Cirrhosis 1:1 matched to AKI†		P-Value	Cirrhosis 1:1 matched to HRS†		P-Value
Patient Characteristics *	AKI	HRS	Cirrhosis Controls	AKI vs. HRS	AKI vs. Controls	HRS vs. Controls	AKI	Cirrhosis Controls		HRS	Cirrhosis Controls	
	(n=34,398)	(n=4,364)	(n=372,887)				(n=34,398)	(n=34,398)		(n=4,364)	(n=4,364)	
Age [Mean (SD)]	53.34 (9.71)	53.06 (9.06)	47.81 (12.34)	0.0640	<0.0001	<0.0001	53.34 (9.71)	53.22 (9.76)	0.1212	53.06 (9.06)	52.88 (9.43)	0.3395
Age Group [n (%)]				<0.0001	<0.0001	<0.0001			1.0000			1.0000
18-34	2,070 (6.02)	215 (4.93)	63,337 (16.99)				2,070 (6.02)	2,070 (6.02)		215 (4.93)	215 (4.93)	
35-44	3,490 (10.15)	484 (11.09)	63,782 (17.10)				3,490 (10.15)	3,490 (10.15)		484 (11.09)	484 (11.09)	
45-54	9,273 (26.96)	1,354 (31.03)	106,231 (28.49)				9,273 (26.96)	9,273 (26.96)		1,354 (31.03)	1,354 (31.03)	
55+	19,565 (56.88)	2,311 (52.96)	139,537 (37.42)				19,565 (56.88)	19,565 (56.88)		2,311 (52.96)	2,311 (52.96)	
Gender [n (%)]				<0.0001	<0.0001	<0.0001			1.0000			1.0000
Male	18,587 (54.04)	2,676 (61.32)	151,686 (40.68)				18,587 (54.04)	18,587 (54.04)		2,676 (61.32)	2,676 (61.32)	
Female	15,811 (45.96)	1,688 (38.68)	221,201 (59.32)				15,811 (45.96)	15,811 (45.96)		1,688 (38.68)	1,688 (38.68)	
Region of Residence [n (%)]				<0.0001	<0.0001	<0.0001			0.9895			0.9999
Northeast	6,100 (17.73)	804 (18.42)	74,324 (19.93)				6,100 (17.73)	6,101 (17.74)		804 (18.42)	805 (18.45)	
North Central	8,084 (23.50)	931 (21.33)	81,326 (21.81)				8,084 (23.50)	8,080 (23.49)		931 (21.33)	928 (21.61)	
South	14,563 (42.34)	1,655 (37.92)	145,890 (39.12)				14,563 (42.34)	14,572 (42.36)		1,655 (37.92)	1,657 (37.97)	
West	5,078 (14.76)	894 (20.49)	63,852 (17.12)				5,078 (14.76)	5,090 (14.80)		894 (20.49)	896 (20.53)	
Unknown	573 (1.67)	80 (1.83)	7,495 (2.01)				573 (1.67)	555 (1.61)		80 (1.83)	78 (1.79)	
Type of Health Insurance [n (%)]				0.0266	<0.0001	<0.0001			0.9999			1.0000
Preferred Provider Organization	20,622 (59.95)	2,591 (59.37)	231,396 (62.06)				20,622 (59.95)	20,638 (60.00)		2,591 (59.37)	2,593 (59.42)	
Health maintenance organization	3,569 (10.38)	518 (11.87)	41,550 (11.14)				3,569 (10.38)	2,567 (10.37)		518 (11.87)	518 (11.87)	
Comprehensive	1,657 (4.82)	196 (4.49)	10,457 (2.80)				1,657 (4.82)	1,649 (4.79)		196 (4.49)	195 (4.47)	
Point-of- Service with Capitation	2,899 (8.43)	377 (8.64)	29,356 (7.87)				2,899 (8.43)	2,895 (8.42)		377 (8.64)	376 (8.62)	
Other	5,651 (16.43)	682 (15.63)	60,128 (16.12)				5,651 (16.43)	5,649 (16.42)		682 (15.63)	682 (15.63)	
Comorbidity Profile ‡												
Charlson Comorbidity Index [Mean (SD)]	2.16 (1.59)	1.64 (1.53)	0.88 (1.13)	<0.0001	<0.0001	<0.0001	2.16 (1.59)	2.12 (1.52)	0.0011	1.64 (1.53)	1.63 (1.50)	0.6814
Charlson Comorbidity Index [n (%)]				<0.0001	<0.0001	<0.0001			1.0000			1.0000
0	5,511 (16.02)	1,226 (28.09)	185,795 (49.83)				5,511 (16.02)	5,511 (16.02)		1,226 (28.09)	1,227 (28.12)	
1	7,444 (21.64)	1,111 (25.46)	100,589 (26.98)				7,444 (21.64)	7,444 (21.64)		1,111 (25.46)	1,110 (25.44)	

Table II (continued)

2	8,568 (24.91)	909 (20.83)	51,937 (13.93)				8,568 (24.91)	8,566 (24.90)		909 (20.83)	908 (20.81)	
3	6,352 (18.47)	576 (13.20)	21,850 (5.86)				6,352 (18.47)	6,360 (18.49)		576 (13.20)	577 (13.22)	
4+	6,523 (18.96)	542 (12.42)	12,716 (3.41)				6,523 (18.96)	6,517 (18.95)		542 (12.42)	542 (12.42)	
Diabetes [n (%)]	13,514 (39.29)	1,404 (32.17)	78,827 (21.14)	<0.0001	<0.0001	<0.0001	13,514 (39.29)	13,520 (39.30)	0.9626	1,404 (32.17)	1,404 (32.17)	1.0000
* Variables above are involved in the logistic regression model.												
Year [n (%)]				<0.0001	<0.0001	<0.0001			<0.0001			<0.0001
2008	1,182 (3.44)	138 (3.16)	23,401 (6.28)				1,182 (3.44)	18.23 (5.30)		138 (3.16)	250 (5.73)	
2009	3,150 (9.16)	453 (10.38)	45,657 (12.24)				3,150 (9.16)	4,173 (12.13)		453 (10.38)	539 (12.35)	
2010	3,493 (10.15)	500 (11.46)	43,999 (11.80)				3,493 (10.15)	4,174 (12.13)		500 (11.46)	487 (11.16)	
2011	3,848 (11.19)	510 (11.69)	45,741 (12.27)				3,848 (11.19)	4,390 (12.76)		510 (11.69)	506 (11.59)	
2012	4,693 (13.64)	633 (14.51)	53,202 (14.27)				4,693 (13.64)	4,909 (14.27)		633 (14.51)	561 (12.86)	
2013	3,899 (11.33)	513 (11.76)	38,363 (10.29)				3,899 (11.33)	3,270 (9.51)		513 (11.76)	446 (10.22)	
2014	4,286 (12.46)	505 (11.57)	40,631 (10.90)				4,286 (12.46)	3,599 (10.46)		505 (11.57)	507 (11.62)	
2015	3,382 (9.83)	371 (8.50)	28,822 (7.73)				3,382 (9.83)	2,649 (7.70)		371 (8.50)	342 (7.84)	
2016	3,363 (9.78)	403 (9.23)	27,728 (7.44)				3,363 (9.78)	2,731 (7.94)		403 (9.23)	370 (8.48)	
2017	3,102 (9.02)	338 (7.75)	25,343 (6.80)				3,102 (9.02)	2,680 (7.79)		338 (7.75)	356 (8.16)	
BMI				0.6028	<0.0001	0.4342			<0.0001			0.3631
≤ 25	460 (15.28)	42 (15.56)	3,685 (16.11)				460 (15.28)	360 (14.39)		42 (15.56)	38 (12.79)	
25-30	499 (16.57)	52 (19.26)	4,063 (17.76)				499 (16.57)	464 (18.55)		52 (19.26)	50 (16.84)	
30-35	501 (16.64)	50 (18.52)	4,103 (17.93)				501 (16.64)	482 (19.26)		50 (18.52)	64 (21.55)	
35-40	296 (9.83)	24 (8.89)	2,893 (12.64)				296 (9.83)	311 (12.43)		24 (8.89)	39 (13.13)	
40+	1,255 (41.68)	102 (37.78)	8,135 (35.56)				1,255 (41.68)	885 (35.37)		102 (37.78)	106 (35.69)	
Smoking [n (%)]	7,917 (23.02)	904 (20.71)	63,686 (17.08)	0.0006	<0.0001	<0.0001	7,917 (23.02)	8,183 (23.79)	0.0166	904 (20.71)	912 (20.90)	0.8329
Alcohol [n (%)]	5,514 (16.03)	1,571 (36.00)	26,270 (7.05)	<0.0001	<0.0001	<0.0001	5,514 (16.03)	2,852 (8.29)	<0.0001	1,571 (36.00)	423 (9.69)	<0.0001
Ascites [n (%)]	22,608 (65.72)	2,674 (61.27)	180,188 (48.32)	<0.0001	<0.0001	<0.0001	22,608 (65.72)	16,604 (48.27)	<0.0001	2,674 (61.27)	1,992 (45.65)	<0.0001
Spomtaneous Bacterial Peritonitis [n (%)]	838 (2.44)	456 (10.45)	582 (0.16)	<0.0001	<0.0001	<0.0001	838 (2.44)	75 (0.22)	<0.0001	456 (10.45)	6 (0.14)	<0.0001
Encephalopathy [n (%)]	5,113 (14.86)	1,638 (37.53)	9,154 (2.45)	<0.0001	<0.0001	<0.0001	5,113 (14.86)	1,446 (4.20)	<0.0001	1,638 (37.53)	149 (3.41)	<0.0001
Variceal bleeding [n (%)]	2,406 (6.99)	857 (19.64)	8,264 (2.22)	<0.0001	<0.0001	<0.0001	2,406 (6.99)	880 (2.56)	<0.0001	857 (19.64)	101 (2.31)	<0.0001
GI bleed [n (%)]	5,580 (16.22)	997 (22.85)	19,322 (5.18)	<0.0001	<0.0001	<0.0001	5,580 (16.22)	3,027 (8.80)	<0.0001	997 (22.85)	307 (7.03)	<0.0001
Rectal bleed [n (%)]	3,459 (10.06)	449 (10.29)	24,566 (6.59)	0.6302	<0.0001	<0.0001	3,459 (10.06)	3,101 (9.02)	<0.0001	449 (10.29)	394 (9.03)	0.0463
Sepsis [n (%)]	11,292 (32.83)	684 (15.67)	63,916 (17.14)	<0.0001	<0.0001	0.0105	11,292 (32.83)	6,276 (18.25)	<0.0001	684 (15.67)	811 (18.58)	0.0003
Septic shock [n (%)]	2,482 (7.22)	155 (3.55)	2,119 (0.57)	<0.0001	<0.0001	<0.0001	2,482 (7.22)	433 (1.26)	<0.0001	155 (3.55)	39 (0.89)	<0.0001
Octreotide [n (%)]	12 (0.03)	2 (0.05)	36 (0.01)	0.7200	<0.0001	0.0715	12 (0.03)	8 (0.02)	0.3710	2 (0.05)	2 (0.05)	1.0000

Table II (continued)

Midodrine [n (%)]	109 (0.32)	60 (1.37)	228 (0.06)	<0.0001	<0.0001	<0.0001	109 (0.32)	53 (0.15)	<0.0001	60 (1.37)	6 (0.14)	<0.0001
Dialysis [n (%)]	403 (1.17)	57 (1.31)	852 (0.23)	0.4394	<0.0001	<0.0001	403 (1.17)	267 (0.78)	<0.0001	57 (1.31)	27 (0.62)	0.0010
Kidney transplant [n (%)]	1,035 (3.01)	39 (0.89)	1,423 (0.38)	<0.0001	<0.0001	<0.0001	1,035 (3.01)	322 (0.94)	<0.0001	39 (0.89)	36 (0.82)	0.7279
Respiratory failure [n (%)]	12,368 (35.96)	1,284 (29.42)	24,014 (6.44)	<0.0001	<0.0001	<0.0001	12,368 (35.96)	4,300 (12.50)	<0.0001	1,284 (29.42)	470 (10.77)	<0.0001
Pulmonary edema [n (%)]	1,376 (4.00)	149 (3.41)	1,949 (0.52)	0.0607	<0.0001	<0.0001	1,376 (4.00)	436 (1.27)	<0.0001	149 (3.41)	46 (1.05)	<0.0001
Ventilator dependence [n (%)]	1,848 (5.37)	150 (3.44)	2,506 (0.67)	<0.0001	<0.0001	<0.0001	1,848 (5.37)	543 (1.58)	<0.0001	150 (3.44)	53 (1.21)	<0.0001
Total Death [n (%)]	5,408 (15.72)	1,039 (23.81)	6,930 (1.86)	<0.0001	<0.0001	<0.0001	5,408 (15.72)	1,425 (4.14)	<0.0001	1,039 (23.81)	152 (3.48)	<0.0001
7 Days Mortality [n (%)]	217 (0.63)	86 (1.97)	364 (0.10)	<0.0001	<0.0001	<0.0001	217 (0.63)	76 (0.22)	<0.0001	86 (1.97)	10 (0.23)	<0.0001
30 Days Mortality [n (%)]	626 (1.82)	205 (4.70)	1,249 (0.33)	<0.0001	<0.0001	<0.0001	626 (1.82)	281 (0.82)	<0.0001	205 (4.70)	23 (0.53)	<0.0001
90 Days Mortality [n (%)]	1,052 (3.06)	274 (6.28)	2,216 (0.59)	<0.0001	<0.0001	<0.0001	1,052 (3.06)	459 (1.33)	<0.0001	274 (6.28)	46 (1.05)	<0.0001
180 Days Mortality [n (%)]	1,336 (3.88)	321 (7.36)	2,885 (0.77)	<0.0001	<0.0001	<0.0001	1,336 (3.88)	588 (1.71)	<0.0001	321 (7.36)	59 (1.35)	<0.0001
365 Days Mortality [n (%)]	1,573 (4.57)	337 (7.72)	2,523 (0.94)	<0.0001	<0.0001	<0.0001	1,573 (4.57)	722 (2.10)	<0.0001	337 (7.72)	80 (1.83)	<0.0001
30 Days Inpatient Admission [n (%)]	30,320 (88.14)	3,330 (76.31)	160,157 (42.95)	<0.0001	<0.0001	<0.0001	30,320 (88.14)	17,218 (50.06)	<0.0001	3,330 (76.31)	2,089 (47.87)	<0.0001
90 Days Inpatient Readmission [n (%)]	8,341 (24.25)	907 (20.78)	26,936 (7.22)	<0.0001	<0.0001	<0.0001	8,341 (24.25)	3,588 (10.43)	<0.0001	907 (20.78)	430 (9.85)	<0.0001
180 Days Inpatient Readmission [n (%)]	10,600 (30.82)	1,056 (24.20)	38,642 (10.36)	<0.0001	<0.0001	<0.0001	10,600 (30.82)	4,956 (14.41)	<0.0001	1,056 (24.20)	596 (13.66)	<0.0001

*All demographics data were obtained on the first date of AKI or HRS diagnosis for cases and random record after first Cirrhosis diagnosis for controls; †AKI cases and AKI-free cirrhosis and HRS cases and HRS-free cirrhosis controls were matched 1:1 using propensity scoring. The logistic regression model used to estimate propensity scores included age group, region of residence, sex, type of health insurance, CCI, ascites, spontaneous bacterial peritonitis, encephalopathy, vatical bleeding, GI bleed, rectal bleed, sepsis, septic shock, octreotide, midodrine, dialysis, kidney transplant, respiratory failure, pulmonary edema, and ventilator dependence. ‡Estimated from records before the first date of AKI or HRS diagnosis for cases and records before the randomdate for controls.

Table III. Healthcare resource utilization in the AKI and Cirrhosis cohort within 12 months after index

Healthcare Utilization	AKI (n=34,398)	Cirrhosis Controls (n=34,398)	p*	Difference (95% CI)
Total Number of Claims				
Mean (SD)	60.30 (58.40)	47.09 (46.18)	<0.0001	13.21 (12.44, 13.99)
Median [25th, 75th Percentile]	43 (16, 87)	34 (15, 64)		
Inpatient Admissions				
Prevalence of at least one visit [n (%)]	31,427 (91.36)	20,414 (59.35)	<0.0001	0.32 (0.31, 0.33)
Number of Admissions				
Mean (SD)	16.84 (24.56)	6.68 (13.14)	<0.0001	10.16 (9.87, 10.46)
Median [25th, 75th Percentile]	9 (4, 20)	2 (0, 8)		
Total Length of Stay [days]				
Mean (SD)	12.50 (23.38)	5.51 (13.13)	<0.0001	6.99 (6.71, 7.27)
Median [25th, 75th Percentile]	5 (0, 14)	0 (0, 6)		
Emergency Department Visits				
Prevalence of at least one visit [n (%)]	12,166 (35.37)	12,595 (36.62)	<0.0001	-0.01 (-0.02, -0.01)
Number of Visits				
Mean (SD)	0.89 (2.42)	0.85 (2.25)	0.1964	0.03 (0, 0.07)
Median [25th, 75th Percentile]	0 (0, 1)	0 (0, 1)		
Outpatient Visits				
Prevalence of at least one visit [n (%)]	31,661 (92.04)	33,696 (97.96)	<0.0001	-0.06 (-0.06, -0.06)
Number of Visits				
Mean (SD)	28.16 (33.72)	25.59 (30.90)	<0.0001	2.58 (2.10, 3.06)
Median [25th, 75th Percentile]	18 (4, 40)	16 (7, 34)		
Pharmaceutical Claims				
Number of Claims				
Mean (SD)	14.41 (19.03)	13.97 (17.34)	0.7870	0.44 (0.17, 0.71)
Median [25th, 75th Percentile]	6 (0, 24)	8 (0, 21)		

AKI: acute kidney injury; CI: confidence interval; SD: standard deviation. *For the comparisons between pre- and post-AKI diagnosis, all p values were obtained from Wilcoxon signed rank tests for continuous variables and McNemar tests for binary variables.

Table IV. Healthcare costs in the AKI and Cirrhosis cohort within 12 months after index

Healthcare Cost ($)	AKI (n=34,398)	Cirrhosis Controls (n=34,398)	p	Difference (95% CI)
Total Cost				
Mean (SD)	105,555 (187,588)	62,548 (108,199)	<0.0001	43,007 (40734, 45280)
Median [25th, 75th Percentile]	46,150 (16246, 119407)	26,340 (8963, 71260)		
Inpatient Cost				
Mean (SD)	72,720 (164,086)	29,111 (72,436)	<0.0001	43,609 (41716, 45503)
Median [25th, 75th Percentile]	24,470 (5836, 72987)	4,732 (0, 30146)		
Emergency Department Cost				
Mean (SD)	1,737 (7,323)	1,733 (6,239)	0.0007	4 (-97, 105)
Median [25th, 75th Percentile]	0 (0, 1008)	0 (0, 1190)		
Outpatient Cost				
Mean (SD)	26,046 (59,283)	26,851 (63,316)	0.2602	-805 (-1713, 104)
Median [25th, 75th Percentile]	8,030 (1667, 25807)	8,408 (2778, 23343)		
Pharmaceutical Cost				
Mean (SD)	5,052 (18,221)	4,854 (16,670)	0.0032	198 (-63, 460)
Median [25th, 75th Percentile]	345 (0, 3488)	420 (0, 3040)		

All costs were adjusted to the 2019 United States Dollar (US$) using the medical care component of the Consumer Price Index. Wilcoxon signed rank test for cost differences before and after first AKI diagnosis. For abbreviations see Table III.

Table V. Healthcare resource utilization in the HRS and Cirrhosis cohort within 12 months after index

Healthcare Utilization	HRS (n=4,364)	Cirrhosis Controls (n=4,364)	p*	Difference (95% CI)
Total Number of Claims				
Mean (SD)	44.96 (54.64)	43.50 (43.06)	0.0009	1.46 (-0.59, 3.51)
Median [25th, 75th Percentile]	22 (8, 60)	30 (14, 59)		
Inpatient Admissions				
Prevalence of at least one visit [n (%)]	3,455 (79.17)	2,426 (55.59)	<0.0001	0.24 (0.22, 0.25)
Number of Admissions				
Mean (SD)	15.49 (22.93)	5.91 (11.43)	<0.0001	9.58 (8.83, 10.33)
Median [25th, 75th Percentile]	7 (1, 20)	2 (0, 7)		
Total Length of Stay [days]				
Mean (SD)	13.76 (24.13)	4.79 (11.05)	<0.0001	8.97 (8.19, 9.75)
Median [25th, 75th Percentile]	5 (0, 17)	0 (0, 5)		
Emergency Department Visits				
Prevalence of at least one visit [n (%)]	1,124 (25.76)	1,510 (34.60)	<0.0001	-0.09 (-0.11, -0.07)
Number of Visits				
Mean (SD)	0.60 (2.07)	0.73 (1.78)	<0.0001	-0.12 (-0.20, -0.04)
Median [25th, 75th Percentile]	0 (0, 1)	0 (0, 1)		
Outpatient Visits				
Prevalence of at least one visit [n (%)]	3,911 (89.62)	4,271 (97.87)	<0.0001	-0.08 (-0.09, -0.07)
Number of Visits				
Mean (SD)	19.56 (28.60)	23.47 (28.51)	<0.0001	-3.91 (-5.11, -2.71)
Median [25th, 75th Percentile]	7 (2, 26)	15 (6, 30)		
Pharmaceutical Claims				
Number of Claims				
Mean (SD)	9.31 (15.79)	13.40 (16.41)	<0.0001	-4.09 (-4.77, -3.42)
Median [25th, 75th Percentile]	1 (0, 12)	7 (0, 20)		

*For the comparisons between pre- and post-first HRS diagnosis, all p values were obtained from Wilcoxon signed rank tests for continuous variables and McNemar tests for binary variables. HRS: hepatorenal syndrome. For the rest of abbreviations see Table III.

Table VI. Healthcare costs in the HRS and Cirrhosis cohort within 12 months after index

Healthcare Cost($)	HRS (n=4,364)	Cirrhosis Controls (n=4,364)	p	Difference (95% CI)
Total Cost				
Mean (SD)	123,243 (236,800)	57,422 (101,490)	<0.0001	65,822 (58249, 73394)
Median [25th, 75th Percentile]	34,912 (9097, 127538)	23,354 (7467, 63774)		
Inpatient Cost				
Mean (SD)	98,246 (209,263)	27,503 (68,183)	<0.0001	70,743 (64229, 77257)
Median [25th, 75th Percentile]	25,490 (1995, 89301)	2,303 (0, 27713)		
Emergency Department Cost				
Mean (SD)	1,198 (5,387)	1,536 (4,903)	<0.0001	-338 (-555, -122)
Median [25th, 75th Percentile]	0 (0, 148)	0 (0, 1017)		
Outpatient Cost				
Mean (SD)	19,457 (57,848)	23,376 (58,064)	<0.0001	-3,919 (-6346, -1492)
Median [25th, 75th Percentile]	3,183 (682, 16330)	7,305 (2468, 20553)		
Pharmaceutical Cost				
Mean (SD)	4,342 (15,788)	5,007 (17,742)	<0.0001	-664 (-1371, 42)
Median [25th, 75th Percentile]	0 (0, 1949)	457 (0, 3064)		

All costs were adjusted to the 2019 United States Dollar (US$) using the medical care component of the Consumer Price Index. Wilcoxon signed rank test for cost differences before and after first HRS diagnosis. For the rest of abbreviations see Table III.

In addition, the prevalence of at least one inpatient admission was significantly higher in the HRS cohort compared to the control cohort during the period (79.17% vs. 55.59%; p<0.0001). The average length of inpatient stay in the HRS cohort was significantly higher compared to the control cohort (mean total length of stay, 13.76 vs 4.79, p<0.0001), representing an increase of 8.97 (95% CI: 8.19, 9.75) days in the 12-month period following index date.

Health care costs were then compared between matched HRS cases and cirrhosis only controls (Table VI). The total cost of health care services over the 12 months following the index dates were significantly higher in the HRS cases than in the cirrhosis only control (median total cost, $34,912 vs $23,354; p<0.0001). The increase in the total cost was explained by the increase in inpatient costs (HRS vs. control, $25,490 vs $2,303; p<0.0001).

DISCUSSION

Using real-world claims data from the US, we investigated outcomes, mortality, and drivers of increased health care utilization associated with AKI and HRS in patients with cirrhosis. Compared to patients with cirrhosis only, patients with cirrhosis and either AKI or HRS were older, more likely to be male, and had a higher rate of comorbidities, including diabetes mellitus (39.29% vs 32.17% vs 21.14%; p<0.0001). Patients in the AKI cohort had a significantly higher rate of a diabetes mellitus diagnosis compared to those in the HRS cohort. Diabetes is the most common cause of CKD and patients with both diabetes and baseline CKD are at a higher risk of developing an AKI [24]. Substance abuse, such as smoking and alcohol intake, was significantly higher among the AKI and HRS cohorts. However, alcohol use was more prevalent in the HRS group compared to the AKI group.

In our case-control analysis, we found a higher rate of complications and morbidity in the patients with cirrhosis and either AKI or HRS. Compared to the cirrhosis only cohort, patients with AKI or HRS had higher rates of complications, such as ascites, SBP, encephalopathy, gastrointestinal bleeding, septic shock, pulmonary edema, respiratory failure, and ventilator dependence. In a comparison between the AKI to HRS cohorts, patients with HRS demonstrated higher rates of SBP, encephalopathy, variceal bleeding, and gastrointestinal bleeding. Unsurprisingly, the constellation of complications associated with the HRS cohort is a manifestation of decompensated cirrhosis. Patients with cirrhosis and AKI had a higher prevalence of ascites, respiratory failure, ventilator dependence, sepsis, and septic shock. In a meta-analysis, sepsis was a statistically significant risk factor for AKI in patients with cirrhosis [25]. Rate of readmission within 30, 90, and 180-days were higher in patients with AKI or HRS compared to the control cohort. Total mortality and mortality within 7, 30, 90, 180, and 365 days were higher in the AKI and HRS groups compared to the controls.

Our results showed that both AKI and HRS were associated with increased readmissions, complications, and mortality. These findings are similar to other studies. One study showed a significant association between AKI and mortality with infections, hypovolemia due to gastrointestinal bleeding, and refractory ascites as major precipitating factors leading to renal dysfunction [26]. Similarly, patients with cirrhosis and AKI had lower 30-, 90-, and 180-day survival rates compared to patients without an AKI [27, 28]. Survival rates were inversely proportional to the stage of AKI [28]. In a meta-analysis including 18,794 patients with cirrhosis, inpatient mortality was 6-fold higher in AKI patients compared to those without AKI. Mortality was significantly higher at 30-day, 90 day, and 1 year follow up following the development of AKI [25]. In a single-center prospective study, AKI due to HRS had the highest 30-day mortality followed by AKI due to infection in this cohort [29].

Our findings show that patients with a diagnosis of AKI and cirrhosis have an excess annual health care utilization of 13.21 claims per patient and an additional $43,007 in per-patient annual health care cost when compared to cirrhosis control with the same demographics and comorbidity profiles. The difference in claims is driven by a higher number of inpatient admissions and outpatient visits. The higher annual health care cost is primarily driven by an increase in inpatient costs. In accord with a study using the NIS, patients with cirrhosis and AKI had significantly higher inpatient mortality, length of stay, and health care utilization and cost burden (cirrhosis and AKI vs. cirrhosis only, $43,939 vs. $22,270; p<0.001) [30]. Similarly, patients with alcoholic cirrhosis and AKI had a higher risk of mortality, longer hospitalizations, and increased total hospital charges ($50,284; 95%CI: 45 829-54 739; p<0.0001) [31].

Hepatorenal syndrome was associated with significant excess in health care use and costs compared to patients with cirrhosis alone. The difference in utilization and costs were primarily driven by an increase in inpatient admission claims and costs. In a study using claims databases of commercially insured patients and Medicare beneficiaries, patients with HRS had a significant economic burden, which was driven primarily due to inpatient costs [32]. Patients with HRS had a higher prevalence of requiring an inpatient admission, total number of admissions, and total length of stay in the 12 months following the index date. A retrospective study including 2,542 patients hospitalized with HRS showed a high mortality rate (36.9%), mean length of stay (30.5 days), and average total hospital charge ($91,504 per patient) [20].

This study has several strengths. The use of the MSCC database provides access to the longitudinal data from a large and diverse cohort. The use of a randomized index date in patients with continuous enrollment, 12 months before and after, ensured analysis of disease burden. The use of propensity score matching ensured comparability between groups and helped eliminate confounding variables. However, our study carries some limitations. The use of MSCC may not always capture the entire clinical picture or indirect costs. Furthermore, MSCC captures commercial claims, which only represents the U.S. population with private health insurance. Thus, it may be difficult to generalize the results to uninsured Americans. The database also does not accurately code HRS, as it is believed that HRS is a subset of AKI and is designated as AKI-HRS.

CONCLUSIONS

Few studies have examined health care utilization and cost burden due to AKI and HRS in patients with cirrhosis. The

present findings show that AKI and HRS in cirrhotic patients is associated with higher comorbidities, morbidity, and mortality. Patients with both cirrhosis and an AKI or HRS had a higher health care utilization and cost burden as evidenced by the higher annual number of claims per person and higher annual health care costs. Therefore, our findings show that AKI and HRS are cost multipliers in cirrhosis. These findings emphasize a need for more effective and cost-effective strategies for the diagnosis, monitoring, and treatment of AKI and HRS.

Conflicts of interest: None to declare.

Authors' contribution: A.P., C.Z., C.D.M., K.G., C.C., Y.L., and V.K.R. conceived and designed the study. A.P., Y.L., and V.K.R. provided data support/data collection. Y.L. and V.K.R. analyzed the data. A.P., C.Z., K.G., V.K.R. wrote the manuscript. C.D.M. and V.K.R. provided regulatory support and overall coordination of research required activities. A.P., C.Z., C.D.M., Y.L., C.C., K.G. and V.K.R. provided critical editorial comments. VKR provided study concept and was the overall study supervisor. All authors read and approved the final manuscript.

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