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Authors

Muhammad, Zia Khan
Muhammad, U Khan
Safi, U Khan
et al.

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Atrial Fibrillation is a Risk Factor for Worse Outcomes in Patients with End Stage Liver Disease

Muhammad Zia Khan[1], Muhammad U. Khan[1], Safi U. Khan[1], Anas Alharbi[1], Mohammed Osman[2], Pratik Agrawal[2], Mina M. Benjamin[2], Kinjan Patel[2], Sudarshan Balla[2], Muhammad Bilal Munir[2,3]

[1]Department of Medicine, West Virginia University, Morgantown, WV, USA.
[2]Division of Cardiovascular Medicine, West Virginia University Heart & Vascular Institute, Morgantown, WV, USA.
[3]Section of Electrophysiology, Division of Cardiovascular Medicine, University of California San Diego, La Jolla, CA, USA.

Abstract

Background: Liver disease is a risk factor for development of atrial fibrillation (AF). We aim to study inpatient mortality and resource utilization of end-stage liver disease (ESLD) patients with AF from a nationally representative United States population sample.

Methods: For the purpose of our study, we utilized data from National Inpatient Sample for calendar years 2005-2015. Patients with ESLD and AF were identified using relevant International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Key outcomes of inpatient mortality and resource utilization were assessed. We also constructed a multiple logistic regression model to determine predictors of mortality in ESLD patients. Propensity matching was also done to balance confounding variables.

Results: A total of 309,959 ESLD patients were included in final analysis. Out of these, about 32,858 (10.6%) patients have concomitant AF. ESLD patients with AF were older and had higher burden of key co-morbidities such as heart failure, diabetes and hypertension. Mortality was significantly higher in both unmatched (12.3% vs. 9.2%, $p < 0.01$) and matched cohorts (12.2% vs. 10.8%, $p < 0.01$). Additionally, ESLD patients with AF have longer length of stay, increased facility discharge and cost of hospitalization compared to ESLD patients without AF. In multivariate analysis, AF is an independent predictor of mortality in ESLD patients.

Conclusion: AF portends worse outcomes in patients with ESLD. Strong index of suspicion is warranted to timely identify AF in this patient population.

Introduction

End stage liver disease (ESLD) is a global health burden and one of the leading causes of mortality around the world [1,2]. Majority of ESLD patients frequently get admitted to hospital due to related complications of hepatic encephalopathy, spontaneous bacterial peritonitis (SBP) and gastrointestinal bleeding (3). ESLD is also associated with autonomic dysfunction and increase levels of circulating neuropeptides such as vasoactive intestinal peptide (VIP) and galactin-3 [4,5,6]. These physiological perturbations are proposed in pathogenesis of atrial fibrillation (AF) in ESLD patients [7]. Studies have shown that ESLD is a predictor for new onset AF with advanced ESLD as manifested by worsening Model for End-Stage Liver Disease (MELD) score associated with further increased risk [8]. Till to date, there is no data on how AF affects inpatient outcomes of ESLD patients who are at greatest risk for frequent hospitalizations. In this paper, we aim to study these parameters from a national United States population database.

Key Words

Atrial Fibrillation; End-Stage Liver Disease; Outcomes.

Corresponding Author
Muhammad Bilal Munir, MD
West Virginia University Heart & Vascular Institute and University of California San Diego Sulpizio Cardiovascular Center
1 Medical Center Drive, Morgantown, West Virginia 26505

Methods

Data was collected from National Inpatient Sample (NIS). NIS is part of Healthcare Cost and Utilization Project (HCUP) databases and is made possible by a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is derived from all States for national estimates of healthcare utilization, cost and outcomes [9]. Since NIS is compiled annually, the data can be used for analysis of disease trends over time. The study was deemed exempted from Institutional Review Board approval given the de-identified nature of the NIS database and public availability.

We analyzed NIS database from January 2005 to August 2015 using the International Classification of Diseases, 9th Revision,

Clinical Modification (ICD-9-CM) codes. Patients ≥ 18 years of age were included. Patients with ESLD were identified using Goldberg's third algorithm (10), a well-validated method for identifying ESLD from administrative datasets, generating a positive predictive value of 89.3%. Based on this algorithm, first ICD-9-CM codes were used to select chronic liver disease patients. (ICD-9-CM of 070.20-21, 070.23, 070.30-33, 070.40, 070.42, 070.49, 070.52, 070.59-60, 070.70-71, 070.90, 571.1, 571.40-41, 571.8, and 571.9), then a concurrent diagnosis code of cirrhosis was added (ICD-9-CM of 571.2, 571.5 or 571.6) and finally at least 1 concurrent diagnostic code for hepatic decompensation event (ICD-9-CM of 456.0-2, 789.5, 789.59, 572.2, 567.2, 567.21, 567.29, 567.8-9 or 572.4). Using this algorithm, we were able to extract a total of 309,959 ESLD patients that were included in final analysis. Please see figure 1 for detailed methodology of patient inclusion criteria.

Baseline characteristics and hospital outcomes were derived and compared among ESLD patients with and without AF. To account for potential confounding factors and selection bias, a propensity score-matching model was developed using logistic regression to derive two matched groups for comparative outcomes analysis. A nearest neighbor 1:1 variable ratio, parallel, balanced propensity-matching model was made using a caliper width of 0.2. Descriptive statistics were presented as frequencies with percentages for categorical variables and as means with standard deviations for continuous variables. Baseline characteristics were compared using a Pearson^{x}2 test and Fisher's exact test for categorical variables and independent samples t-test for continuous variables.

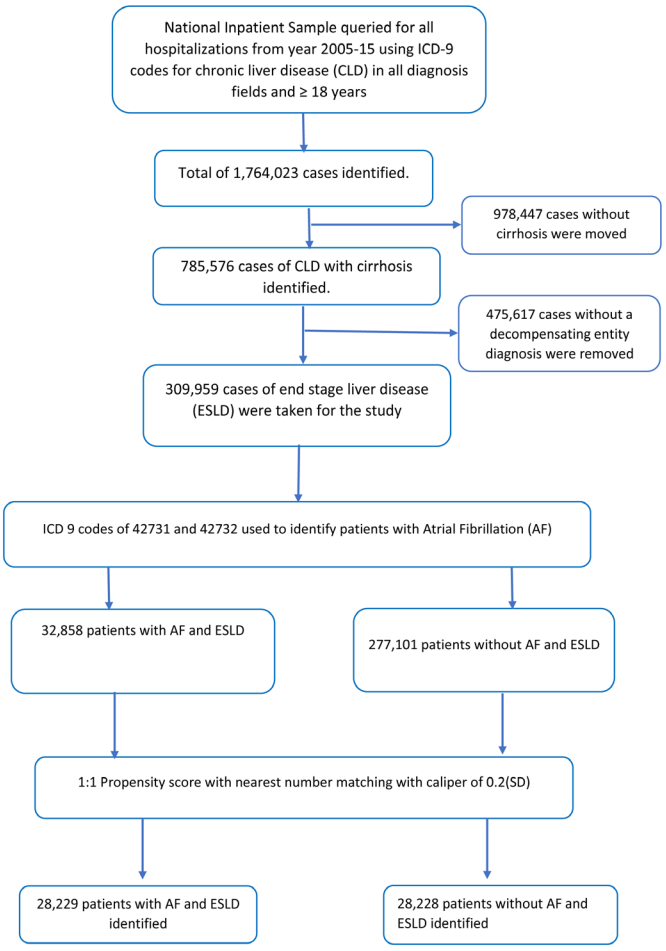

Figure 1: **Flow sheet of our paper**

Logistic regression was performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs) to determine predictors of mortality in ESLD. Initially, binomial logistic regression model was used to identify variables from demographic data (Table 1) that were significantly associated with patient mortality (P value < 0.10). These variables were then subsequently utilized in a multiple logistic regression model to identify predictors of mortality. A type I error rate of <0.05 was considered statistically significant. All statistical analyses were performed using statistical package for social science (SPSS) version 26 (IBM Corp) and R 3.5 for propensity matching

Results

A total of 309,959 patients with ESLD were identified from the NIS dataset. Out of these 32,858 patients had AF (10.6%). Baseline characteristics of the study population are shown in table 1. ESLD patients with AF were older (68.46 vs. 58.14 years, p < 0.01) and had higher burden of key co-morbidities such as diabetes (29.9% vs. 25.3%, p < 0.01), hypertension (53.8% vs. 40.1%, p < 0.01) and congestive heart failure (31.2% vs. 9.3%, p < 0.01). Overall, about 29,487 (9.5%) ESLD patients died at discharge (see table 2). Mortality was 9.2% in ESLD without AF when compared to 12.3% in ESLD with AF (p < 0.01). In a propensity-matched cohort, this mortality difference continues to remain significant (12.2% vs. 10.8%, p < 0.01, supplemental table 2). A gradual downtrend trend in mortality was noted in ESLD patients with and with out AF over our study years (see figure 2). This downward trend is same across both genders although male patients had higher mortality when compared to female patients over our study period (see figure 3).

ESLD patients with AF have longer length of stay (9 vs. 7.36 days, p < 0.01) and increase costs of hospitalization (78,246 $ vs. 63,403 $, p < 0.01) when compared to ESLD patients without AF. Please see figure 4 for length of stay and costs of hospitalization trends over our study years. Predictors of mortality in ESLD are shown in figure 5. Advanced age, AF and African American race were independently associated with increased mortality. Urban and large hospitals were associated with lower mortality. Patients with metabolic acidosis, coagulopathy, pulmonary circulation disorders, congestive heart failure and cancers were also associated with increased mortality in our study cohort.

Discussion

The main findings of our current investigation are: (1) ESLD patients with concomitant AF have increased mortality when compared to ESLD patients without concomitant AF (12.30% vs. 9.20%, p < 0.01) and this difference persisted despite balancing covariates in a propensity matched model (12.2% vs. 10.8%, p < 0.01). (2) The presence of AF is an independent predictor of mortality in ESLD patients and about 10.6% patients in our cohort have AF. (3)

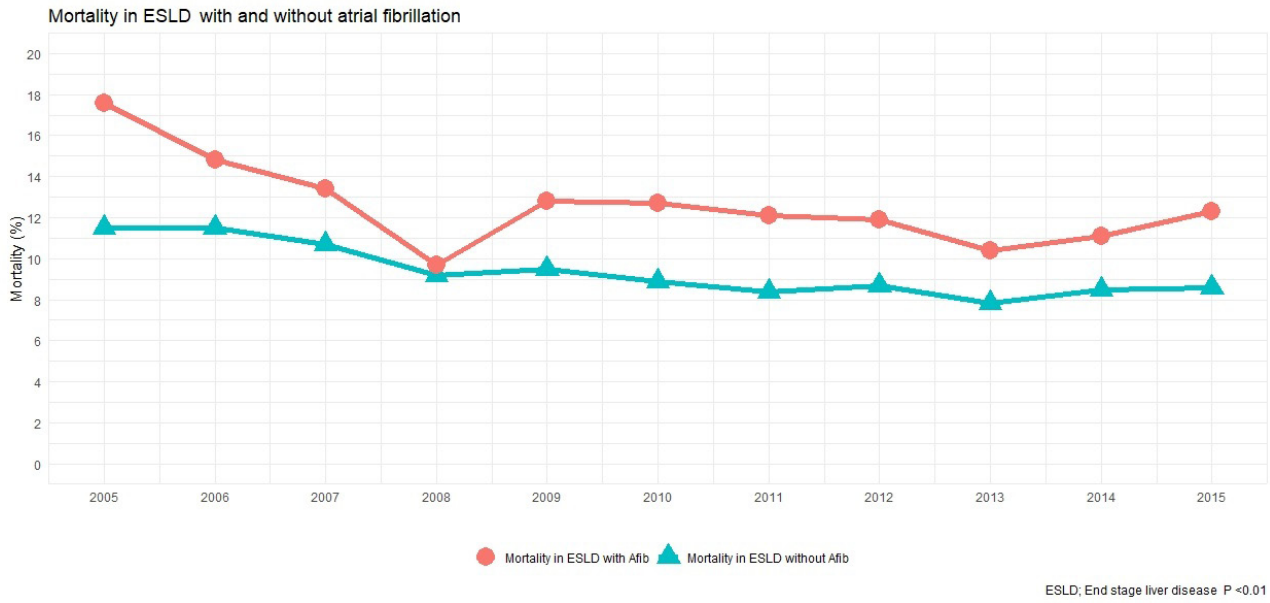

Figure 2: **Mortality in end stage liver disease with and with out atrial fibrillation over study years**

ESLD and AF patients have increased cost of hospitalization as well as length of stay when compared to ESLD patients without AF.

ESLD is a rising global health burden and represents a final sequel in natural history of liver cirrhosis [1,2]. Frequent hospitalizations are common in ESLD patients due to concomitant complications of hepatic encephalopathy, SBP and gastrointestinal bleeding [3]. ESLD patients are more prone to developing AF even in absence of structural heart disease. This increased propensity of developing AF is proposed to be due to autonomic dysfunction and increased levels of circulating neuropeptides such as VIP and galactin-3 that exercise their effect either through modulating autonomic system or inducing fibrosis within the heart muscle [4,5,6,7]. The prevalence of AF in our cohort is about 10.6%, which is consistent with earlier studies. The study by Huang et al. [8] on 1727 consecutive ESLD patients awaiting liver transplantation showed AF prevalence to be about 11.2%. They also found that liver disease is an independent predictor of new onset AF and increased MELD scores are subsequently associated with worsening risk of new AF development. Similarly, another study by Lee et al. [11] has found 46% relative risk of developing AF in patients with liver cirrhosis. In comparison to our study, they did not find AF to be significantly associated with all-cause mortality. It is pertinent to mention here that Lee et al. primarily enrolled patients with various stages of cirrhosis while our study exclusively focused on ESLD cohort which is comparatively more sicker and morbid and that may explain difference in mortality between both studies. In another study on ESLD patients undergoing liver transplantation [12], the occurrence of peri-procedural AF was associated with worsened mortality (HR 5.097, 95% CI 2.189-11.86). In our national cohort of ESLD patients, we have demonstrated that AF is associated with worse in-patient survival and that difference persists despite accounting for confounding variables. We also demonstrated that AF is an independent predictor of mortality in ESLD patients.

The strong association of worse outcomes of ESLD patients with AF poses unique management challenges. Stroke is a leading cause of mortality and disability in AF patients and anti-coagulation is often recommended to mitigate those risks [13,14]. The utilization of anti-coagulation can be especially challenging in ESLD patients due to increased bleeding risk associated with platelet dysfunction and esophageal varices [15]. Additionally, there are studies showing increased propensity of hemorrhagic stroke in ESLD patients and that risk in some cases exceeds those of ischemic stroke [16,17]. Our dataset, unfortunately, is not designed to ascertain causes of mortality but whether embolic or bleeding events contributed to poor outcomes needs further studies. Additionally, the association of worse mortality in ESLD patients with AF also calls into question measures to screen for AF in this patient population. Timely detection of AF and subsequent implementation of relevant therapeutic measures could result in improved outcomes in ESLD patients.

Limitations

NIS is an administrative claim-based database that uses ICD-9-CM codes for diagnosis that may be subjected to error. The hard clinical points such as liver cirrhosis and mortality are, however, less prone to error. There are no well-defined ICD-9-CM codes for ESLD and we have used Goldberg's third algorithm for stratifying these patients as mentioned in methods section. This method yields a positive predictive value of about 89.3% for ESLD but it is still plausible that some patients with ESLD may not have been captured using this methodology. NIS collects data on in-patient discharges and each admission is registered as an independent event. It is possible that same patient may have more than one subsequent admission over time. NIS samples are not designed to follow patients longitudinally so long-term outcomes could not be assessed from

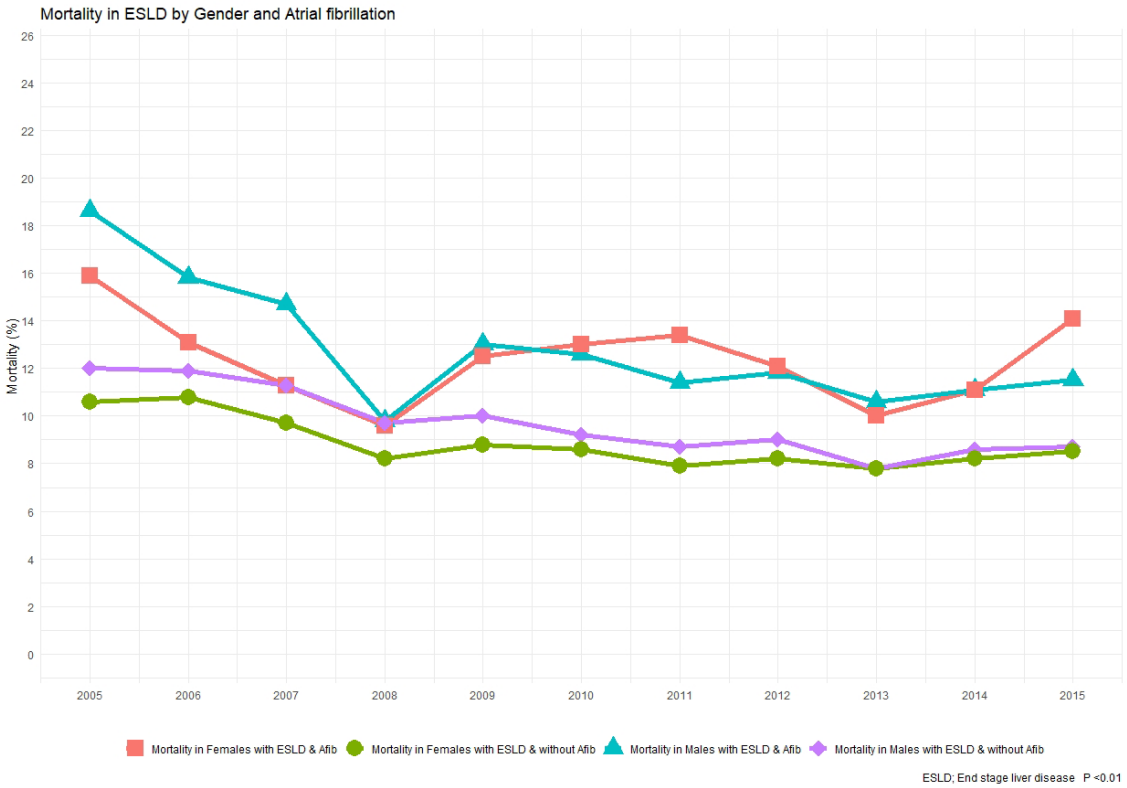

Figure 3: **Mortality in end stage liver disease by gender and atrial fibrillation over study years**

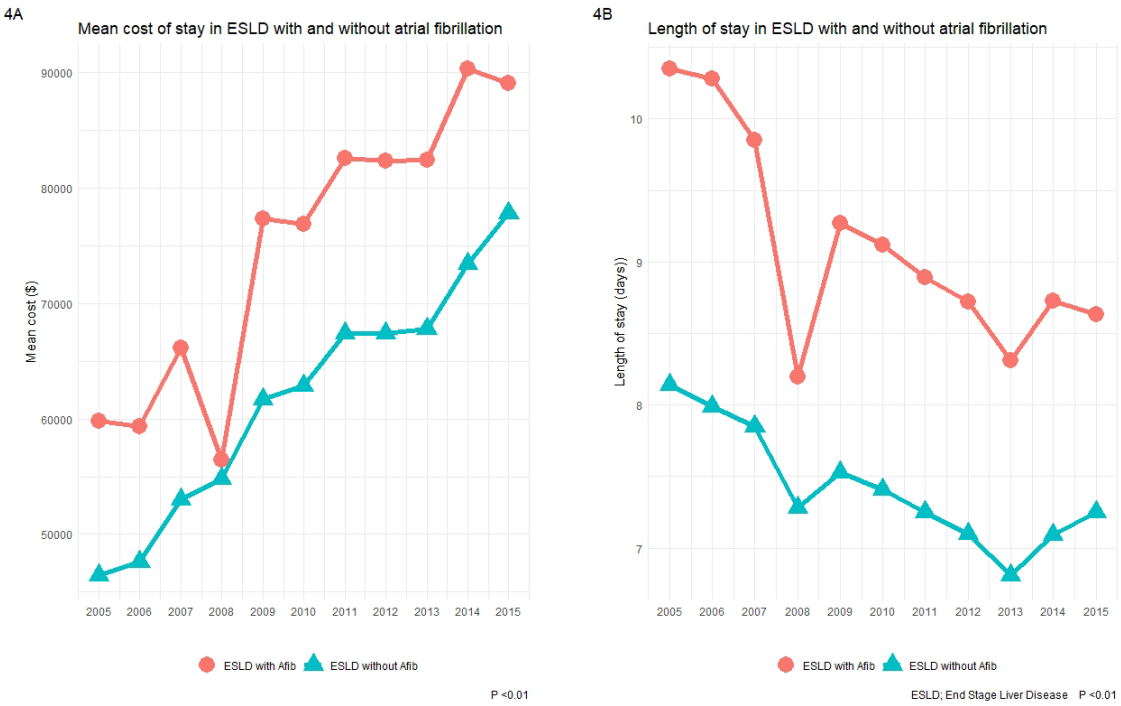

Figure 4: **Mean cost of hospitalization and length of stay over our study period**

Table 1: **Baseline characteristics of the study population**

Variable	Decompensated CLD† patients without atrial fibrillation (n=277,101)	Decompensated CLD† patients with atrial fibrillation (n=32,858)	All Decompensated CLD† patients (n=309959)	P value
Age (mean [SD]) years	58.14(12)	68.46(11.8)	59.23(12.4)	<0.01
Female	104775(37.8%)	11498(35%)	116273(37.5%)	<0.01
Race				
Caucasian	161236(65%)	21996(73.9%)	183232(66%)	<0.01
African American	25435(10.3%)	2895(9.7%)	28330(10.2%)	
Hispanics	44713(18%)	3215(10.8%)	47928(17.3%)	
Asian or Pacific Islander	5431(2.2%)	722(2.4%)	6153(2.2%)	
Native American	3532(1.4%	188(0.6%	3720(1.3%)	
Medical comorbidity				
Acquired immune deficiency syndrome	1920(0.7%)	80(0.2%)	2000(0.6%)	<0.01
Alcohol abuse	108711(39.2%)	8564(26.1%)	117275(37.8%)	<0.01
Anemia (chronic blood loss)	13485(4.9%)	1261(3.8%)	14746(4.8%)	<0.01
Anemia (Deficiency anemia)	83965(30.3%)	11119(33.8%)	95084(30.7%)	<0.01
Collagen vascular diseases	5393(1.9%)	644(2%)	6037(1.9%)	0.865
Congestive heart failure	25819(9.3%)	10260(31.2%)	36079(11.6%)	<0.01
Chronic pulmonary disease	48075(17.3%)	8940(27.2%)	57015(18.4%)	<0.01
Coagulopathy	107493(38.8%)	10294(31.3%)	117787(38%)	<0.01
Diabetes uncomplicated	70187(25.3%)	9821(29.9%)	80008(25.8%)	<0.01
Diabetes with chronic complications	16417(5.9%)	2839(8.6%)	19256(6.2%)	<0.01
Drug abuse	20523(7.4%)	993(3%)	21516(6.9%)	<0.01
Hypertension (combine uncomplicated and complicated)	111152(40.1%)	17685(53.8%)	128837(41.6%)	<0.01
Hypothyroidism	27026(9.8%)	5408(16.5%)	32434(10.5%)	<0.01
Lymphoma	2120(0.8%)	366(1.1%)	2486(0.8%)	0.11
Fluid and electrolyte disorders	125123(45.2%)	15859(48.3%)	140982(45.5%)	<0.01
Metastatic cancer	5567(2%)	594(1.8%)	6161(2%)	0.13
Neurological disorders	18870(6.8%)	2108(6.4%)	20978(6.8%)	<0.12
Obesity	22290(8)	3912(11.9%)	26202(8.5%)	<0.01
Peripheral vascular disorders	10755(3.9%)	2998(9.1%)	13753(4.4%)	<0.01
Pulmonary circulation disorders	8098(2.9%)	2969(9.0%)	11067(3.6%)	<0.01
Renal failure	47511(17.1%)	11568(35.2%)	59079(19.1%)	<0.01
Solid tumor without metastasis	13274(4.8%)	1380(4.2%)	14654(4.7%)	<0.01
Peptic ulcer disease	224(0.1%)	26(0.1%)	250(0.1%)	0.918
Valvular disease	9236(3.3%)	4007(12.2%)	13243(4.3%)	<0.01
Weight loss	35185(12.7%)	4209(12.8%)	39394(12.7%)	0.564
Associated diagnosis				
Acidosis	27135(9.8%)	3332(10.1%)	30467(9.8%)	0.11
Acute Myocardial Infraction	4174(1.5%)	982(3%)	5156(1.7%)	<0.01
Cardiogenic shock	920(0.3%)	452(1.4%)	1372(0.4%)	<0.01
Septic shock	14222(5.1%)	2331(7.1%)	16553(5.3%)	<0.01
Hepatorenal syndrome	15801(5.7%)	1729(5.3%)	17530(5.7%)	0.07
Hepatopulmonary syndrome	452(0.2%)	44(0.1%)	496(0.2%)	0.210
Hyponatremia	55730(20.1%)	6581(20%)	62311(20.1%)	0.722
Cardiac arrest	2656(1%)	561(1.7%)	3217(1%)	<0.01
				<0.01
Hospital Control and or funding				
Government or Private	25427(9.2%)	2539(7.7%)	27966(9%)	<0.01
Government, non-federal	115121(41.5%)	15483(47.1%)	130604(42.1%)	
Private, not-for-profit	32327(11.7%)	3797(11.6%)	36124(11.7%)	
Private, investor-owned	4281(1.5%)	508(1.5%)	4789(1.5%)	
Private, either not-for-profit or investor-owned	25427(9.2%)	2539(7.7%)	27966(9%)	

Hospital Location				
Rural	**23296(8.4%)**	**2823(8.6%)**	**26119(8.4%)**	**0.34**
Urban Non-teaching	**101223(36.5%**	**12801(39%)**	**114024(36.8%)**	
Urban Teaching	**152582(55.1%)**	**17234(52.4%)**	**169816(54.8%)**	
Bed size of the hospital				
small	**32833(11.8%)**	**4062(12.4%)**	**36895(11.9%)**	**0.39**
medium	**68367(24.7%)**	**8301(25.3%)**	**76668(24.7%)**	
large	**175901(63.5%)**	**20495(62.4%)**	**196396(63.4%)**	
Primary payer				
Medicare	**115370(41.7%)**	**22830(69.6%)**	**138200(44.7%)**	**<0.01**
Medicaid	**63817(23.1%)**	**3285(10%)**	**67102(21.7%)**	
Private insurance	**64509(23.3%)**	**5029(15.3%)**	**69538(22.5%)**	
Self-pay	**19293(7%)**	**825(2.5%)**	**20118(6.5%)**	
No charge	**2097(0.8%)**	**124(0.4%)**	**2221(0.7%)**	
other	**11418(4.1%)**	**725(2.2%)**	**12143(3.9%)**	
Region no. (%)				
Northeast	**79265(28.6%)**	**10017(30.5%)**	**89282(28.8%)**	**<0.01**
Midwest	**124166(44.8%)**	**13657(41.6%)**	**137823(44.5%)**	
South	**45619(16.5%)**	**5833(17.8%)**	**51452(16.6%)**	
West	**28051(10.1%)**	**3351(10.2%)**	**31402(10.1%)**	
Median household income no. (%)				
0–25th percentile	**87671(32.7%)**	**9096(28.3%)**	**96767(32.2%)**	**<0.01**
26–50th percentile	**70412(26.3%)**	**8211(25.6%)**	**78623(26.2%)**	
51–75th percentile	**62278(23.2%)**	**7859(24.5%)**	**70137(23.4%)**	
76–100th percentile	**47783(17.8%)**	**6931(21.6%)**	**54714(18.2%)**	
†chronic liver disease				

Table 2: **Outcomes and resource utilization of the study cohort**

Variables	ESLD† patients without atrial fibrillation (N=277,101)	ESLD† patients with atrial fibrillation (n=32, 858)	All ESLD† patients (n=309,959)	P value
Died at discharge	25441(9.2%)	4046(12.3%)	29487(9.5%)	<0.01
Discharge Disposition of surviving patients, No. (%)				
Routine/self-care	150811(60%)	12001(41.7%)	162812(58.1%)	<0.01
Short-term hospital	10822(4.3%)	1260(4.4%)	12082(4.3%)	
Another type of facility	46192(18.4%)	8907(30.9%)	55099(19.7%)	
Home Health Care	37756(15%)	6212(21.6%)	43968(15.7%)	
Resource utilization, Mean (SD), No. (%)				
Length of stay, mean (SD), days	7.36(8.9)	9(9.9)	7.54(9.1)	<0.01
Cost of hospitalization-mean (SD), $	63,403(111050)	78,246(124777)	64,972 (112673)	<0.01
Procedures during stay				
Left heart catheterization	2571(0.9%)	819(2.50%)	3390(1.1%)	<0.01
Undergoing Per Cutaneous Coronary intervention	659(0.2%)	150(0.5%)	809(0.3%)	<0.01
Vasopressin	3097(1.1%)	646(2%)	3743(1.2%)	<0.01
Hemodialysis	18667(6.7%)	4219(12.8%)	22886(7.4%)	<0.01
Ventilator	26963(9.7%)	3777(11.5%)	30740(9.9%)	<0.01
Gastrostomy	2039(0.7%)	406(1.2%)	2445(0.8%)	<0.01
Tracheostomy	2533(0.9%)	447(1.4%)	2980(1%)	<0.01
† End stage liver disease				

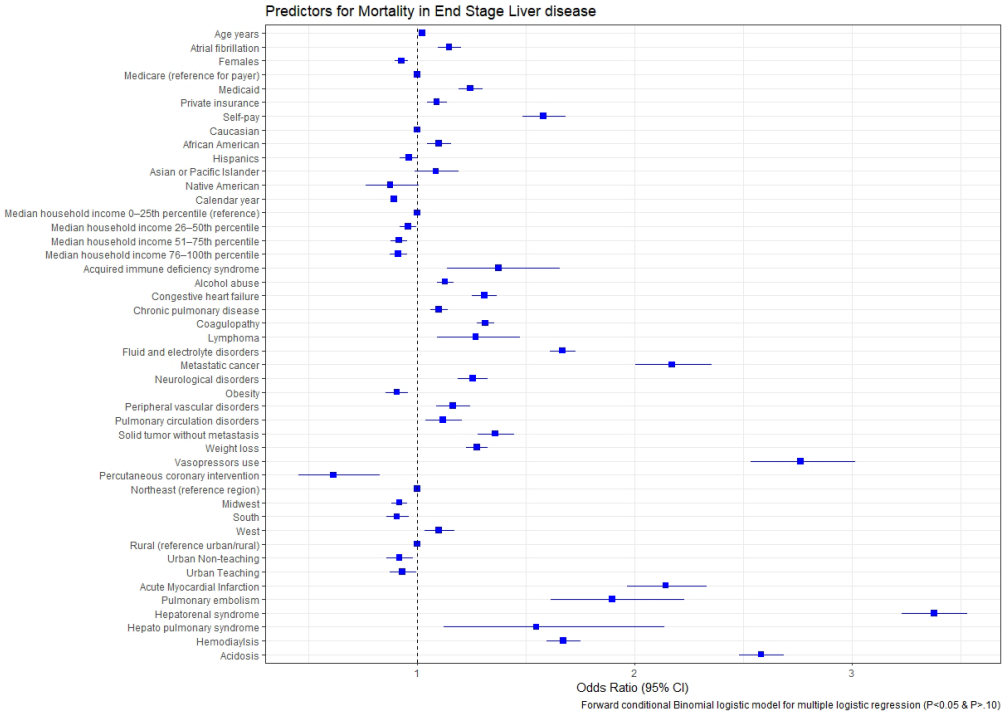

Figure 5: **Predictors of mortality in end stage liver disease patients**

the present dataset. Additionally, data on AF management is lacking from NIS which have important implications on conclusions drawn from the study.

Conclusion

Our study shows AF to be associated with worse outcomes in ESLD patients. It is therefore imperative that treating physicians should have a strong clinical suspicion for AF in this specific patient cohort as timely AF detection could result in improved outcomes.

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Supplemental Data

Table 1S: Baseline characteristics after propensity matching

Variable	DCLD† without Atrial Fibrillation (n=28,229)	DCLD† with Atrial Fibrillation (n=28,229)	P value
Age (mean [SD]) year	61.58(12.39)	68.46(11.81)	
Female	10006(35.4%)	9900(35.1%)	0.349
Race			
Caucasian	20912(74.1%)	20989(74.4%)	0.41
African American	2842(10.1%)	2748(9.7%)	
Hispanics	2944(10.4%)	2972(10.5%)	
Asian or Pacific Islander	671(2.4%)	660(2.3%)	
Native American	139(0.5%)	167(0.6%)	
AHRQ co morbidities			
Anemia (chronic blood loss)	1302(4.6%)	1060(3.8%)	<0.01
Anemia (Deficiency anemia)	9594(34%)	9594(34%)	0.05
Collagen vascular diseases	653(2.3%)	557(2%)	0.05
Congestive heart failure	8502(30.1%)	8502(30.1%)	0.03
Chronic pulmonary disease	7805(27.6%)	7805(27.6%)	0.5
Coagulopathy	9014(31.9%)	9014(31.9%)	0.52
Diabetes, uncomplicated	8762(31%)	8762(31%)	0.89
Diabetes with chronic complications	2372(8.4%)	2372(8.4%)	0.78
Hypertension (combine uncomplicated and complicated)	15832(56.1%)	15832(56.1%)	0.01
Hypothyroidism	4822(17.1%)	4822(17.1%)	0.8
Lymphoma	265(0.9%)	318(1.1%)	0.03
Fluid and electrolyte disorders	13957(49.4%)	13957(49.4%)	0.53
Metastatic cancer	608(2.2%)	608(2.2%)	<0.01
Obesity	3481(12.3%)	3430(12.2%)	0.51
Peripheral vascular disorders	2546(9%)	2532(9%)	0.86
Renal failure	10110(35.8%)	10110(35.8%)	0.6
Solid tumor without metastasis	1244(4.4%)	1225(4.3%)	0.7
Valvular disease	3135(11.1%)	3497(12.4%)	<0.01
Associated diagnosis			
Acute Myocardial Infraction	735(2.6%)	850(3%)	<0.01
Cardiogenic shock	364(1.3%)	399(1.4%)	0.2
Septic shock	2027(7.2%)	2050(7.3%)	0.70
Hepato renal syndrome	1775(6.3%)	1506(5.3%)	<0.01
Hepato Pulmonary syndrome	63(0.2%)	41(0.1%)	0.03
syndrome			
Acidosis	2980(10.6%)	2909(10.3%)	0.33
Hospital Location			
Rural	2201(7.8%)	2264(8%)	0.03
Urban Non-teaching	11053(39.2%)	11305(40%)	
Urban Teaching	14974(53%)	14660(51.9%)	
Bedside of the hospital			
Small	3428(12.1%)	3469(12.3%)	0.15
Medium	7012(24.8%)	7191(25.5%)	
Large	17788(63%)	17569(62.2%)	
Region			
Northeast	7999(28.3%)	8369(29.6%)	<0.01
Midwest	12177(43.1%)	11433(40.5%)	
South	5457(19.3%)	5566(19.7%)	
West	2595(9.2%)	2861(10.1%)	

Median household income no. (%)			
0–25th percentile	**8249(29.2%)**	**8109(28.7%)**	**0.2**
26–50th percentile	**7279(25.8%)**	**7165(25.4%)**	
51–75th percentile	**6724(23.8%)**	**6873(24.3%)**	
76–100th percentile	**5976(21.2%)**	**6082(21.5%)**	
† Decompensated Chronic Liver disease			

Table 2S: Outcomes after propensity score matching

Hospital Outcomes, No. (%)	ESLD without atrial fibrillation (28228)	ESLD with atrial fibrillation (28229)	P value
Died at discharge	3051(10.8%)	3457(12.2%)	P<0.01
Resource utilization, Mean (SD)			
Length of stay, mean (SD), days	8.11(9.6)	9.03(9.63)	<0.01
Mean cost	73408(128412)	80792(128241)	<0.01
PEG	248(0.9%)	357(1.3%)	<0.01
Tracheostomy	327(1.2%)	389(1.4%	0.02
†End Stage Liver Disease			