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ABSTRACT

BACKGROUND: Despite advances of surgical techniques, hepatectomy continues to be potentially dangerous and is associated with postoperative mortality, morbidity and readmission. The objective of this study was to determine the effect of 30-day unplanned readmission on 'conditional' 90-day mortality among hepatocellular carcinoma (HCC) patients who underwent partial hepatectomy.

METHODS: National Cancer Database (NCDB) was queried from 2004 to 2012 for patients with hepatocellular carcinoma (HCC) who underwent partial hepatectomy. Thirty-day unplanned readmission rate, and associated risk factors, was determined for 7,696 patients. The association between 30-day unplanned readmission and conditional 90-day mortality was further addressed.

RESULTS: The 30-day unplanned readmission rate for patients with HCC who underwent partial hepatectomy was 5.2%. Risk factors associated with 30-day unplanned readmission were sex, race/ethnicity, Charlson-Deyo score, and annual hospital hepatectomy volume. An overall adjusted odds of having conditional 90-day mortality was 2.325 times higher (95% CI 1.643 - 3.219) among patients with a history of 30-day unplanned readmission than those without. This association was dependent on age, sex, race/ethnicity, insurance status, alpha-fetoprotein (AFP), liver fibrosis, Charlson-Deyo comorbidity score and annual hospital hepatectomy volume.

CONCLUSION: Efforts in patient care should be taken to reduce 30-day unplanned readmission after partial hepatectomy for patients with HCC to reduce conditional 90-day mortality.

Key words: Hepatocellular carcinoma; Hepatectomy; 30-day readmission; 90-day mortality; Risk factors

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INTRODUCTION

The reported cost of unplanned hospital readmissions is approximately \$44 billion of healthcare spending annually^[1], yet a substantial proportion of these readmissions could be avoidable. The Medicare Payment Advisory Commission estimated that reducing potentially preventable readmissions could save up to \$12 billion every year^[2]. In 2019, the Hospital Readmissions Reduction Program

(HRRP) evaluated 3,129 general hospitals and penalized 83% of these hospitals for excess 30-day readmissions with estimated fines of \$563 million^[3]. Among patients with private insurance, the average cost for readmission after hepatectomy was approximately \$34,100/person^[4], much higher than the average hospital readmission cost of \$14,400 for 18 main diagnosis categories^[5].

Despite advances of surgical techniques, hepatectomy continues to be potentially dangerous and is associated with postoperative mortality, morbidity and readmission. Readmission rates after hepatectomy vary depending on the study population. Three hospital-based studies reported 90-day readmission rates after hepatectomy for any etiology ranging from 14.4% to 18.7%^[6-8], which were higher than the 30-day readmission rates of 13.0% and 14.2% from two other hospital-based studies^[9,10]. A relatively lower 30-day readmission rate of 10.5% was noted in a study using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database^[11].

Contributing factors affecting readmission after hepatectomies include major hepatectomies (≥ 4 segments resected), major postoperative complications and index hospitalization of > 7 days^[6]. However, another study found that neither index hospitalization nor postoperative hepatobiliary complications played a significant role in 45-day readmission^[12]. Other risk factors include extensive blood loss, postoperative pulmonary embolism, red blood cell transfusion, surgical infection, and peak postoperative total bilirubin^[7]. Among these, postoperative complications were identified as the strongest and dominant risk factor affecting readmission^[8,10].

Significant correlations between 30-day readmission and subsequent 90-day mortality have been reported, but results are inconsistent. Evidence suggests that a history of readmission increases the risk of postoperative mortality^[13]. Though not studied in patients with HCC, a 6-fold increase in 90-day mortality was found among lung cancer patients with a history of 30-day readmission compared to those without a 30-day readmission^[14].

Most previous studies were based on single or 2-3 centers with limited sample size where the readmission rate could easily be influenced by small changes in hospital readmission. Furthermore, research on readmission after hepatectomy often include HCC and other primary and secondary liver malignancies as well as benign tumors to increase sample size. These studies cannot measure HCC-specific readmission rate and associated risk factors. Moreover, no studies have evaluated the impact of 30-day unplanned readmission on conditional 90-day mortality in a nationally representative sample in patients with HCC who underwent hepatectomies.

The objective of this study was to determine the effect of 30-day unplanned readmission on conditional 90-day mortality among hepatocellular carcinoma (HCC) patients who underwent partial hepatectomy.

METHODS

Data source

We used the National Cancer Database (NCDB) for all analyses. NCDB, a clinical oncology database, is jointly sponsored by the American College of Surgeons and the American Cancer Society. More than 1,500 Commission on Cancer (CoC) accredited hospitals contribute to the cancer registry data, which represents 70% of newly diagnosed cancer cases nationwide at the institutional level^[15].

Study Population

NCDB was queried for all patients with HCC using International

Classification of Disease for Oncology, third edition (ICD-O-3) code C220 with histology codes 8170, 8171, 8172, 8173, 8174 and 8175. Only patients who were 18 years or older, diagnosed from 2004 to 2012 and underwent partial hepatectomy were included in the study. Patients were excluded if they developed more than two cancers following HCC diagnosis or had total hepatectomy and transplant. Patients who survived less than 30 days after hepatectomy or had missing information on surgery procedures, 30-day readmission status, and 90-day mortality status were also excluded.

Dependent measure

The first outcome measure was 30-day unplanned readmission. In NCDB, this variable became available from 2003 onward. It describes patients' readmission status and is coded as: 0, 1, 2, 3 and 9. A value of 0 indicates that no surgical procedure of the primary site was performed or the patient was not readmitted to the same hospital within 30 days of discharge; value of 1 means a 30-day unplanned readmission to the same hospital after a surgical procedure; value of 2 represents a 30-day planned readmission to the same hospital; value of 3 denotes a patient having both 30-day planned and unplanned readmission after a surgical procedure to the same hospital. For this study, we only used the data for patients with known 30-day unplanned readmission status (status=1). The second outcome measure was conditional 90-day mortality after a hepatectomy.

Independent measures

Independent variables included age, sex, race/ethnicity, insurance status, annual household income, education, urban or rural residence, distance to treatment facility, annual hospital volume, facility type, alpha fetoprotein tumor marker (AFP), liver fibrosis, Charlson/Deyo score, NCDB pathologic/clinical stage, tumor grade, tumor size, and surgical procedure.

Age was grouped as 18-49, 50-64, 65-74 and 75+ years. A new variable "race/ethnicity" was generated based on NCDB variables race and Hispanic origin and classified as (1) White non-Hispanic, (2) Black non-Hispanic, (3) Hispanic, and (4) other non-Hispanic. Insurance status refers to the patient's primary insurance carrier at the time of initial diagnosis and/or treatment and was categorized as not insured, privately insured, Medicaid, Medicare and other government insurance plans, and unknown status. Income is the estimation of median household income derived from 2000 US Census data by matching patients' zip code of residence. It was grouped into four levels: less than \$30,000, \$30,000-\$34,999, \$35,000- \$45,999 and \$46,000 and above. The percentage of adults not graduated from high school in patients' zip code of residence was used as a measure of education and was categorized as 29% or more, 20%-28.9%, 14%-19.9%, less than 14%. In NCDB, patient state and county of Federal Information Processing Standard (FIPS) code recorded at diagnosis is matched against 2003 files published by the USDA Economic Research Service to determine patient metro/urban/rural status of residence. NCDB defines metro counties as counties in metro areas with a population ranging from fewer than 250,000 to 1 million or more. Urban counties refer to areas with a population ranging from 2,500 to 20,000 or more either adjacent or not adjacent to a metro area. Rural counties include completely rural or less than 2,500 urban population either adjacent or not adjacent to a metro area.

AFP was grouped into two levels of negative/normal and positive/elevated while liver fibrosis was categorized as none to moderate and severe to cirrhosis based on Ishak score of 0-4 and 5-6, respectively^[16]. The Charlson/Deyo value is a weighted score derived from the sum of scores for all comorbid conditions. Each of the ten

reported ICD-9-CM secondary diagnoses below has a score of 1 for each condition: (1) myocardial infarction, (2) congestive heart failure, (3) peripheral vascular disease, (4) cerebrovascular disease, (5) dementia, (6) chronic pulmonary disease, (7) rheumatologic disease, (8) peptic ulcer disease, (9) mild liver disease and (10) diabetes. In addition, a patient is given a score of 2 if the patient has diabetes with chronic complications, hemiplegia or paraplegia, or renal disease. A score of 6 is given to patients with AIDS. Charlson/Deyo score is reported in the NCDB for patients diagnosed in 2003 and later and categorized as 0, 1 and 2 or more. Tumor grade describes the resemblance of tumor cells to the normal cells and is grouped as well differentiated, moderately differentiated, poorly differentiated and undifferentiated which represents the most aggressive grade that grows and spreads faster than tumors with lower grades. NCDB analytic stage group was categorized as I, II, III, IV and unknown. Its value reflects reported pathologic stage group, or clinical stage group if the former is not available. Tumor size describes the largest diameter of the primary tumor in millimeter (mm). The variable tumor size was categorized as ≤ 30 mm, > 30 and ≤ 50 , > 50 . Surgical procedures were grouped as wedge or segmental resection, lobectomy, extended lobectomy and unknown type.

Facility type was categorized as (1) Community Cancer Program, (2) Comprehensive Community Cancer Program, (3) Academic Comprehensive Cancer Program and NCI-Designated Network Cancer Program, (4) Integrated Network Cancer Program, and (5) other or unknown type of cancer program. In the NCDB, the name of the facility is replaced with a unique random identifier, which can be used to calculate the total number of hepatectomies performed annually in each facility (annual hospital volume). Annual hospital volume was then grouped into low (< 4 /year), medium (4-15/year), and high (> 15 /year) categories.

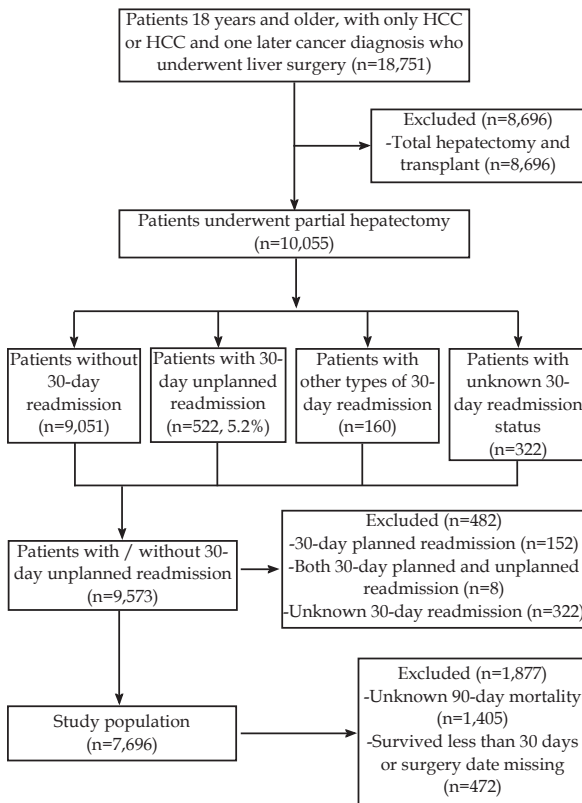


Figure 1 Flow chart of study population.

Statistical analysis

We first calculated overall 30-day unplanned readmission rate among patients with HCC and underwent hepatectomies and then compared patients' demographic, clinical and facility characteristics between patients with and without 30-day unplanned readmission using Pearson Chi-Square test for categorical variables. Independent t-test was used to compare mean difference between the two groups. A multiple logistic regression model was performed, which included all variables with a p value less than or equal to 0.1 in the univariate analysis. Adjusted odds ratios, 95% confidence intervals and p values were reported. To evaluate the effect of 30-day unplanned readmission on conditional 90-day mortality, we fit simple and multiple logistic regression models using 30-day unplanned readmission as an independent variable and conditional 90-day mortality as the dependent variable. Selected subgroup analysis was conducted to further investigate how the association between 30-day unplanned readmission and conditional 90-day mortality varied between subgroups.

RESULTS

A total of 18,751 patients who were 18 years or older, diagnosed with HCC between 2004 to 2012, had no more than one other cancer diagnosis during this time period, and underwent partial hepatectomy were identified in the database. We excluded 8,696 patients who underwent total hepatectomy and transplant, leaving 10,055 patients for calculating overall unplanned readmission rate. Of the 10,055 patients, 522 patients experienced 30-day unplanned readmission, 152 patients experienced 30-day planned readmission, 8 patients experienced both planned and unplanned readmission, and 322 patients whose readmission status was unknown. The overall 30-day unplanned readmission rate was 5.2%. After further excluding patients who had planned readmission, had both planned and unplanned readmission, survived fewer than 30 days, had missing 90-day mortality status, and had missing surgery date, we identified 7,696 patients to be included in the study (Figure 1). The average age of patients was 61.7 ± 12.9 and 5,329 were male (69.2%). Approximately 42.7% of patients were aged 50-64, 58.1% were white, non-Hispanic, 83.6% had private insurance, Medicare or other, 39.2% had median annual household income of \$46,000 or more, and 68.6% were treated in academic or research type facilities (Table 1a). Additionally, over half (55.0%) of patients had a Charlson-Deyo score of 0, 42.5% belonged to stage I, and 43.9% were diagnosed with grade II tumor (Table 1b). The major surgery procedures these patients underwent were wedge or segmental resection, which accounted for 53.3%.

Comparison of patients experiencing 30-day unplanned readmission vs. those without readmission

Univariate analysis demonstrated differences of patient demographics, hospital and clinical characteristics between patients with 30-day unplanned readmission and patients without readmission (Tables 1a and 1b). Patients with 30-day unplanned readmission were slightly younger compared to those without a readmission (60.2 years vs. 61.8 years, $p = 0.01$), more likely to be male (74.4% vs. 68.9%, $p = 0.02$), Hispanic (17.9% vs. 12.3%, $p < 0.01$), and to have private insurance (45.7% vs. 41.6%, $p < 0.01$). In addition, patients with 30-day unplanned readmission were more likely to have a Charlson-Deyo score of ≥ 1 (53.6% vs. 44.4%, $p < 0.01$), and to be diagnosed with grade II tumor vs. all other grade tumor (48.6% vs. 43.6%, $p = 0.028$). Although a higher proportion of readmitted patients had severe fibrosis/cirrhosis (12.2% vs. 9.0%, $p = 0.011$), over three

Table 1a Demographic and Facility Characteristics of Patients Undergoing Partial Hepatectomy (2004-2012), by 30-Day Unplanned Readmission Status.

Variable	Characteristics	All, n (%)	30-Day Unplanned Readmission, n (%)		p-value
			No	Yes	
Total		7696	7254	442	
Age (mean years± †SD)		61.7 ± 12.9	61.8 ± 12.9	60.2 ± 13.5	0.010
Age group	18-49	1074 (14.0)	994 (13.7)	80 (18.1)	0.059
	50-64	3283 (42.7)	3096 (42.7)	187 (42.3)	
	65-74	2080 (27.0)	1969 (27.1)	111 (25.1)	
	>74	1259 (16.4)	1195 (16.5)	64 (14.5)	
Sex	Male	5329 (69.2)	5000 (68.9)	329 (74.4)	0.015
	Female	2367 (30.8)	2254 (31.1)	113 (25.6)	
Race/ethnicity	White, non-Hispanic	4468 (58.1)	4218 (58.2)	250 (56.6)	0.003
	Black, non-Hispanic	1030 (13.4)	971 (13.4)	59 (13.4)	
	Hispanic	974 (12.7)	895 (12.3)	79 (17.9)	
	Others, non-Hispanic	1224 (15.9)	1170 (16.1)	54 (12.2)	
Insurance status	Not insured	245 (3.2)	227 (3.1)	18 (4.1)	0.003
	Private insurance	3216 (41.8)	3014 (41.6)	202 (45.7)	
	Medicaid	707 (9.2)	661 (9.1)	46 (10.4)	
	Medicare or other	3214 (41.8)	3042 (41.9)	172 (38.9)	
	Unknown	314 (4.1)	310 (4.3)	4 (0.9)	
Percentage of residents not graduated from high school	29% or more	1547 (20.1)	1454 (20.0)	93 (21.0)	0.917
	20%-28.9%	1729 (22.5)	1630 (22.5)	99 (22.4)	
	14%-19.9%	1620 (21.0)	1526 (21.0)	94 (21.3)	
	Less than 14%	2478 (32.2)	2342 (32.3)	136 (30.8)	
	Missing	322 (4.2)	302 (4.2)	20 (4.5)	
Annual median household income	Less than \$30,001	1156 (15.0)	1083 (14.9)	73 (16.5)	0.091
	\$30,000-\$34,1000	1290 (16.8)	1228 (16.9)	62 (14.0)	
	\$35,000-\$45,1000	2039 (26.5)	1905 (26.3)	134 (30.3)	
	\$46,000 or more	2891 (37.6)	2738 (37.7)	153 (34.6)	
	Missing	320 (4.2)	300 (4.1)	20 (4.5)	
Urban or rural residence	Metro	6283 (81.6)	5920 (81.6)	363 (86.1)	0.333
	Urban	991 (12.9)	942 (13.0)	49 (11.1)	
	Rural	113 (1.5)	104 (1.4)	9 (2.0)	
	Missing	309 (4.0)	288 (4.0)	21 (4.8)	
Distance to facility	Less than 12.5 miles	3390 (44.0)	3192 (44.0)	198 (44.8)	0.206
	12.5 to 49.9 miles	2334 (30.3)	2188 (30.2)	146 (33.0)	
	51 miles or more	1810 (23.5)	1720 (23.7)	90 (20.4)	
	Missing	162 (2.1)	154 (2.1)	8 (1.8)	
Facility type	Community	230 (3.0)	223 (3.1)	7 (1.6)	0.060
	Comprehensive	1616 (21.0)	1540 (21.2)	76 (17.2)	
	Academic/research	4986 (64.8)	4683 (64.6)	303 (68.6)	
	Other	436 (5.7)	410 (5.7)	26 (5.9)	
	Missing	428 (5.6)	398 (5.5)	30 (6.8)	
Annual hospital hepatectomy volume	<4/year	2633 (34.2)	2492 (34.4)	141 (31.9)	0.013
	4-15/year	2383 (31.0)	2264 (31.2)	119 (26.9)	
	>15/year	2680 (34.8)	2498 (34.4)	182 (41.2)	

†SD: standard deviation.

quarters (76.5%) of patients did not have fibrosis scores available. Annual household income, education, distance to treating facility, urban or rural residence, AFP tumor marker, NCDB analytic stage group, tumor size and surgical procedures did not differ by 30-day unplanned readmission status (Tables 1a and 1b).

Risk factors of 30-day unplanned readmission

Table 2 shows the odds ratios and 95% confidence intervals from multiple logistic regression investigating risk factors associated with 30-day unplanned readmission. After adjusting for age, sex, race/ethnicity, insurance status, annual median household income,

facility type, hospital hepatectomy volume, Charlson-Deyo score, and tumor grade, males had 29% increased odds of experiencing a 30-day unplanned readmission than females. Hispanics had 39% increased odds of 30-day unplanned readmission compared to non-Hispanic white. Patients with Charlson-Deyo scores of 1 and 2 had 31% and 55% increased odds experiencing 30-day unplanned readmission compared to patients with Charlson-Deyo score of 0, respectively. In addition, patients treated in hospitals where annual hospital hepatectomy volume was 4-15/year had 38% lower odds experiencing 30-day unplanned readmission compared to those treated in hospitals performing more than 15 hepatectomies annually.

Table 1b Clinical Characteristics of Patients Undergoing Partial Hepatectomy (2004-2012), by 30-Day Unplanned Readmission Status.

Variable	Characteristics	All, n (%)	30-Day Unplanned Readmission, n (%)		p-value
			No	Yes	
‡AFP tumor marker	Negative/normal	1914 (24.9)	1818 (25.1)	96 (21.7)	0.202
	Positive/elevated	3315 (43.1)	3124 (43.1)	191 (43.2)	
	Unknown	2467 (32.1)	2312 (31.9)	155 (35.1)	
Fibrosis score	0-4 (none-moderate fibrosis)	1099 (14.3)	1024 (14.1)	75 (17.0)	0.011
	5-6 (severe fibrosis/cirrhosis)	706 (9.2)	652 (9.0)	54 (12.2)	
	Unknown	5891 (76.5)	5578 (76.9)	313 (70.8)	
Charlson-Deyo score	0	4236 (55.0)	4031 (55.6)	205 (46.4)	<0.001
	1	2203 (28.6)	2067 (28.5)	136 (30.8)	
	2	1257 (16.3)	1156 (15.9)	101 (22.9)	
NCDB analytic stage group	I	3268 (42.5)	3102 (42.8)	166 (37.6)	0.115
	II	1821 (23.7)	1706 (23.5)	115 (26.0)	
	III	1576 (20.5)	1469 (20.3)	107 (24.2)	
	IV	291 (3.8)	276 (3.8)	15 (3.4)	
	Unknown	740 (9.6)	701 (9.7)	39 (8.8)	
Tumor grade	I	1547 (20.1)	1467 (20.2)	80 (18.1)	0.028
	II	3378 (43.9)	3163 (43.6)	215 (48.6)	
	III	1408 (18.3)	1323 (18.2)	85 (19.2)	
	IV	251 (3.3)	246 (3.4)	5 (1.1)	
	Not determined	1112 (14.4)	1055 (14.5)	57 (12.9)	
Tumor size	≤ 30 mm	1410 (18.3)	1317 (18.2)	93 (21.0)	0.392
	>30mm and ≤ 50 mm	1816 (23.6)	1712 (23.6)	104 (23.5)	
	>50 mm	4202 (54.6)	3969 (54.7)	233 (52.7)	
	Unknown	268 (3.5)	256 (3.5)	12 (2.7)	
Surgical procedure	Wedge or segmental resection	4099 (53.3)	3863 (53.3)	236 (53.4)	0.965
	Lobectomy	2434 (31.6)	2298 (31.7)	136 (30.8)	
	Extended lobectomy	551 (7.2)	518 (7.1)	33 (7.5)	
	Unknown type	612 (8.0)	575 (7.9)	37 (8.4)	

‡AFP: alpha-fetoprotein.

Effect of 30-day unplanned readmission on conditional 90-day mortality

The conditional 90-day mortality refers to those patients who died between 31 and 90 days after partial hepatectomy. The conditional 90-day mortality rate for patients with an unplanned readmission was 10.0% while the rate for those not readmitted was only 4.5%. The crude odds of conditional 90-day mortality was 2.342 (95% CI: 1.663 - 3.225, $p < 0.001$) times higher in patients with a 30-day unplanned readmission than in patients without a readmission (Table 3). After adjusting for sex, age group, race/ethnicity, insurance status, Charlson -Deyo score and annual hospital hepatectomy volume, the odds of conditional 90-day mortality was similar to the crude odds, 2.325 (95% CI: 1.643-3.219, $p < 0.001$) (Table 3).

Association between 30-day unplanned readmission and conditional 90-day mortality in selected subgroups (Table 4)

Age and sex

Patients 75 years and older who experienced 30-day unplanned readmission had the highest odds of conditional 90-day mortality (OR 3.081, 95% CI 1.453-6.044, $p = 0.002$) followed by age 50-64 (OR 2.846, 95% CI 1.626-4.728, $p < 0.001$). Female patients who had 30-day unplanned readmission, had twice the odds of 90-day mortality (OR 3.809, 95% CI 1.909-7.114, $p < 0.001$) compared to male patients (OR 1.985 95% CI 1.314-2.903, $p < 0.001$).

Race/Ethnicity and insurance type

The association between 30-day unplanned readmission and

conditional 90-day mortality was only significant among white, non-Hispanic patients (OR 3.287, 95% CI 2.164-4.862, $p < 0.001$). Thirty-day unplanned readmission was also associated with a 11-fold (OR 11.247, 95% CI 1.666-77.316, $p = 0.01$) increased odds of conditional 90-day mortality among uninsured patients, 2.4 fold (OR 2.391, 95% CI 1.347-4.012, $p < 0.01$) increased odds in privately insured patients and twice the odds (OR 2.140, 95% CI 1.252-3.472, $p < 0.01$) in patients enrolled in Medicare or other government insurance programs.

AFP tumor marker and cirrhosis score

AFP tumor marker was reported for 5,229 (out of 7,696) patients, of whom, more than one-third ($n = 1,914$, 36.6%) had negative/normal AFP values and the rest ($n = 3,315$, 63.4%) had positive/elevated values. Among patients with an elevated AFP, the adjusted odds of conditional 90-day mortality after partial hepatectomy were 2.1 times higher for those with a 30-day unplanned readmission than those without. No significant association between 30-day unplanned readmission and conditional 90-day mortality was noted in patients with a normal AFP. In addition to AFP, NCDB also provides liver fibrosis information based on Ishak score^[16] starting in 2004. For our dataset, only 1,805 (out of 7,696) patients had complete fibrosis information where 1,099 patients were reported as having none-moderate fibrosis and 706 having severe fibrosis to cirrhosis. Significant impact of 30-day unplanned readmission on conditional 90-day mortality was identified only in patients with Ishak score of 5-6 (adjusted OR 3.768, 95% CI 1.478-8.815, $p = 0.003$).

Table 2 Multiple Logistic Regression Analysis of the Risk Factors for 30-Day Unplanned Readmission After Partial Hepatectomy.

Variable	Characteristics	Total	Readmission, n (%)	Adjusted †OR (95% ‡CI)	p-value
		7696	442 (5.7)		
Age				0.992 (0.980 – 1.004)	0.213
Sex	Female	2367	113 (4.8)	Reference	
	Male	5329	327 (6.1)	1.294 (1.025 – 1.649)	0.033
Race/Ethnicity	White, non-Hispanic	4468	250 (5.6)	Reference	
	Black, non-Hispanic	1030	59 (5.7)	0.953 (0.682 – 1.311)	0.774
	Hispanic	974	79 (8.1)	1.394 (1.037 – 1.851)	0.025
	Others, non-Hispanic	1224	54 (4.4)	0.746 (0.532 – 1.026)	0.08
Insurance Status	Private insurance	3216	202 (6.3)	Reference	
	Not insured	245	18 (7.3)	0.901 (0.465 – 1.592)	0.738
	Medicaid	707	46 (6.5)	0.821 (0.549 – 1.196)	0.32
	Medicare or other	3214	172 (5.4)	0.861 (0.663 – 1.119)	0.264
	Unknown	314	4 (1.3)	0.216 (0.062 – 0.572)	0.006
Annual median household income	\$46,000 or more	2891	153 (5.3)	Reference	
	\$35,000-\$45,999	2039	134 (6.6)	1.187 (0.923 – 1.525)	0.181
	\$30,000-\$34,999	1290	62 (4.8)	0.770 (0.553 – 1.059)	0.114
	Less than \$30,000	1156	73 (6.3)	1.152 (0.841 – 1.566)	0.372
Facility type	Academic/research	4986	303 (6.1)	Reference	
	Community	230	7 (3.0)	0.567 (0.234 – 1.172)	0.162
	Comprehensive	1616	76 (4.7)	0.831 (0.611 – 1.120)	0.229
	Other	436	26 (6.0)	1.035 (0.657 – 1.564)	0.876
Annual hospital hepatectomy volume	>15/year	2680	182 (6.8)	Reference	
	4-15/year	2383	119 (5.0)	0.619 (0.477 – 0.799)	<0.001
	<4/year	2633	141 (5.4)	0.765 (0.575 – 1.015)	0.065
Charlson-Deyo score	0	4236	205 (4.8)	Reference	
	1	2203	136 (6.2)	1.309 (1.032 – 1.658)	0.026
	2	1257	101 (8.0)	1.550 (1.179 – 2.025)	0.002
Tumor grade	I	1547	80 (5.2)	Reference	
	II	3378	215 (6.4)	1.180 (0.896 – 1.569)	0.248
	III	1408	85 (6.0)	1.192 (0.855 – 1.664)	0.299
	IV	251	5 (2.0)	0.834 (0.271 – 2.066)	0.722
	Not determined	1112	57 (5.1)	0.943 (0.644 – 1.369)	0.76

†odds ratio, ‡confidence interval.

Table 3 Association Between 30-Day Unplanned Readmission and 90-Day Mortality after Partial Hepatectomy.

Predictor	Unadjusted †OR (95% ‡CI)	p-value	§Adjusted †OR (95% ‡CI)	p-value
30-Day Unplanned Readmission				
No	Reference		Reference	
Yes	2.342 (1.663-3.225)	<0.001	2.325 (1.643-3.219)	<0.001

†OR: odds ratios; ‡ CI: confidence interval; § Adjusted for age, sex, race/ethnicity, insurance status, annual hospital volume and Charlson-Deyo score.

A significant impact of 30-day unplanned readmission on conditional 90-day mortality was observed across all subgroups of Charlson-Deyo Score and showed a linear trend with increasing score. Specifically, 30-day unplanned readmission was associated with 2.0 (OR 2.002, 95% CI 1.139-3.312, $p = 0.01$), 2.4 (OR 2.435, 95% CI 1.257-4.383, $p < 0.01$) and 2.7 (OR 2.741, 95% CI 1.410-5.029, $p < 0.01$) fold increased odds of having 90-day mortality in patients with Charlson-Deyo scores of 0, 1 and 2, respectively. In patients treated in facilities that performed more than 15 hepatectomies annually, 30-day unplanned readmission increased the odds of 90-day mortality by approximately 4-fold (OR 3.969, 95% CI 2.312-6.561, $p < 0.01$).

DISCUSSION

In this study, we used one of the largest cancer databases in the

world to investigate the rate and associated risk factors of 30-day unplanned readmission after partial hepatectomy and evaluated how this readmission impacted conditional 90-day mortality in patients with HCC. The study found that the overall 30-day unplanned readmission rate following partial hepatectomy was 5.2%, which was much lower than previously reported rates of 10.2% for partial hepatectomy from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) dataset^[11], 14.2% from a hospital-based study^[10] and 15.5% from a population-based study using Surveillance, Epidemiology, and End Results (SEER) database^[17]. Studies on readmission after partial hepatectomy have been very limited and the definition of readmission varied largely across studies. Readmission at 30-day, 90-day and 1 year after discharge following a surgical procedure has been reported^[7-9,12,18]. To our knowledge, this study was the first to describe the 30-day unplanned readmission rates after partial hepatectomy in patients

Table 4 Impact of 30-Day Unplanned Readmission on Conditional 90-Day Mortality in Selected Subgroups.

Factor	Characteristics	Unadjusted			Adjusted		
		†OR	95% ‡CI	p value	†OR	95% ‡CI	p value
Age	18-49	1.442	0.423-3.730	0.499	1.44	0.413-3.871	0.512
	50-64	2.736	1.578-4.493	<0.001	2.846	1.626-4.728	<0.001
	65-74	1.993	0.983-3.677	0.039	1.947	0.953-3.628	0.049
	75 and above	3.190	1.525-6.155	0.001	3.081	1.453-6.044	0.002
Sex	Male	1.960	1.303-2.854	<0.001	1.985	1.314-2.903	<0.001
	Female	3.777	1.946-6.818	<0.001	3.809	1.909-7.114	<0.001
Race/Ethnicity	White, non-Hispanic	3.334	2.213-4.887	<0.001	3.287	2.164-4.862	<0.001
	Black, non-Hispanic	1.369	0.403-3.512	0.559	1.165	0.336-3.080	0.781
	Hispanic	1.095	0.373-2.582	0.851	1.186	0.396-2.880	0.731
	Others, non-Hispanic	1.033	0.166-3.485	0.964	1.374	0.214-4.945	0.677
Insurance Status	Private	2.521	1.432-4.187	<0.001	2.391	1.347-4.012	0.002
	Not insured	7.367	1.446-31.021	0.008	11.247	1.666-77.316	0.011
	Medicaid	1.653	0.478-4.381	0.361	1.692	0.471-4.766	0.362
	Medicare or others	2.180	1.281-3.516	0.002	2.14	1.252-3.472	0.003
§ AFP tumor marker	Negative/normal	2.264	0.853-5.021	0.066	2.716	0.805-4.952	0.088
	Positive/elevated	2.545	1.548-4.005	<0.001	2.149	1.245-3.529	0.004
Fibrosis score	0-4 (none-moderate)	2.146	0.717-5.212	0.123	2.511	0.820-6.342	0.072
	5-6 (severe fibrosis/cirrhosis)	3.606	1.471-7.987	0.003	3.768	1.478-8.815	0.003
Charlson-Deyo score	0	2.067	1.187-3.379	0.006	2.002	1.139-3.312	0.01
	1	2.270	1.182-4.032	0.008	2.435	1.257-4.383	0.005
	2	2.658	1.385-4.795	0.002	2.741	1.410-5.029	0.002
Annual Hospital Volume	<4/year	1.881	1.012-3.244	0.032	1.667	0.888-2.910	0.089
	4-15/year	1.682	0.774-3.238	0.149	1.633	0.743-3.191	0.182
	>15/year	3.749	2.231-6.095	<0.001	3.969	2.312-6.561	<0.001

† OR: odds ratios; ‡ CI: confidence interval; § AFP: alpha-fetoprotein

with HCC using a national database that captures 70% of newly diagnosed cancer cases. The NCDB collects information only on 30-day readmission, which includes unplanned readmission, planned readmission and both planned and unplanned readmission; therefore, we were unable to compare 90-day or 1-year readmission with other studies. The lower rate of 30-day unplanned readmission for the current study may partially reflect the fact that NCDB only captures patients readmitted to the same treating facility. In another words, if a patient was discharged from hospital A, but readmitted to hospital B due to postoperative complications, then the patient was not considered having an unplanned readmission in NCDB. In our study, patients with an unplanned 30-day readmission resided in zip code areas that were significantly closer to their treating facility than those without readmission (37.6 miles vs 56.1 miles, $p < 0.001$). Saunders and colleagues also found that patients living far away from treating hospitals would go to a closer hospital for readmission either because of convenience or patients being too sick to return to the original hospital^[19]. In a study that used States Inpatient Database of 5 states, researchers reported that almost 1 of 4 readmissions were to a different hospital than the original facility^[20].

Risk factors independently associated with 30-day unplanned readmission were sex, race/ethnicity, Charlson-Deyo score, and annual hospital hepatectomy volume. Consistent with other studies^[10,12], our results did not indicate a significant association between age and 30-day unplanned readmission. However, we found that male sex was associated with a 29% increased odds of 30-day unplanned readmission. One explanation may be the negative role of liver fibrosis/cirrhosis in readmission^[21]. Our study showed that 41.9% of males had severe fibrosis or cirrhosis compared to 32.6% of females who had the same condition ($p < 0.001$). The

other explanation is the lack of social support which is not directly measured in NCDB. Previous studies have reported that men are less likely to seek help and more likely to be socially isolated than women, which contributes to worse health outcomes^[22,23]. Our study also indicated a racial disparity on 30-day unplanned readmission. Hispanics had a 39% increased odds of 30-day unplanned readmission than Caucasians. The risk of 30-day readmission after partial hepatectomy in Hispanics had not been reported and the comparison was often made between white and non-white races in past studies, especially hospital-based studies. Even though individual comorbidity cannot be identified in NCDB, research has reported higher prevalence of obesity, diabetes, hypertension and metabolic syndrome among Hispanic patients^[24]. These chronic conditions along with language barriers and lower overall health literacy^[25], have adversely impacted Hispanics' health behavior and clinical outcomes including readmission.

The current study found that the Charlson-Deyo score was significantly associated with 30-day unplanned readmission. Males and Hispanics had higher proportion of index score > 0. The overall odds of 30-day unplanned readmission were 1.3 and 1.6 times higher in patients with an index score of 1 and ≥ 2 , respectively when compared to the index score of 0. This finding was consistent with a study that reported 30-day unplanned readmission among general medicine patients at six academic medical centers^[26] They used self-reported Charlson comorbidity index of 0-9 and found the odds of readmission increased 9% with each one-unit increase in the index. A second study that used the NCDB for parotid cancer research discovered 57% and 108% increased odds of readmission for the index scores of 1 and > 1, respectively^[27]. For adult patients undergoing otolaryngology surgery in New York State within

Statewide Planning and Research Cooperative System (SPARCS), a Charlson comorbidity index score > 1 was associated with 2.3-fold increased odds of 30-day readmission^[28]. We believe a higher Charlson-Deyo index has a negative impact on 30-day unplanned readmission. The impaired physiological system and depleted physiological reserve at discharge puts patients in a vulnerable situation^[29] where comorbidities might be exacerbated and lead to new acute conditions that increase the risk of readmission^[30].

The major goal of this study was to evaluate the impact of 30-day unplanned readmission on conditional 90-day mortality. Patients who died between 30 and 90 days were considered as having conditional 90-day mortality. The conditional 90-day mortality rate was 10.0% in patients who experienced a 30-day unplanned readmission and was 4.5% among those without readmission. This translated to an unadjusted 86% higher rate of conditional 90-day mortality in patients with a 30-day unplanned readmission than those without. After adjusting for covariates, a higher odds of 2.3 for conditional 90-day mortality was noted among patients readmitted within 30 days. This is the first time that the effect of 30-day unplanned readmission in future conditional 90-day mortality following a partial hepatectomy among patients with HCC is reported using a national cancer database. This association is likely reflective of the impact of comorbidities and perioperative complications on mortality. We have shown that Charlson-Deyo score was a strong, independent predictor of 30-day unplanned readmission. Comorbidity has been reported as an independent risk factor of postoperative complications^[31], and postoperative complication was also significantly associated with 90-day mortality^[32]. This finding is in concordance with outcomes derived from 2006-2010 SEER-Medicare database showing a 6-fold increase in odds of 90-day mortality among lung cancer patients with a 30-day readmission history^[14]. One earlier study using the 1992-2002 SEER-Medicare database found that among patients undergoing colectomy, 1-year postoperative mortality was 16% in those readmitted within 30 days of discharge compared to 7% in those not readmitted^[33]. Awareness of patient 30-day readmission status may assist further monitoring and managing postoperative care that aims to reduce 90-day mortality.

The finding that 30-day unplanned readmission affects 90-day mortality is especially obvious in certain subgroups of patients. More specifically, among patients 75 years and older, 30-day unplanned readmission was associated with a 3.1-fold increase in subsequent conditional 90-day mortality. The significant association between 30-day readmission and 90-day mortality was observed in both sexes, but the odds were higher in female than male patients (OR: 3.809 and 1.985, respectively). This indicated that despite the overall lower odds of short-term readmission and mortality for females, the odds of 90-day mortality was higher than males once female patients were readmitted within 30 days of discharge. One important finding of this study was that the impact of 30-day readmission on conditional 90-day mortality was only significant among the white, non-Hispanic group. This may be related to the relatively older age of patients in this group compared to other race groups. Patients aged 65 years and above accounted for 20% in the white, non-Hispanic group, while they accounted for only 11.4% in all other groups combined.

Variations in the risk of 90-day mortality were also found among patients enrolled in different insurance programs. In the subgroup of uninsured patients, the odds of 90-day mortality were 21 times higher for those with a 30-day readmission history compared to those without. On the other hand, among patients with private insurance, the odds was only 1.9 times higher. Previous studies

have demonstrated that uninsured patients had poorer survival than privately insured patients and this may be related to poorer overall health with more comorbidities^[34] and no or inadequate management of chronic conditions prior to cancer diagnosis^[35].

The association between 30-day unplanned readmission and conditional 90-day mortality was significant in patients with an elevated AFP tumor marker and in patients with severe liver fibrosis. However, this significant association was not noted in patients with a negative AFP tumor marker and in patients with none-moderate liver fibrosis. No studies have addressed how the level of AFP and extent of fibrosis influence on the association between 30-day unplanned readmission and conditional 90-day mortality. However, previous studies have indicated that markedly elevated serum AFP was an indicator of poor prognosis^[36]. Decreased survival among HCC resection patients was not associated with progressive increase in fibrosis stage until complete cirrhosis is established^[37]. Severe fibrosis/cirrhosis may diminish liver coagulability^[38] and increase susceptibility to infection^[39], which may then lead to the rise of postoperative complications and the risk of mortality.

Our study has several limitations. Given the retrospective nature of the NCDB, we were able to demonstrate associations and not causative relationships between predictors and outcomes. NCDB only records readmissions to the same hospital, consequently the recorded 30-day unplanned readmission may underestimate the true readmission rate due to not tracking patients readmitted to a different hospital. The causes of 30-day unplanned readmission are not collected in NCDB making the analysis for the most common causes for early readmission unfeasible. Although NCDB included liver fibrosis information, data were not available for more than three quarters of patients; therefore, we were unable to verify the conclusion from one study that claimed neither cirrhosis nor fibrosis is associated with readmission^[8]. Instead, we addressed the association between 30-day unplanned readmission and conditional 90-day mortality by fibrosis score.

Despite these limitations, NCDB provides national level readmission and mortality information with a large sample size for HCC patients undergoing partial hepatectomies, which enables us to explore the relationship between 30-day unplanned readmission and conditional 90-day mortality among subgroups. This is the first study based on NCDB to identify multiple predictors of 30-day unplanned readmission for HCC patients following partial hepatectomies. Most importantly, this was the first time to report that 30-day unplanned readmission was significantly associated with conditional 90-day mortality after partial hepatectomy. The study also detailed how this association varied among different subgroups.

CONCLUSION

In this study, we demonstrated that male sex, Hispanic ethnicity, higher Charlson-Deyo score, and higher annual hospital hepatectomy volume were significant predictors of 30-day unplanned readmission. We further demonstrated that 30-day unplanned readmission had a significant impact on conditional 90-day mortality among patients with HCC who underwent partial hepatectomies. The study documented more than 3-fold increases in the odds of 90-day mortality in subgroups of patients 75 years and older, female sex, white, non-Hispanic race, uninsured, with severe fibrosis/cirrhosis and treated in hospitals with more than 15 hepatectomies annually.

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