Racial and Health Disparities among cirrhosis related hospitalizations in the US

Ashwani K Singal (ashwanisingal.com@gmail.com)
Avera McKennan Hospital and University Health Center https://orcid.org/0000-0003-1207-3998
Yong-Fang Kuo
UTMB: The University of Texas Medical Branch at Galveston
Juan P. Arab
University of Chile: Universidad de Chile
Ramon Bataller
UPMC Health Plan

Research Article

Keywords: AH, ACLF, ALD, American Indians, Alaska Natives, Native Americans, Healthcare burden, Epidemiology, Magnitude, Transplant.

Posted Date: May 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-503173/v1

Abstract

Data are scanty on racial disparities in alcohol-associated liver disease (ALD) hospitalizations. National Inpatient Sample on 199,748 cirrhosis hospitalizations, 14,241 (2,893 AI/AN, 2,893 whites, 2,882 blacks, 2,879 Hispanics, and 2,694 Asian/other race) was matched 1:1 for demographics, insurance, and income quartile of residence zip code. After controlling for geographic location and hospital type, ALD etiology was higher by 1.6 folds in AI/AN vs. whites by 1.9 folds vs. blacks and Hispanic, and 2,2 folds vs. Asian/other race. Alcohol use disorder (AUD) was present in 38% of admissions in AI/AN vs. 24–30% in other races, $P < 0.001$. 5.9% admissions were associated with in-hospital mortality, with 34% reduced odds in AI/AN vs. blacks. Among cirrhosis related hospitalizations in the US, racial and ethnic disparities exist with alcohol as the commonest etiology in AI/AN, and highest in-hospital mortality in blacks. Public health policies are needed to reduce the health disparities individuals with ALD.

Introduction

Alcohol-associated liver disease (ALD) is one of the most common liver diseases worldwide leading to advanced fibrosis and alcohol-associated cirrhosis (AC) in 10–20% of cases. Further, advanced fibrosis among individuals at risk for ALD is increasing in the US from 2.2% in 2001 to 6.6% in 2016.[1] In 2017, a total of 123 million people worldwide and about 2.2 million in the US had AC.[2] Currently, ALD is the leading indication for liver transplantation (LT), with over 40% of LT in the US performed in 2018 for this indication.[3] AC contributes to about 27% of all cirrhosis-related deaths, with a total of 332,268 deaths due to AC in 2017 in the US.[2]

Patients with ALD are often hospitalized for complications of cirrhosis or for more severe forms of the disease with alcohol-associated hepatitis (AH) or acute-on-chronic liver failure (ACLF). The proportion of all hospitalizations in the US due to ALD is increasing from 19.4% in 2012 to 37.7% in 2016, with estimated direct cost of hospitalizations of $22.7 billion during this period.[4] Patient mortality during ALD related hospitalization is about 12%,[4] and can be up to approximately 40% for those with ACLF.[5]

American Indian/Alaska Native (AI/AN) contribute to about 1.7% of the US population, with a total of about 5.2 million AI/AN individuals as per 2010 census.[6] Mortality among AI/AN individuals has been shown to be disproportionately higher compared to whites for many diseases including chronic liver disease and cirrhosis.[7, 8] Increased use of alcohol and other recreational drugs in the AI/AN population is likely contributing to high rates of cirrhosis-related mortality. For example, AC related mortality in 45–64 years age group was 75 per 100,000 individuals with AI/AN race, and was 15 per 100,000 in white individuals.[7] However, data are scanty in cirrhosis patients comparing ALD as cirrhosis etiology in AI/AN vs. other races and ethnicities. In a cohort of hospitalized patients with cirrhosis in the US, we compared AI/AN to matched cohorts of other races for ALD as cause of liver disease and for in-hospital mortality. We also examined subgroup cohorts with decompensated cirrhosis or with ACLF.

Methods

Study Population

National Inpatient Sample (NIS) database was used for the study. Using the Healthcare Cost and Utilization Project, NIS database is developed and maintained by the Agency for Healthcare Research and Quality, and is the largest inpatient database in the US, representing hospital discharges from 46 states (approximately 97% of the US population). It contains data from over 7 million hospital discharges annually yielding national estimates of hospital inpatient stays. The NIS includes up to 25 discharge diagnoses using the International Classification of Diseases (ICD) codes. The clinical discharge records also include patient demographics, payer status, procedure codes, hospital costs, comorbidities, inpatient mortality, and hospital characteristics such as region and teaching status. Cirrhosis-related hospitalizations in the NIS database (10/01/2015-12/31/2016) were identified using one of the discharge diagnosis ICD-10 codes (**Supplementary Table 1**).[9]

Hospitalizations with AI/AN race identification were matched 1:1 on demographics (age and gender) and the socio-economic status [insurance and income quartile of the residence zip code] to each of another race and ethnicity group. As 71% of AI/AN people according to the 2010 census have migrated to urban cities for better education, housing, and employment, matching was also done for the type of hospital (urban vs. rural and teaching vs. non-teaching). From this matched cohort, subgroups of hospitalizations with decompensated cirrhosis, with ACLF, or with in-hospital mortality were extracted (Fig. 1). The whole and subgroup cohorts were examined for primary and secondary outcomes. As the cirrhosis-related disparities in AI/AN individuals may be related to their socioeconomic status, [10] the analyses were controlled for this potential confounder.

Outcomes

Primary outcome was ALD as cause for hospitalization, identified using the ICD-10 codes (K70.30 and K70.31 for AC, K70.10 and K70.11 for AH), **Supplementary Table 1**.[5, 11] Secondary outcome was hospitalization with one of the discharge diagnoses of AH.

Definitions

AI/AN

The NIS database captures the information on self-reported race of the patient and is stratified in the database to white, black, Hispanic, Asian, AI/AN, and other race.

Socioeconomic status

Insurance status (Medicare, Medicaid, Private or other) and quartile distribution on the household income in the patient's Zip code of residence were used to define the socioeconomic status.[12]

Decompensated cirrhosis

was defined with presence of either of the complications of ascites, hepatic encephalopathy, or variceal bleeding. ICD-10 codes used for these (**Supplementary Table 1**).

Acute-on-chronic liver failure

As the NIS database does not provide laboratory values, ACLF among ALD related admissions was defined using the North American Consortium for the Study of End-stage Liver Disease definition, with presence of two or more extrahepatic organ failures.[5, 13] Those with three and four organ failures defined s ACLF-2 and ACLF-3 grades respectively. ICD-10 codes were used to define cardiovascular failure (central venous pressure, arterial line, pulmonary wedge pressure, septic shock), pulmonary failure (mechanical ventilation), brain failure (hepatic encephalopathy), and renal failure (dialysis or hepatorenal syndrome), **Supplementary Tables 1 and 2**.[5, 14]

Statistical Analyses

Baseline characteristics of cirrhosis related hospitalizations were compared stratified by race to AI/AN with the other races. Chi-square test was used for comparing categorical variables. On the continuous variables, analysis of variance test was used for comparing means, and non-parametric test for comparing medians. Logistic regression analysis models were built to determine independent association of AI/AN race with the primary outcome of ALD etiology and the secondary outcome of AH. P-values < 0.05 were considered significant. SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analyses.

Results

Study Population

Between 10/01/2015 and 12/31/2016, there were 199,748 hospitalizations with discharge diagnosis of cirrhosis. Among them, 3,226 (1.6%) hospitalizations were in AI/AN compared to those in other races (133,306 whites, 21,929 blacks, 31,298 Hispanics, and 9,678 Asian or other race/ethnicity). AI/AN individuals were more likely to be younger, females, clustered in mountain and west north central divisions, income below median, insured with Medicaid pay source, ALD etiology, and have decompensated disease (**Supplementary Table 3**). Matched cohort of 14,241 hospitalizations (2,893 AI/AN, 2,893 whites, 2,882 blacks, 2,879 Hispanics, and 2,694 Asian or other race) was examined for further analyses.

Comparison of hospitalizations in AI/AN vs. other races

Analysis of the whole cohort: After matching for age, gender, type of hospital (urban vs. rural and teaching vs. non-teaching), and the socioeconomic status, hospitalizations in AI/AN individuals compared to all other races were more likely to have decompensated disease and discharged with a diagnosis of ALD or AH (Table 1). Admissions in AI/AN individuals compared to other races had higher

frequency of alcohol use disorder (AUD), 38 vs. 24–30%, P < 0.001 (Fig. 2). In a logistic regression model controlling for demographics (age, gender, and race), payer source, zip code income quartile, and hospital type, hospitalization with AI/AN compared to white race was 55% [1.55 (1.37–1.75)] and 21% [1.21 (1.05–1.40)] more likely to be discharged with a diagnosis of ALD and AH respectively. Odds of ALD and of AH as cause of admission was also higher in AI/AN by 1.87 and 1.26 compared with black, 1.89 and 1.86 compared with Hispanic, and 2.24 and 1.72 compared with Asian or other races. Other predictors of ALD or AH etiology were young age, male gender, Medicaid or private insurance, and admission in a rural or urban non-teaching hospital (Table 2).

Table 1
Baseline characteristics of hospitalizations in the US with discharge diagnosis of cirrhosis.

	White (N = 2893)	Black (N = 2882)	Hispanic (N = 2879)	Asian or other (N = 2694)	AI/NA (N = 2893)	P
Age in years (mean, SD)	52, 13	52, 14	51, 15	52, 15	52, 13	< 0.09
% Females	44	44	43	42	45	0.72
% Elective admissions	8.2	8.4	7.3	7.4	8.5	0.84
% Pay source (MC, MD, Pvt.)	29, 49, 22	30, 49, 21	29, 51, 20	31, 48, 21	29, 49, 22	0.98
% Hospital type (R, U non-teaching, U teaching)	15, 17, 68	14, 16, 70	14, 16, 70	7, 19, 74	15, 17, 68	0.044
% Zip code income quartile (Q1-Q4)	55, 24, 15, 6	55, 24, 15, 6	53, 26, 15, 6	52, 26, 16, 6	54, 25, 15, 6	0.26
% Alcohol-associated cirrhosis	38	31	40	33	50	< 0.001
% Alcohol-associated hepatitis	24	22	18	19	28	0.038
% Alcohol-associated liver disease	53	47	49	44	64	< 0.001
% Decompensated cirrhosis	35	28	37	33	40	< 0.001

SD: Standard deviation; MC: Medicare; MD: Medicaid; R: Rural; U: Urban

Table 2
Logistic regression analyses on the matched cohort of hospitalizations with cirrhosis for predictors of ALD or of AH as etiology of liver disease.

	Predictors of discharge diagnosis of ALD		Predictors of discharge diagnosis of AH	
	OR (95% CI)	P	OR (95% CI)	P
Age in years	0.977 (0.974–0.980)	< 0.001	0.959 (0.956–0.962)	< 0.001
Females vs. Males	0.50 (0.46–0.53)	< 0.001	0.67 (0.62–0.73)	< 0.001
Medicaid vs. Medicare	2.22 (2.0-2.4)	< 0.001	2.03 (1.79–2.32)	< 0.001
Pvt. vs. Medicare	1.87 (1.68–2.08)	< 0.001	2.13 (1.85–2.46)	< 0.001
AI/AN vs. White	1.55 (1.37–1.75)	< 0.001	1.21 (1.05–1.40)	< 0.001
AI/AN vs. Black	1.87 (1.65–2.11)	< 0.001	1.26 (1.09–1.46)	< 0.001
AI/AN vs. Hispanic	1.89 (1.68–2.13)	< 0.001	1.86 (1.61–2.14)	< 0.001
AI/AN vs. Asian or other	2.24 (1.98–2.53)	< 0.001	1.72 (1.48-2.00)	< 0.001
Rural vs. Urban teaching hospital	1.11 (0.99–1.24)	0.94	1.30 (1.14–1.48)	< 0.003
Urban non-teaching vs. Urban teaching hospital	1.23 (1.11–1.35)	< 0.004	1.12 (0.99–1.26)	0.73
Zip income Quartile 1 vs. 4	0.90 (0.77–1.05)	< 0.09	0.63 (0.53–0.76)	< 0.001
Zip income Quartile 2 vs. 4	0.94 (0.80–1.09)	0.77	0.71 (0.59–0.86)	0.03
Zip income Quartile 3 vs. 4	0.95 (0.80–1.13)	0.87	0.82 (0.68–0.997)	0.28

OR: Odds ratio; CI: Confidence interval; AI/AN: American Indian / Alaska Native

Subgroup of hospitalizations with decompensated cirrhosis: In a matched cohort of 4,649 hospitalizations with decompensated cirrhosis, hospitalizations in AI/AN individuals compared to all other races were more likely to be due to ALD including AH (Table 3). There was no difference on proportion of hospitalizations on cirrhosis-related complications (**Supplementary Fig. 1**). In an adjusted logistic regression model, hospitalization with AI/AN compared to white race was 30% [1.30 (1.04–1.63)] and 38% [1.38 (1.10–1.74)] more likely to be due to ALD and AH respectively. Admission in AI/AN compared to other race was also associated with increased odds of ALD or AH as discharge diagnosis.

Other predictors of ALD or AH etiology were young age, male gender, and Medicaid or private insurance (**Supplementary Table 4**).

Table 3
Baseline characteristics of hospitalizations in the US with decompensated cirrhosis.

	White (N = 1006)	Black (N = 819)	Hispanic (N = 1066)	Asian or other (N = 890)	AI/NA (N = 1165)	P
Age in years (mean, SD)	51, 12	52, 14	51, 13	52, 14	52, 12	0.55
% Females	41	46	44	40	45	0.7
% Elective admissions	5.6	7.2	5.4	5.1	6.8	0.72
% Pay source (MC, MD, Pvt.)	25, 53, 22	29, 48, 23	27, 54, 19	28, 50, 22	29, 51, 20	0.77
% Hospital type (R, U non-teaching, U teaching)	12, 16, 72	15, 17, 68	14, 17, 69	6, 20, 74	13, 16, 71	0.32
% Zip code income quartile (Q1-4)	53, 24, 17, 6	57, 23, 14, 6	53, 28, 14, 5	52, 26, 16, 6	56, 23, 15, 6	0.91
% Alcohol-associated cirrhosis	65	59	62	56	71	< 0.02
% Alcohol-associated hepatitis	23	16	18	17	28	0.002
% Alcohol-associated liver disease	70	63	65	60	76	< 0.03

SD: Standard deviation; MC: Medicare; MD: Medicaid; R: Rural; U: Urban

Subgroup of hospitalizations with ACLF at or during admission: In a matched cohort of 350 hospitalizations with ACLF, hospitalizations in AI/AN individuals compared to all other races were more likely to be due to ALD (**Supplementary Table 5**). In an adjusted logistic regression model, there was no difference based on race for a discharge diagnosis of ALD or AH, except for about five- and four-folds higher risk of ALD as discharge diagnosis among admissions in AI/AN compared to Hispanics and Asian or other race respectively. Predictors of ALD or AH etiology were young age, male gender, and Medicaid or private insurance (**Supplementary Table 6**).

In-hospital Mortality in Hospitalizations due to Cirrhosis

A total of 838 of 14,241 (5.9%) hospitalizations were associated with in-hospital mortality, 7% in blacks followed by 6.4% in Asian or other, 6% in AI/AN, and 5.1% in Hispanics and White, P = 0.34. In a logistic regression model controlling for demographics (age, gender, and race), payer source, zip code income quartile, and hospital type, admission in an AI/AN individual was less likely to be associated with in-hospital mortality compared to black race, 0.66 (0.51–0.84). Comparison with other race/s was not

significant (Table 4). Diagnosis of AH and of decompensated cirrhosis were associated with higher odds of in-hospital mortality, and a diagnosis of ALD without AH were associated with a lower odds of in-hospital mortality (Table 4). Other predictors were age and private or other mode of insurance. Race was not associated with in-hospital mortality in subgroup analyses of 7,354 hospitalizations with discharge diagnosis of ALD or 3,128 hospitalizations with discharge diagnosis of AH (*data not shown*).

Table 4
Logistic regression analyses on the matched cohort of hospitalizations with cirrhosis for predictors of in-hospital mortality.*

	OR (95% CI)	P
Age in years	1.02 (1.01–1.03)	< 0.001
Females vs. Males	0.84 (0.73–0.98)	< 0.03
AI/AN vs. White	1.02 (0.79–1.32)	0.35
AI/AN vs. Black	0.66 (0.51–0.84)	0.26
AI/AN vs. Hispanic	1.15 (0.91–1.47)	0.26
AI/AN vs. Asian or other	0.84 (0.66–1.07)	0.26
Medicaid vs. Medicare insurance	1.16 (0.95–1.41)	0.16
Pvt. or other vs. Medicare insurance	1.57 (1.27–1.93)	< 0.001
Rural vs. urban teaching hospital	0.78 (0.62–0.98)	0.32
Urban non-teaching vs. urban teaching hospital	0.77 (0.63–0.95)	0.22
Zip income Quartile 1 vs. 4	1.16 (0.84–1.60)	0.15
Zip income Quartile 2 vs. 4	1.21 (0.87–1.69)	< 0.06
Zip income Quartile 3 vs. 4	0.9 (0.63–1.29)	< 0.06
Alcohol-associated hepatitis	1.41 (1.14–1.74)	< 0.002
Alcohol-associated liver disease	0.67 (0.55–0.79)	< 0.001
Decompensated cirrhosis	3.2 (2.8–3.7)	< 0.001
OR: Odds ratio; CI: Confidence interval; AI/AN: American Indian / Alaska Native		
**Analysis for ALD etiology did not show any differences on race with OR (95% CI) for AI/AAN vs. black race 0.79 (0.56–1.14). Other predictors being patient's age, private or other insurance, decompensated ALD, and presence of AH.*		

Discussion

The main finding of our study is that ALD including AH is the most common etiology in AI/AN individuals compared to other races and ethnicities among cirrhosis-related admissions in the US. A total of 6% admissions result in in-hospital mortality, which is increased in blacks compared to AI/AN, and is similar to admissions in non-black races or ethnicities.

Several previous studies have shown that AI/AN individuals have high prevalence of cirrhosis compared to other races. [7, 8] For example, mortality from any cause between 1999 and 2009 in AI/AN located in contract health services delivery area counties was 46% greater than among non-Hispanic whites. Further, ALD was the leading cause of cirrhosis related mortality for AI/AN as well as non-Hispanic whites.[15] Moreover, healthcare burden from ALD is increasing among individuals aged 25–44 years, a population at the prime of productivity and contribution to the national growth. [2, 5, 7, 8, 16] Our study on hospitalized patients with cirrhosis including subgroups of decompensated cirrhosis or those with ACLF showed a novel finding that admissions in AI/AN individuals were more likely to have diagnosis of ALD including AH.

Higher prevalence of AUD in AI/AN as observed in this and earlier studies may likely explain this finding. AUD is known to be associated with geographic location, socioeconomic status, and education of the individual.[17] Higher prevalence in this study was observed in AI/AN individuals after controlling for these potential confounders. Patients with ALD compared to other liver diseases are known to often present at an advances stage of cirrhosis and/or complications.[18] Several factors including gender, alcohol use patterns (binge use, drinking outside meals, type of alcohol, and severity of AUD), socioeconomic status, having insurance, receipt of treatment for risk factor of AUD, and specialty care for liver disease determine receipt of treatment of any liver disease including ALD.[19, 20] Further, genetic polymorphisms of alcohol metabolizing enzymes may predispose an individual to AUD, and polymorphisms of *PNPLA3, TMSF62, and MBOAT7* genes have been shown to predispose an individual with AUD to development of and severity of ALD.[21] Although, we were able to account for socioeconomic and insurance status, lack of availability of data on other clinical variables in the NIS database and blood samples for genetic analyses limited assessment on association of other variables with predisposition of AUD and ALD in AI/AN individuals.

About 6% of admissions with discharge diagnosis of cirrhosis were associated with in-hospital mortality. These data are similar to in-hospital mortality observed in other studies using the NIS database on admissions with cirrhosis. The in-hospital mortality was higher in blacks compared to AI/AN, but similar to other races. In another study using the death certificate data (1999–2016) from the Center for Disease Control, the overall mortality was projected to increase by 10.1% between 2017 and 2030 for AI/AN and for white men, contributing to 239,700 excess deaths.[22] In the same study, mortality from chronic liver disease/cirrhosis was projected to increase for all races, except black men, similar to what we observed in the current study.[22] Other factors such as genetic polymorphisms, obesity and other comorbidities are known to modify disease progression in ALD.

Large sample size using the national US database on a homogeneous population of admissions with cirrhosis is a potential strength of our study. Further, using a cohort of AI/AN individuals matched for other races and analysis controlled for some of the potential confounders like geographic location, socioeconomic status, and insurance payer is another strength. However, a cautious approach is suggested on the interpretation of our observations as the authors recognize few limitations of this study. For example, potential coding error in adjudicating the discharge diagnosis as the study population was identified using the ICD codes. Further, admissions were not linkable to patient identifier, which limited evaluation of readmissions. Unavailability of laboratory values during the hospitalization and post-discharge follow up data, and lack of data from Veteran hospitals are some other limitations of this study.

In summary, this study on hospitalized patients with cirrhosis in the US shows that ALD and/or AH is the most common cirrhosis etiology in AI/AN individuals compared to other races. The in-hospital mortality among cirrhosis related hospitalizations is increased in blacks compared to AI/AN, while this is similar to non-black race. Large multicenter studies are needed to examine other factors such as alcohol use patterns, receipt and type of provider care for AUD and for liver disease, genetic polymorphisms to further study mechanisms of our findings. Further, these studies would also provide useful data to derive public health policies like prevention or treatment of AUD, early detection of silent advanced fibrosis, and increased access to healthcare, and reduce ALD related healthcare burden,[20] especially in AI/AN.

Declarations

Data Availability: The study used a publicly available database with de-identified data, and hence did not require any IRB approval.

Animal Research (Ethics): Not applicable.

Consent to participate: Waiver given a database study.

Consent to publish (Ethics): Health Care Utilization Project provided the database for analysis and publication of study results.

Plant Reproducibility: Not applicable

Clinical Trials Registration: Not applicable.

Availability of data and material: The National Inpatient Sample database is a publicly available database.

Authors' contributions: AKS and YFK conceived the study idea, designed the study, performed statistical analyses and interpreted the data. AKS wrote the manuscript and all the authors contributed to the intellectual component of the manuscript. All the authors reviewed the final version and approved for submission.

Conflicts of interest/Competing interests: None of the authors have financial or any other conflicts of interest to disclose.

Funding: The study is not funded by any grant or received any financial support.

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Figures

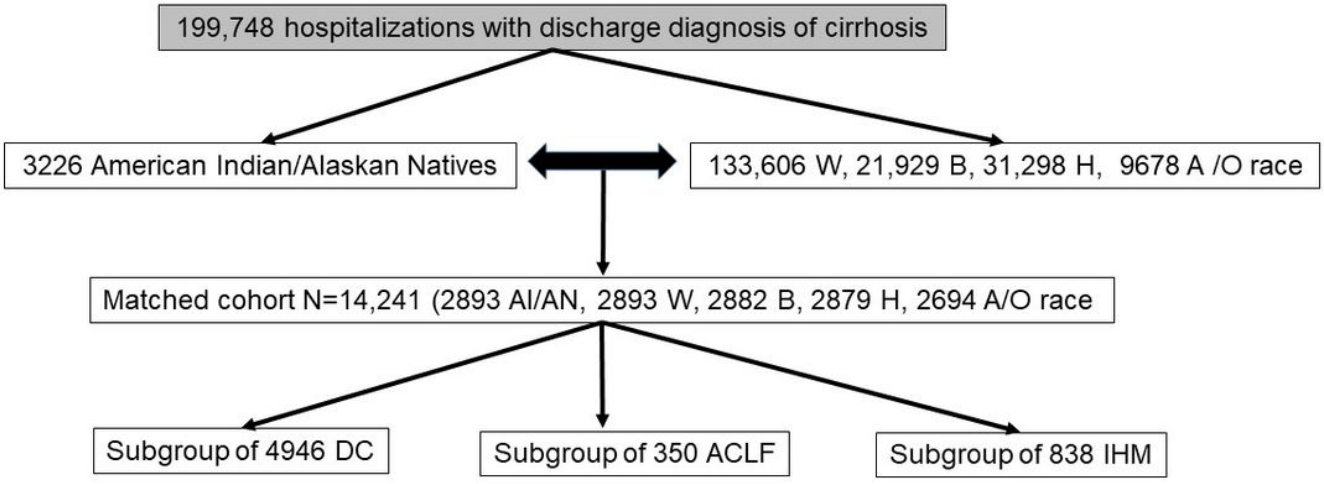

Figure 1

Flow diagram of study population cohort matched for American Indian / Alaska Native with other races or ethnicities.

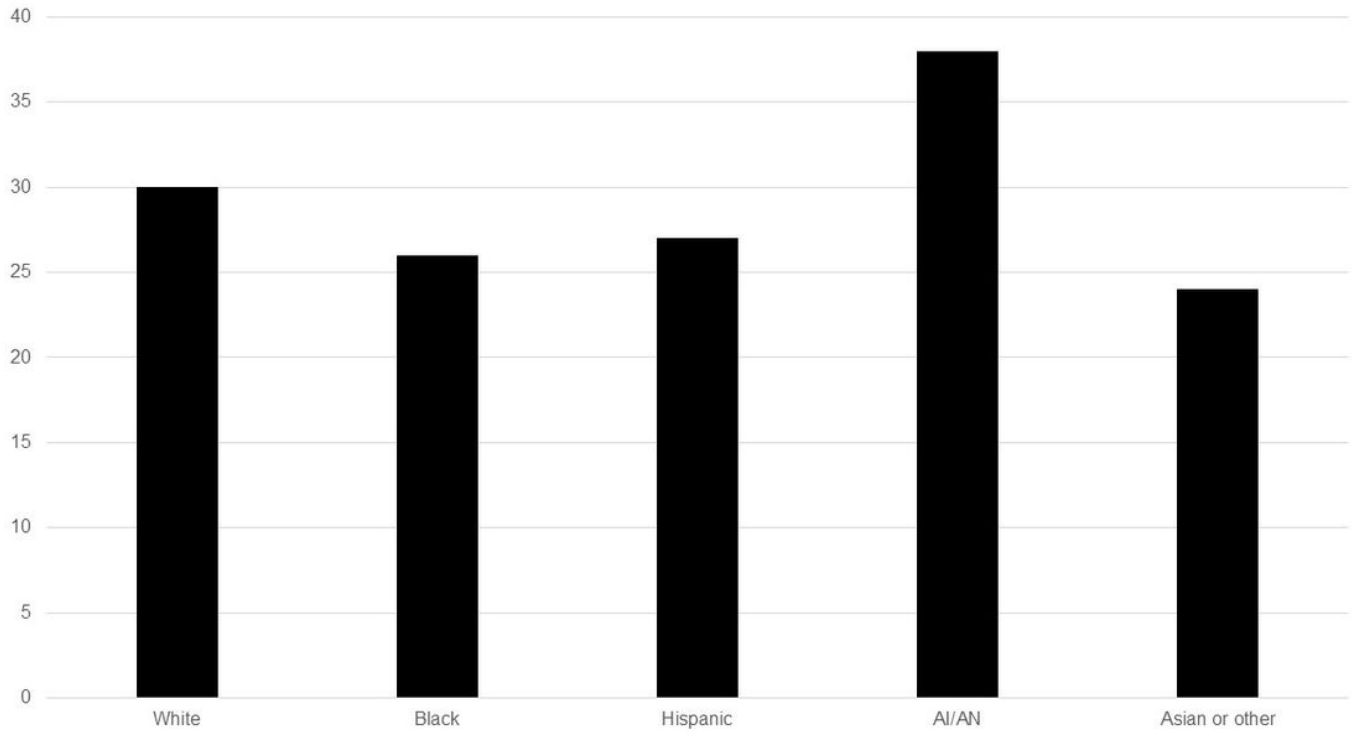

Figure 2

Proportion of admissions in different races associated with alcohol use disorder.

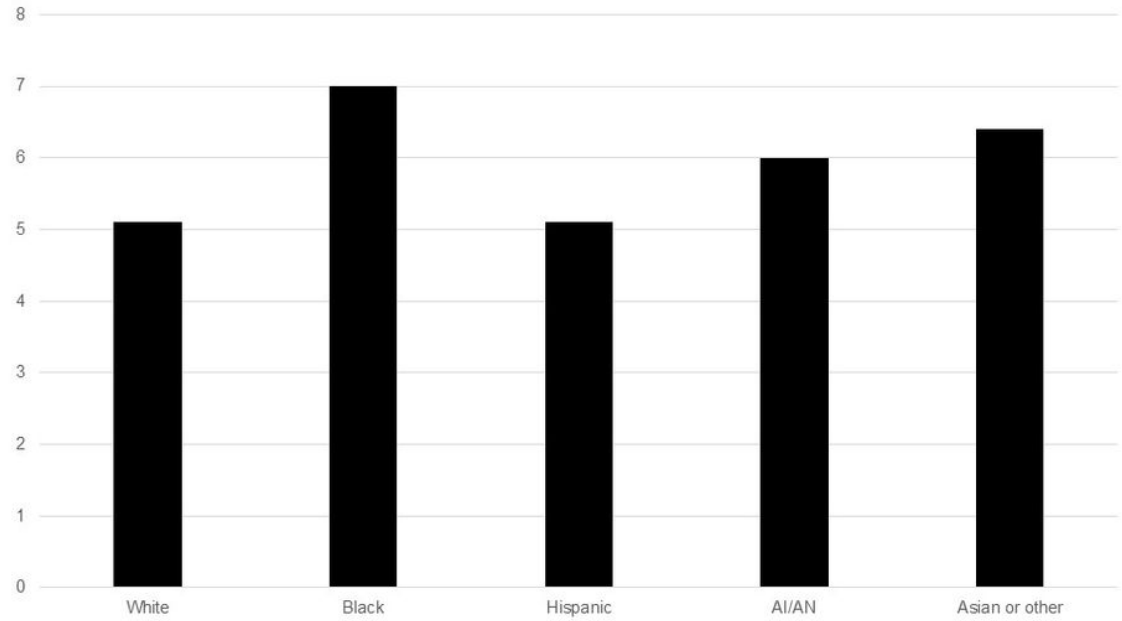

Figure 3

Proportion of admissions in different races associated with in-hospital mortality.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementdocument.docx