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HEPATOBILIARY

Genetic Ancestry, Race, and Severity of Acutely Decompensated Cirrhosis in Latin America

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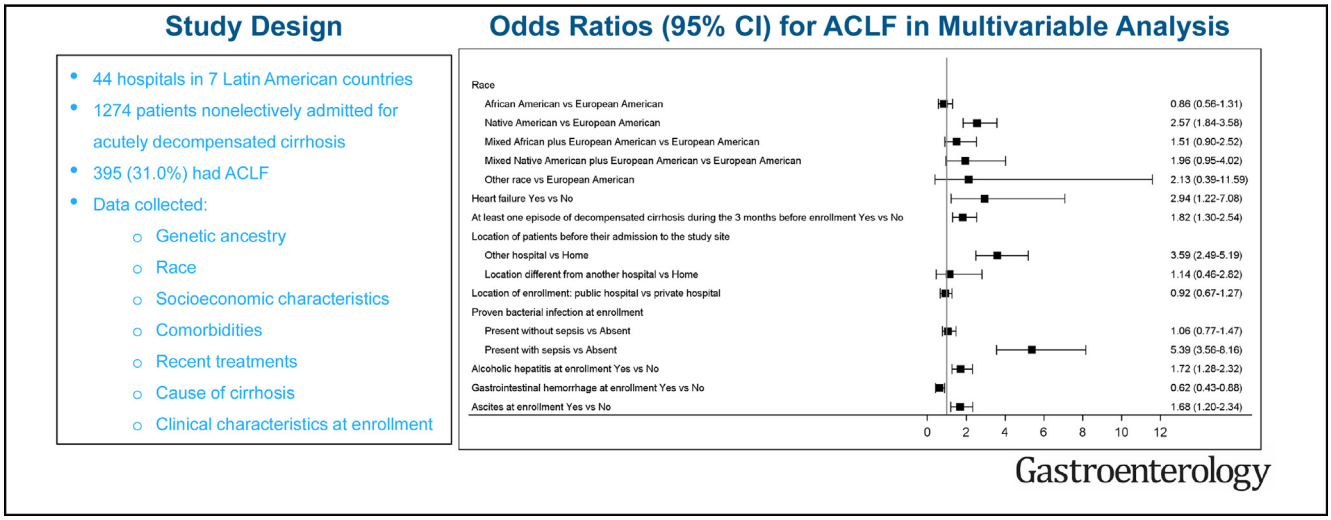

BACKGROUND & AIMS: Genetic ancestry or racial differences in health outcomes exist in diseases associated with systemic inflammation (eg, COVID-19). This study aimed to investigate the association of genetic ancestry and race with acute-on-chronic liver failure (ACLF), which is characterized by acute systemic inflammation, multi-organ failure, and high risk of short-term death. **METHODS:** This prospective cohort study analyzed a comprehensive set of data, including genetic ancestry and race among several others, in 1274 patients with acutely decompensated cirrhosis who were nonelectively admitted to 44 hospitals from 7 Latin American countries. **RESULTS:** Three hundred ninety-five patients (31.0%) had ACLF of any grade at enrollment. Patients with ACLF had a higher median percentage of Native American genetic ancestry and lower median percentage of European ancestry than patients without ACLF (22.6% vs 12.9% and 53.4% vs 59.6%, respectively). The median percentage of African genetic ancestry was low among patients with ACLF and among those without ACLF. In terms of race, a higher percentage of patients with ACLF than patients without ACLF were Native American and a lower percentage of patients with ACLF than patients without ACLF were European American or African American. In multivariable analyses that adjusted for differences in sociodemographic and clinical characteristics, the odds ratio for ACLF at enrollment was 1.08 (95% CI, 1.03–1.13) with Native American genetic ancestry and 2.57 (95% CI, 1.84–3.58) for Native American race vs European American race **CONCLUSIONS:** In a large cohort of Latin American patients with acutely decompensated cirrhosis, increasing percentages of Native American ancestry and Native American race were factors independently associated with ACLF at enrollment.

Keywords: Systemic Inflammation; Ethnicity; Sociodemographic Data; Liver Transplantation; Outcomes.

Acutely decompensated cirrhosis, which is a universally accepted condition, refers to the recent development of ascites, encephalopathy, gastrointestinal hemorrhage, or any combination of these disorders in patients with cirrhosis.[1–3] Acutely decompensated cirrhosis has been found to be the most frequent cause of nonelective hospital admission among patients with cirrhosis.[4] A large, prospective, observational, agnostic European study (CANONIC [European Association for the Study of the Liver-Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure in Cirrhosis] study) identified acute-on-chronic liver failure (ACLF) as a distinct syndrome among patients with acutely decompensated cirrhosis.[1] ACLF was identified as the most severe form of acutely decompensated cirrhosis, characterized by intense acute systemic inflammation, presence of hepatic failure, extrahepatic organ failures, or a combination (Supplementary Table 1), and a high risk of short-term death, that is, death without liver transplantation within 28 days after hospital admission.[1,3,5–7] Among European patients nonelectively admitted for acutely decompensated cirrhosis, 30% either presented with ACLF or presented without ACLF but developed ACLF during the days or weeks after admission,[1,5] whereas the remaining 70% were free of ACLF at presentation and remained free of ACLF within 28 days and had a very low short-term mortality.[1,5] These "ACLF-free" patients also had less-intense systemic inflammation than seen among those with ACLF.[1,5] The prevalence of ongoing clinically apparent proinflammatory precipitants (mainly bacterial sepsis, alcoholic hepatitis, or both) was higher among patients with ACLF than among those without.[1,5,6]

In the United States, racial minority groups are disproportionately affected by acute infectious inflammatory

Abbreviations used in this paper: **ACLARA, Prevalence, Epidemiology, Characterization and Mechanisms of Acute-on-Chronic Liver Failure in Latin America; ACLF, acute-on-chronic liver failure; FiO_2, fraction of inspired oxygen; HR, hazard ratio; PAMP, pathogen-associated molecular pattern; SpO_2, pulse oximetry saturation.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

A significant proportion of patients nonelectively admitted for acutely decompensated cirrhosis present with acute-on-chronic liver failure (ACLF). Inflammatory complications, such as bacterial sepsis or alcoholic hepatitis, are known to precipitate ACLF. Presentation with ACLF is known to be associated with high risk of short-term death; the risk increases with higher grade of ACLF.

NEW FINDINGS

Multivariable logistic regression identified increasing percentages of Native American ancestry and Native American race as factors associated with ACLF, independent of other covariates, in particular, proven bacterial infection with sepsis or alcoholic hepatitis. Adjusted time-to-event multivariable analyses identified factors that were independently associated with higher short-term mortality. Among these there was a social factor (ie, admission to public hospitals vs private hospitals) and markers of perturbed function of 5 organ systems.

LIMITATIONS

In this study, models were built following data-driven approaches, which may limit the external validity of the interpretations offered in this article. This study enrolled patients living in urban areas, and two-thirds of patients were from medium or high socioeconomic levels, limiting external generalizability to patients living in rural area or to those from low socioeconomic levels in Latin America. A limitation may be confounding by unmeasured or unrecognized social determinants of health and access to health care.

CLINICAL RESEARCH RELEVANCE

Improvement of the function of each of the 6 major organ systems should be an objective for future therapies that aim to prevent the progression to ACLF. This study sheds light on Native American genetic ancestry (and race), which are underrepresented in the ACLF medical literature and should therefore be emphasized in future interventional studies that aim to prevent or treat ACLF.

BASIC RESEARCH RELEVANCE

Future research should investigate the molecular mechanisms by which elevated percentages of Native American genetic ancestry may drive multi-organ failure independent of clinically apparent inflammatory precipitants.

diseases, such as sepsis and COVID-19. The prevalence and severity of bacterial sepsis are higher among the African American population than the European American population.[8] Moreover, a study examining population differences in the immune response to pathogens found that African ancestry is associated with a stronger inflammatory response to pathogens than European ancestry.[9] The rate of hospitalization for COVID-19 is higher among non-Hispanic Black patients, Hispanic or Latino patients, and non-Hispanic American Indian or Alaska Native patients than among non-Hispanic White patients.[10,11] In the United Kingdom, Black and South Asian people are at higher risk of COVID-19–related death than White people.[12] In contrast, whether there are genetic-ancestry– or race-related differences in health outcomes (eg, ACLF or short-term death) has yet to be investigated in depth among patients with acutely decompensated cirrhosis.

We recently completed the Prevalence, Epidemiology, Characterization and Mechanisms of ACLF in Latin America (ACLARA) study, which is the first large, prospective, observational investigation of patients nonelectively hospitalized for acutely decompensated cirrhosis in Latin America. The ACLARA study was conducted in Latin America because different races, including European American, African American, Native American, and mixed, are living on this continent. The ACLARA study was unique because it collected a comprehensive set of data. Indeed, not only was patient race reported, but DNA was collected to assess the individual distribution of each of the 3 major genetic ancestries (ie, European, African, and Native American). In addition, the ACLARA study collected sociodemographic characteristics, comorbidities, information on treatments administered before enrollment, and history of cirrhosis; clinical and laboratory data at enrollment; and outcomes within 28 days (including liver transplantation and death among nontransplanted patients). Therefore, the data obtained in the ACLARA study enabled us to construct multivariable models with the objective to assess whether differences in genetic ancestry or race are associated with ACLF at enrollment and short-term death among patients nonelectively admitted to the hospital for acutely decompensated cirrhosis.

Methods

Study Design and Oversight

The ACLARA study was an investigator-initiated, multicenter, prospective, observational investigation conducted at 44 university hospitals from 27 large Latin American cities in 7 countries (Figure 1, Supplementary Material). The European Foundation for the Study of Chronic Liver Failure (EF CLIF) sponsored the study; the protocol was approved by the Institutional Review Board at each center. Written informed consent was obtained from patients or their legal surrogates before enrollment. A coordinating investigator was responsible for enrolling patients at each center, ensuring adherence to the protocol, and completing the electronic case-report form. Data were monitored online by a central office in São Paulo in close connection with the Data Management Center of the EF CLIF in Barcelona. The study protocol and electronic case-report form are available in the Supplementary Material.

Patients

Patients nonelectively hospitalized for acutely decompensated cirrhosis (defined as ascites, encephalopathy, gastrointestinal hemorrhage, or any combination of these disorders) were eligible. Inclusion and exclusion criteria are detailed in the Supplementary Methods. Recommendations on treatment for complications of decompensated cirrhosis were provided in the study protocol.

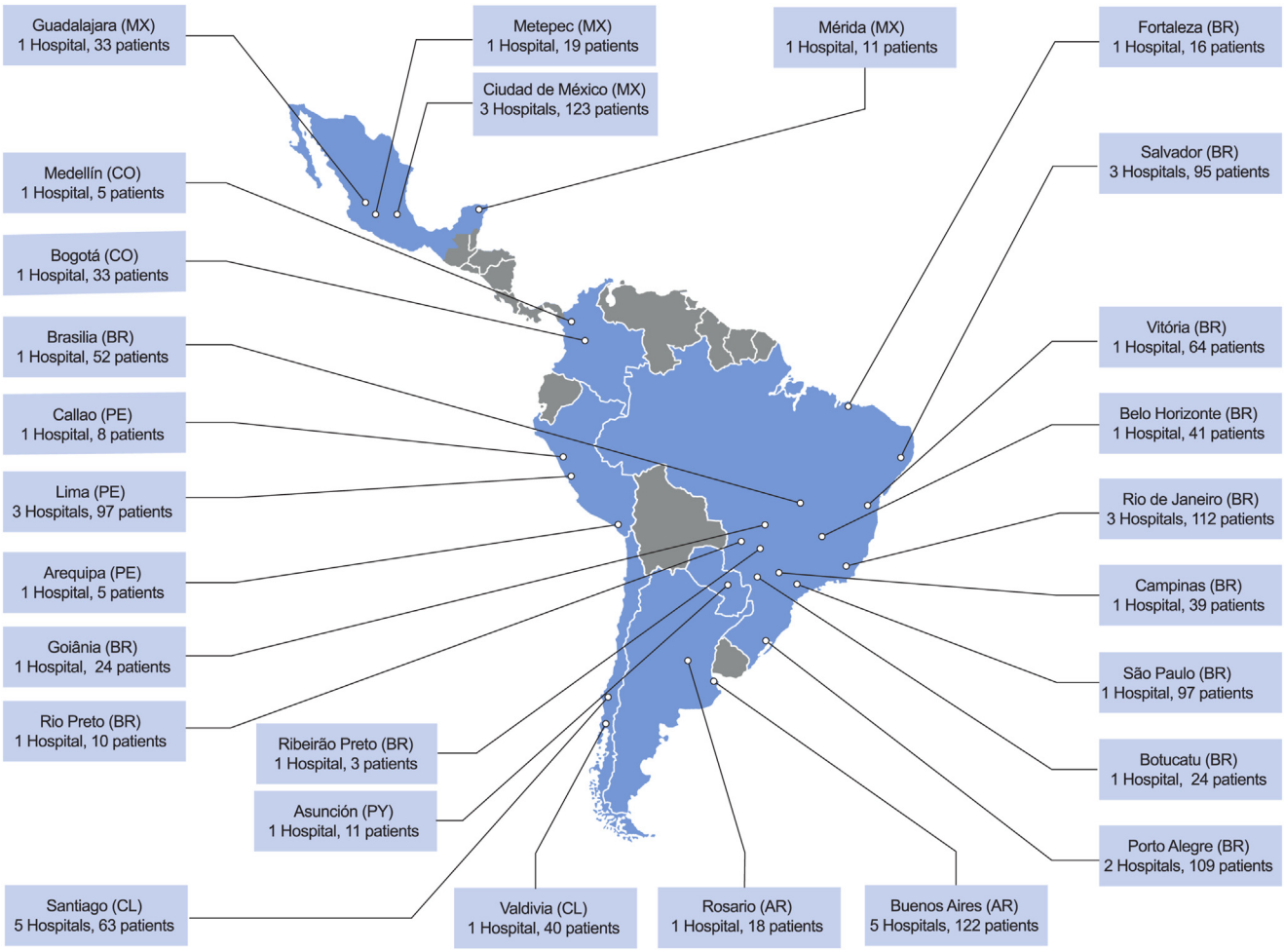

Figure 1. Map showing the Latin American countries involved in the study, the location of recruiting hospitals, and the number of enrolled patients per hospital. Each cell includes the name of the city, the number of recruiting hospitals in the city, and the total number of patients enrolled in the city. AR, Argentina; BR, Brazil; CL, Chile; PY, Paraguay; PE, Peru; CO, Colombia; MX, Mexico.

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Prespecified Study Variables

Clinical variables obtained at enrollment included demographic characteristics, tobacco consumption, comorbidities (including chronic obstructive pulmonary disease, heart failure, arterial hypertension, coronary artery disease, chronic kidney disease not requiring renal-replacement therapy, cerebrovascular disease and other neurologic diseases, diabetes, and other chronic systemic disease), cause of cirrhosis, recent treatments (ie, received during the 2 weeks before admission and including immunosuppressive drugs, beta-blockers, proton-pump inhibitors, prophylactic antibiotics, and antidiabetics), body mass index, patient's location just before admission to the participating hospital, location of admission, presence of ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, alcoholic hepatitis, standard laboratory data (including markers of systemic inflammation, white blood cell count, and plasma levels of C-reactive protein),[1] severity scores (Model of End-Stage Liver Disease–sodium score[13] and Chronic Liver Failure Consortium Organ Failure score[7]), presence of ACLF and its grade according to European criteria (Supplementary Table 1).[1] Race was assessed by the attending physician and the study coordinator during the initial physical examination process. This manner of reporting race was used instead of self-reporting because of the high frequency of hepatic encephalopathy in this patient population. Five different races were considered in the case-report form, including European American, African American, and Native American. Two races or more could be selected for a given participant. Data on area of residence, socioeconomic level, educational level, and familial and social contexts were obtained by interviewing patients or close relatives. Data obtained during follow-up included newly developed sepsis or ACLF during hospitalization and liver transplantation and death within 28 days after enrollment. Peripheral blood mononuclear cells were obtained to assess genetic ancestry.

Clinical definitions used during the study and a detailed description of assignment of genetic ancestry are provided in the Supplementary Material. Of note, we assessed genetic ancestry with the use of autosomal markers of ancestry and not by parental indicators of ancestry.

Statistical Analysis

Table 1 summarizes the baseline characteristics and outcomes of patients with ACLF at enrollment and those without.

Table 1. Characteristics of the Patients According to the Presence or Absence of Acute-on-Chronic Liver Failure at Enrollment and of Patients Who Died and Those Who Survived by 28 Days

Characteristic	ACLF at enrollment		Died by 28 d	
	No (n = 879)	Yes (n = 395)	No (n = 1031)	Yes (n = 243)
Age, *y*, median (IQR)	58.0 (52.0–66.0)	57.0 (48.0–64.0)	57.0 (51.0–65.0)	60.0 (53.0–68.0)
Female sex, n (%)	321 (36.5)	147 (37.2)	374 (36.3)	94 (38.7)
Genetic ancestry, % of genetic makeup				
European, median (IQR)	59.6 (40.6–79.9)	53.4 (33.2–73.2)	58.1 (38.9–79.2)	54.0 (30.0–76.5)
African, median (IQR)	6.5 (1.8–23.3)	6.9 (2.4–22.0)	7.6 (2.0–23.8)	4.9 (1.4–18.1)
Native American, median (IQR)	12.9 (5.2–45.5)	22.6 (7.4–55.2)	13.8 (5.4–45.9)	22.7 (8.1–63.9)
Missing, n (%)	182 (20.7)	78 (19.7)	200 (22.8)	60 (15.2)
Race, n (%)[a]				
European American	492 (56.0)	178 (45.1)	554 (53.7)	116 (47.7)
African American	127 (14.4)	46 (11.6)	147 (14.3)	26 (10.7)
Native American	165 (18.8)	126 (31.9)	208 (20.2)	83 (34.2)
Mixed (European American and African American)	64 (7.3)	29 (7.3)	84 (8.1)	9 (3.7)
Mixed (European American and Native American)	26 (3.0)	14 (3.5)	32 (3.1)	8 (3.3)
Other, n (%)	5 (0.6)	2 (0.5)	6 (0.6)	1 (0.4)
Residence in urban area, n (%)	812 (92.4)	362 (91.6)	949 (92.0)	225 (92.6)
Educational level, n (%)[b]				
None	46 (5.2)	11 (2.8)	50 (4.8)	7 (2.9)
Primary school or equivalent	396 (45.1)	179 (45.3)	465 (45.1)	110 (45.3)
High school or equivalent	288 (32.8)	135 (34.2)	338 (32.8)	85 (35.0)
University or higher	149 (17.0)	70 (17.7)	178 (17.3)	41 (16.9)
Socioeconomic level, n (%)[b]				
Low	281 (32.0)	157 (39.7)	352 (34.1)	86 (35.4)
Medium	549 (62.5)	218 (55.2)	624 (60.5)	143 (58.8)
High	49 (5.6)	20 (5.1)	55 (5.3)	14 (5.8)
Family or social support, n (%)[b]				
Insufficient/absent	22 (2.5)	10 (2.5)	24 (2.3)	8 (3.3)
Limited	194 (22.1)	86 (21.8)	224 (21.7)	56 (23.0)
Adequate	663 (75.4)	299 (75.7)	783 (75.9)	179 (73.7)
Smoking, n (%)				
Never	610 (69.4)	291 (73.7)	722 (70.0)	179 (73.7)
Former	189 (21.5)	70 (17.7)	210 (20.4)	49 (20.2)
Current	80 (9.1)	34 (8.6)	99 (9.6)	15 (6.2)
Comorbidity, n (%)				
Diabetes mellitus	332 (37.8)	111 (28.1)	370 (35.9)	73 (30.0)
Arterial hypertension	270 (30.7)	117 (29.6)	312 (30.3)	75 (30.9)
Chronic kidney disease not requiring hemodialysis	26 (3.0)	33 (8.4)	51 (4.9)	8 (3.3)
Coronary artery disease	27 (3.1)	16 (4.1)	33 (3.2)	10 (4.1)
Cerebrovascular disease or other neurologic disease	21 (2.4)	9 (2.3)	24 (2.3)	6 (2.5)
Chronic obstructive pulmonary disease	19 (2.2)	8 (2.0)	19 (1.8)	8 (3.3)
Heart failure	13 (1.5)	13 (3.3)	17 (1.6)	9 (3.7)
Other chronic systemic disease	128 (14.6)	58 (14.7)	151 (14.6)	35 (14.4)
Cause of cirrhosis, n (%)				
Alcohol	379 (43.1)	177 (44.8)	445 (43.2)	111 (45.7)
Hepatitis C	123 (14.0)	47 (11.9)	135 (13.1)	35 (14.4)
Nonalcoholic fatty liver disease	260 (29.6)	88 (22.3)	294 (28.5)	54 (22.2)
Autoimmune liver disease	88 (10.0)	63 (15.9)	122 (11.8)	29 (11.9)
Cryptogenic	85 (9.7)	37 (9.4)	95 (9.2)	27 (11.1)
Other	61 (6.9)	30 (7.6)	80 (7.8)	11 (4.5)

Table 1. Continued

Characteristic	ACLF at enrollment		Died by 28 d	
	No (n = 879)	Yes (n = 395)	No (n = 1031)	Yes (n = 243)
Treatments received during the 2 wk before hospital admission, n (%)				
Diuretics	366 (41.6)	169 (42.8)	430 (41.7)	105 (43.2)
Nonselective beta-blockers	344 (39.1)	143 (36.2)	410 (39.8)	77 (31.7)
Proton-pump inhibitors	163 (18.5)	60 (15.2)	184 (17.8)	39 (16.0)
Biguanide (metformin or other)	137 (15.6)	32 (8.1)	137 (15.6)	32 (8.1)
Insulin	104 (11.8)	34 (8.6)	116 (11.3)	22 (9.1)
Antibiotic prophylaxis	73 (8.3)	32 (8.1)	87 (8.4)	18 (7.4)
Any immunosuppressive drug[c]	25 (2.4)	10 (4.1)	66 (6.4)	15 (6.2)
Glucagon-like peptide 1 analogue	23 (2.6)	12 (3.0)	25 (2.4)	10 (4.1)
Any episode of decompensated cirrhosis during the last 3 mo before enrollment, n (%)	595 (68.9)	316 (80.4)	729 (71.7)	182 (75.8)
Missing, n (%)	15 (1.7)	2 (0.5)	3 (0.8)	—
No. of patients (%) according to their location before admission to the participating center				
Home	784 (89.2)	295 (74.7)	887 (86.0)	192 (79.0)
Another hospital	76 (8.6)	92 (23.3)	123 (11.9)	45 (18.5)
Location different from home or another hospital	19 (2.2)	8 (2.0)	21 (2.0)	6 (2.5)
Category of the participating center				
Public hospital	666 (75.8)	297 (75.2)	766 (74.3)	197 (81.1)
Private hospital	213 (24.2)	98 (24.8)	265 (25.7)	46 (19.9)
Time between hospital admission and enrollment, d, median (IQR)	1.5 (0.8-2.5)	1.2 (0.7-2.3)	1.5 (0.8-2.5)	1.1 (0.7-2.1)
Location of enrollment, n (%)				
Emergency department	300 (34.1)	126 (31.9)	348 (33.8)	78 (32.1)
Intensive care unit	90 (10.2)	104 (26.3)	134 (13.0)	60 (24.7)
Regular ward	489 (55.6)	165 (41.8)	549 (53.2)	105 (43.2)
Clinical data at enrollment[b]				
Body mass index, *kg/m²*, median (IQR)	26.5 (23.3–29.8)	26.6 (23.4–30.2)	26.6 (23.5–30.2)	26.3 (22.7–29.4)
Missing, n (%)	180 (20.5)	61 (15.4)	196 (22.3)	45 (11.4)
Proven bacterial infection, n (%)				
Absent	628 (71.4)	207 (52.4)	712 (69.1)	123 (50.6)
Without sepsis	42 (4.8)	102 (25.8)	58 (5.6)	86 (35.4)
With sepsis	209 (23.8)	86 (21.8)	261 (25.3)	34 (14.0)
Alcoholic hepatitis	188 (21.4)	121 (30.6)	219 (21.2)	90 (37.0)
Gastrointestinal hemorrhage, n (%)	265 (30.1)	67 (17.0)	284 (27.5)	48 (19.8)
Ascites, n (%)	581 (66.1)	319 (80.8)	709 (68.8)	191 (78.6)
Hepatic encephalopathy, n (%)	338 (38.5)	241 (61.0)	428 (41.5)	151 (62.1)
Mean arterial pressure, *mm Hg*, median (IQR)	83.0 (73.3–90.3)	76.7 (70.0-87.3)	82.0 (73.3-90.3)	75.5 (69.7-86.7)
Missing, n (%)	8 (0.9)	2 (0.5)	9 (1.0)	1 (0.3)
SpO_2/FiO_2, median (IQR)	462 (452–467)	457 (343-467)	462 (452-467)	448 (303-462)
Missing, n (%)	26 (3.0)	7 (1.8)	30 (3.4)	3 (0.8)
Laboratory values at enrollment				
Bilirubin, *mg/dL*, median (IQR)	2.0 (1.1–4.0)	5.6 (2.0-17.0)	2.1 (1.1–4.8)	5.5 (2.5–12.9)
Missing, n (%)	4 (0.5)	2 (0.5)	3 (0.3)	3 (0.8)
Creatinine, *mg/dL*, median (IQR)	0.9 (0.7–1.2)	2.2 (1.4–2.9)	1.0 (0.7–1.4)	1.7 (1.1–2.7)
International normalized ratio, median (IQR)	1.5 (1.3–1.8)	1.9 (1.5–2.7)	1.5 (1.3–1.8)	2.0 (1.5–2.6)
Missing, n (%)	1 (0.1)	1 (0.3)	2 (0.2)	0 (0.0)
White blood cell count, *10^9 cells/L*, median (IQR)	5.3 (3.7–7.7)	8.5 (5.3–13.5)	5.5 (3.8–8.2)	9.4 (5.9–14.1)
Missing, n (%)	22 (2.5)	8 (2.0)	22 (2.5)	8 (2.0)

Table 1. Continued

Characteristic	ACLF at enrollment		Died by 28 d	
	No (n = 879)	Yes (n = 395)	No (n = 1031)	Yes (n = 243)
Serum C-reactive protein, *mg/L*, median (IQR)	23.4 (10.7–47.6)	42.0 (21.5–76.7)	25.7 (11.6–49.6)	42.8 (22.4–77.6)
Missing, n (%)	80 (9.1)	22 (5.6)	92 (10.5)	10 (2.5)
Serum albumin, *g/dL*, median (IQR)	2.9 (2.5–3.3)	2.7 (2.3–3.1)	2.9 (2.5–3.3)	2.6 (2.3–3.0)
Missing, n (%)	22 (2.5)	9 (2.3)	22 (2.5)	9 (2.3)
Aspartate aminotransferase, *U/L*, median (IQR)	49 (34–83)	58 (36121)	49 (34-84)	68 (41–135)
Missing, n (%)	32 (3.6)	11 (2.8)	32 (3.6)	11 (2.8)
Serum sodium, *mEq/L*, median (IQR)	136 (133–139)	134 (129–138)	136 (132–139)	135 (129–138)
Missing, n (%)	2 (0.2)	5 (1.3)	6 (0.7)	1 (0.3)
Assessment of severity at enrollment				
MELD-sodium score, median (IQR)	18.0 (14.0–23.0)	30.0 (25.0–34.0)	20.0 (15.0–25.0)	29.0 (23.0–34.0)
Missing, n (%)	7 (0.8)	7 (1.8)	10 (1.1)	4 (1.0)
ACLF of any grade, n (%)	—	395 (100.0)	231 (22.4)	164 (67.5)
Grade of ACLF, n (%)				
ACLF-1	—	213 (54.2)	159 (69.1)	54 (33.1)
ACLF-2	—	98 (24.9)	48 (20.9)	50 (30.7)
ACLF-3	—	82 (20.9)	23 (10.0)	59 (36.2)
Missing	—	2 (0.5)	1 (0.4)	1 (0.6)
Clinical outcomes within 28 d after enrollment, n (%)				
Received a liver transplant	24 (2.7)	42 (10.6)	66 (6.4)	0 (0.0)
Died without transplantation	79 (9.0)	164 (41.5)	0 (0.0)	243 (100.0)

IQR, interquartile range; MELD, Model for End-Stage Liver Disease.
[a]Race was reported by the attending physician and the study coordinator.
[b]See the Supplementary Material.
[c]Immunosuppressive drugs included corticosteroids, azathioprine, mycophenolate mofetil, and anti–tumor necrosis factor therapies.

In addition, Table 1 summarizes baseline characteristics of patients who died by 28 days and those who survived. Factors that are associated with ACLF at enrollment were examined with the use of multivariable logistic regression. Factors that are associated with short-term death (defined as death without transplantation within 28 days after enrollment) were examined within Fine and Gray's competing risks framework, with liver transplantation as the competing event, and models were fitted using Cox proportional hazards regression. ACLF is known to increase the risk of rapid organ failure and short-time death; an intervention such as liver transplantation can reduce the risk of short-term death, thus liver transplantation and short-term death can be considered as competing events in statistical analyses.

All model covariates were selected on the basis of the results of univariable analyses, considering an association as significant if the 95% CI did not overlap with a value of 1 (see below). Although our Latin American population was admixed (Figure 2), the European American race significantly correlated with the percentage of European ancestry, and the Native American race significantly correlated with the percentage of Native American genetic ancestry (Supplementary Table 2). In addition, genetic ancestry was missing for 260 patients (20%). These findings indicated that race and genetic ancestry cannot be used in the same multivariable model; consequently, each clinical characteristic indicating severity (ACLF at enrollment and short-term death) was assessed with 2 models. Model 1 included genetic ancestry with additional covariates and model 2 included race with additional covariates. Because the 3 genetic ancestries were strongly colinear, one of these ancestries had to be removed from the multivariable models to avoid redundancy. European genetic ancestry was excluded from model 1 because of its strong correlation with the Native American ancestry (Pearson correlation coefficient, −0.80; $P < .001$).

The statistical analysis plan did not include a provision for correcting for multiplicity when tests were conducted to evaluate associations, and results are reported as point estimates with 95% CIs. Results from the analysis of ACLF are presented in Table 2 as odds ratios. Results from the analyses of short-term death are presented in Table 3 as subdistribution hazard ratios (HRs).

Before the construction of the multivariable models for ACLF, variables were assessed through univariable logistic regression. Results of univariable analyses are shown in Supplementary Table 3; of note, these analyses showed that diabetes was among the variables associated with ACLF. Of the variables that were associated with ACLF in univariable analyses, all except nonalcoholic fatty liver disease, recent treatment with biguanides, and chronic kidney disease were included in the initial multivariable models (Table 2). Nonalcoholic fatty liver disease and recent treatment with biguanides were not included in the multivariable models because these variables were correlated with diabetes (Pearson correlation

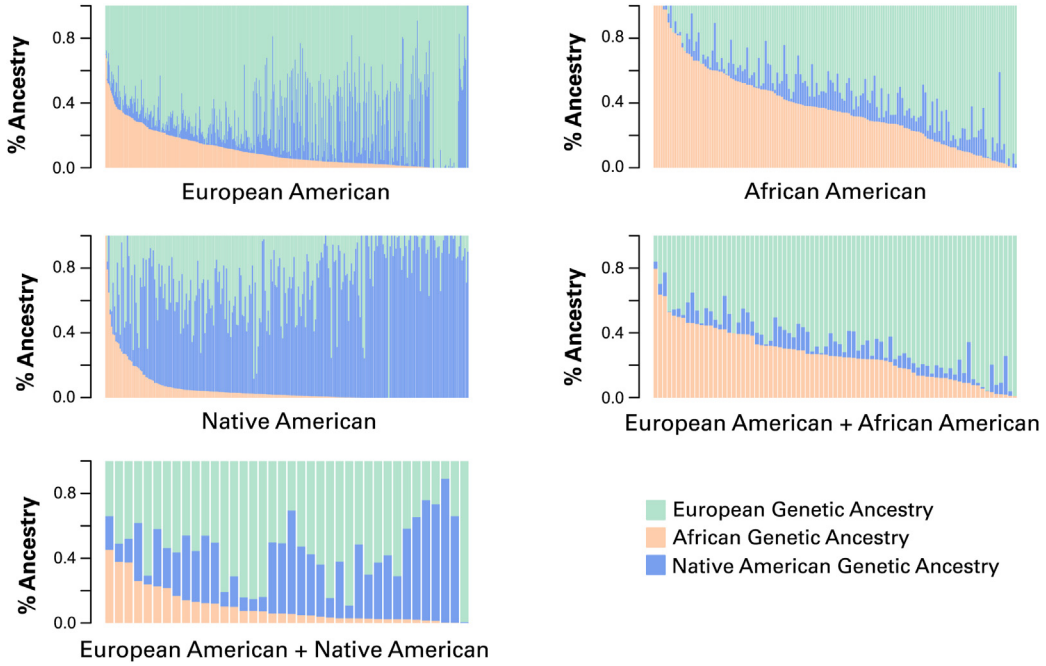

Figure 2. Percentages of each genetic ancestry according to reported races. Genetic data were available from 487 (72.7%) of 670 European American patients, 157 (90. 8%) of 173 African American patients, 253 (86.9%) of 291 Native American patients, 79 (84. 9%) of 93 European American and African American mixed-race patients, and 38 (95.0%) of 40 European American and African American mixed-race patients. The analysis of the structure of each racial group was based on genotyping data of 529,687 single-nucleotide polymorphisms. Each individual is represented by a *vertical line*. Cluster membership proportions are depicted in *blue* (inferred percentage of Native American ancestry), *green* (inferred percentage of European ancestry), and *orange* (inferred proportion of African ancestry).

coefficient, 0.48; $P < .001$ and 0.53; $P < .001$, respectively). Chronic kidney disease was not included in the models because elevated serum creatinine is an important criterion for defining the presence of ACLF (Supplementary Table 1). In addition, the variable "location of enrollment, public hospital vs private hospital," which was not significant in the univariable analysis was nevertheless included in the multivariable models because of its socioeconomic relevance (see Table 3). Because genetic ancestry was associated with ACLF in univariable analyses and because genetic ancestry was missing for 20% of patients, values were imputed with the use of multiple imputation with chained equations,[14] and then multiple imputed data sets were used in multivariable models. Thereafter, estimates and SEs were calculated in each of the 25 imputations that have been carried out and pooled into 1 overall estimate and SE. From the set of variables included initially in each model, only variables that were related to ACLF after backwards elimination procedures remained in the 2 final models, the variables with the largest nonsignificant P value were removed iteratively. Because each model has been adjusted independently from the other, the set of covariates included in the final models may differ.

The models for short-term death considered time to death, from the date of enrollment (day 0) to day 28. Before the construction of the multivariable models for short-term death, variables were assessed through time-to-event analyses using univariable Cox regression with liver transplantation as the competing event. Results of univariable analyses are shown in Supplementary Table 3. Of the variables that were associated with short-term death in univariable analyses, all, except serum bilirubin, were included in the initial multivariable models (Table 3). Bilirubin was not included in the models because of its correlation with international normalized ratio (Pearson correlation coefficient, 0.40; $P < .001$). Among variables associated with short-term death in univariable analyses, mean arterial pressure was missing for 10 patients, pulse oximetry saturation to fraction of inspired oxygen (SpO_2/FiO_2) ratio for 33 patients, albumin for 31 patients, international normalized ratio for 2 patients, aspartate aminotransferase for 43 patients, sodium for 7 patients, white blood cell count for 30 patients, and C-reactive protein for 102 patients. Multiple imputation was used to estimate missing values for all of these variables together with genetic ancestry before their inclusion in the initial multivariable models. From the set of variables included initially in each model, only those that were related to short-term death after backwards elimination procedures remained in the 2 final models (ie, model 1 and model 2). The proportional hazards assumption was explored (by testing for a zero slope in the scaled Schoenfeld residuals) and confirmed.

Sensitivity analyses of factors associated with ACLF and factors associated with short-term death were also performed using complete records only; results are shown in Supplementary Tables 4 and 5, respectively. The cumulative incidence of death was estimated within the first 28 days after enrollment according to categories of genetic ancestries (see below) and race, with liver transplantation as the competing risk. The resulting cumulative incidence curves were compared between groups by means of Gray's test.

Table 2. Odds Ratios (95% CI) for Acute-on-Chronic Liver Failure at Enrollment

Variable	Univariable analysis, OR (95% CI)	Multivariable analysis, OR (95% CI)	
		Model 1 (genetic ancestry)	Model 2 (race)
Percentage of genetic ancestry, in 10% units			
European	0.93 (0.89–0.98)	—	—
African	0.99 (0.92–1.06)	—	—
Native American	1.06 (1.02–1.11)	1.08 (1.03–1.13)	—
Race			
European American	1 (ref)	—	1 (ref)
African American	1.00 (0.69–1.46)	—	0.86 (0.56–1.31)
Native American	2.11 (1.58–2.82)	—	2.57 (1.84–3.58)
Mixed African and European American	1.25 (0.78–2.01)	—	1.51 (0.90–2.52)
Mixed Native American and European American	1.49 (0.76–2.91)	—	1.96 (0.95–4.02)
Other	1.11 (0.21–5.75)	—	2.13 (0.39–11.59)
Socioeconomic level			
Low	1 (ref)	—	—
Medium	0.71 (0.55–0.91)	—	—
High	0.73 (0.42–1.27)	—	—
Comorbidity			
Diabetes	0.64 (0.50–0.83)	—	—
Heart failure	2.27 (1.04–4.94)	2.61 (1.09–6.26)	2.94 (1.22–7.08)
Cause of cirrhosis			
Autoimmune liver disease, yes vs no	1.71 (1.20–2.42)	—	—
At least 1 episode of decompensated cirrhosis during the 3 mo before enrollment, yes vs no	1.86 (1.39–2.47)	1.77 (1.27–2.46)	1.82 (1.30–2.54)
Location of patients before their admission to the study site			
Home	1 (ref)	1 (ref)	1 (ref)
Other hospital	3.22 (2.31–4.48)	3.15 (2.20–4.51)	3.59 (2.49–5.19)
Location different from home or another hospital	1.12 (0.49–2.58)	0.98 (0.40–2.42)	1.14 (0.46–2.82)
Location of enrollment, public hospital vs private hospital	0.97 (0.74–1.28)	0.95 (0.70–1.29)	0.92 (0.67–1.27)
Proven bacterial infection at enrollment			
Absent	1 (ref)	1 (ref)	1 (ref)
Present without sepsis	1.25 (0.93–1.68)	1.08 (0.78–1.48)	1.06 (0.77–1.47)
Present with sepsis	7.37 (4.98–10.91)	5.74 (3.80–8.65)	5.39 (3.56–8.16)
Alcoholic hepatitis at enrollment, yes vs no	1.62 (1.24–2.12)	1.65 (1.22–2.21)	1.72 (1.28–2.32)
Gastrointestinal hemorrhage at enrollment, yes vs no	0.47 (0.35–0.64)	0.67 (0.47–0.95)	0.62 (0.43–0.88)
Ascites at enrollment, yes vs no	2.15 (1.62–2.87)	1.71 (1.23–2.39)	1.68 (1.20–2.34)

NOTE. The covariate of "location of enrollment, public hospital vs private hospital" that was not significant in univariable analysis was nevertheless included in the multivariable models because of its socioeconomic relevance (see Table 3). Multiple imputation was used to estimate missing values for genetic ancestry (260 patients) and the covariate of at least 1 episode of decompensated cirrhosis during the 3 months before enrollment (17 patients).
OR, odds ratio.

Supplementary Figure 1 includes a flow chart summarizing all statistical methods. All analyses were conducted using SAS, version 9.4 for Windows (SAS Institute).

Results

Patients

Overall cohort. Of the 1398 patients who were screened from November 21, 2018 to September 8, 2020, 124 were excluded and 1274 were enrolled (Supplementary Figure 2). Characteristics of the enrolled patients are shown in Supplementary Table 6. Of the 1274 enrolled patients, 50% were younger than 58 years and 468 (36.7%) were female. Among the 1014 patients (79.6%) with data available on genetic ancestry, the median percentage of genetic ancestries were 57.3% for European ancestry, 14.6% for Native American ancestry, and 6.5% for African ancestry. Race was reported in each of the 1274 enrolled patients; of

Table 3. Subdistribution Hazard Ratios for Short-Term Death Within 28 Days After Enrollment in the Study

Variable	Univariable analysis, subdistribution HR (95% CI)	Multivariable analysis, subdistribution HR (95% CI)	
		Model 1 (genetic ancestry)	Model 2 (race)
Age, in 10-y units	1.01 (1.00–1.03)	1.34 (1.19–1.51)	1.35 (1.20–1.52)
Percentage of genetic ancestry, in 10% units			
European	0.94 (0.89–0.99)	—	—
African	0.92 (0.84–1.01)	—	—
Native American	1.08 (1.03–1.13)	—	—
Race			
European American	1 (ref)	—	—
African American	0.84 (0.56–1.28)	—	—
Native American	1.80 (1.36–2.38)	—	—
Mixed African and European American	0.55 (0.28–1.10)	—	—
Mixed Native American and European American	1.24 (0.58–2.64)	—	—
Other	0.86 (0.11–7.09)	—	—
Comorbidity			
Heart failure, yes vs no	2.03 (1.06–3.91)	—	—
Cause of cirrhosis			
Nonalcoholic fatty liver disease, yes vs no	0.73 (0.54–0.99)	—	—
Recent treatment with a nonselective beta-blocker, yes vs no	0.72 (0.55–0.94)	—	—
Recent treatment with a biguanide, yes vs no	0.55 (0.35–0.87)	—	—
Location of patients before their admission to the study site			
Home	1 (ref)	—	—
Other hospital	1.58 (1.15–2.18)	—	—
Location different from home or another hospital	1.22 (0.56–2.65)	—	—
Location of enrollment, public hospital vs private hospital	1.42 (1.03–1.96)	1.71 (1.20–2.44)	1.70 (1.19–2.43)
Infection at enrollment			
No proven infection	1 (ref)	1 (ref)	1 (ref)
Proven infection without sepsis	0.75 (0.52–1.09)	0.68 (0.47–0.98)	0.68 (0.47–0.98)
Proven infection with sepsis	5.90 (4.46–7.81)	2.52 (1.79–3.55)	2.50 (1.77–3.52)
Alcoholic hepatitis at enrollment, yes vs no	2.00 (1.55–2.59)	1.55 (1.16–2.07)	1.54 (1.15–2.06)
Gastrointestinal hemorrhage at enrollment, yes vs no	0.70 (0.51–0.97)	—	—
Ascites at enrollment, yes vs no	1.55 (1.14–2.11)	—	—
Hepatic encephalopathy at enrollment, yes vs no	2.18 (1.68–2.82)	—	—
Mean arterial pressure at enrollment, in 1-mm Hg unit	0.96 (0.95–0.98)	0.98 (0.97–1.00)	0.99 (0.97–1.00)
SpO_2/FiO_2 ratio at enrollment, in 1 units	0.99 (0.99–0.99)	0.96 (0.95–0.98)	0.96 (0.95–0.98)
Serum creatinine at enrollment, in 1-mg/dL units	1.39 (1.24–1.54)	1.20 (1.11–1.30)	1.20 (1.11–1.30)
International normalized ratio at enrollment, in 1 units	1.59 (1.42–1.78)	1.40 (1.23–1.60)	1.41 (1.24–1.60)
Serum albumin at enrollment, in 1-g/dL units	0.48 (0.37–0.6)	0.68 (0.54–0.87)	0.68 (0.53–0.86)
Aspartate aminotransferase at enrollment, in 1-U/L units	1.00 (1.00–1.00)	—	—
White blood cell count at enrollment, in 10^9-cells/L units	1.09 (1.08–1.11)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
C-reactive protein at enrollment, in 10-mg/L units	1.01 (1.01–1.01)	—	—
Serum sodium at enrollment, in 1-mEq/L units	0.97 (0.95–1)	—	—

NOTE. Multiple imputation was used to estimate missing values for genetic ancestry (260 patients); mean arterial pressure (10 patients); SpO_2/FiO_2 ratio (33 patients); and blood levels of international normalized ratio (2 patients), albumin (31 patients), aspartate aminotransferase (43 patients), C-reactive protein (102 patients), sodium (7 patients), and white blood cell count (30 patients).

these, 670 (52.6%) were European American, 291 (22.8%) were Native American, 173 (13.6%) were African American, 93 (7.3%) were mixed European American and African American, and 40 (3.1%) were mixed European American and Native American. Overall, 1174 patients (92.2%) lived in an urban area and 836 patients (65.6%) were from medium or high socioeconomic levels. The most common comorbidity was diabetes mellitus, followed by arterial hypertension; the prevalence of the other comorbidities was low (<5%). The most common causes of cirrhosis were excessive alcohol consumption, followed by nonalcoholic fatty liver disease and hepatitis C. The most common treatment used before admission was diuretics, followed by nonselective beta-blockers, proton-pump inhibitors, and biguanides. Of the 1274 patients, 1079 (84.7 %) were at home before admission and 168 (13.2%) were referred from another hospital; median time between admission and enrollment was 1.38 days. Among the 1274 patients, 395 (31.0%) had ACLF at enrollment (of these, 213 [54.2%] had ACLF-1, 98 [24.9%] had ACLF-2, and 82 [20.9%] had ACLF-3); 66 patients (5.2%) underwent early liver transplantation (ie, transplantation within 28 days after enrollment) and 243 (19.1%) died without early liver transplantation.

Acute-on-chronic liver failure at enrollment. Table 1 summarizes the characteristics at enrollment of the 395 patients who had ACLF and the 879 who did not. Compared with patients without ACLF, those with ACLF were considerably younger, had a higher median percentage of Native American genetic ancestry, and had lower median percentage of European genetic ancestry. The median percentage of African genetic ancestry did not differ between the 2 groups. A higher percentage of patients with ACLF than patients without ACLF were Native American. In contrast, a lower percentage of patients with ACLF than patients without ACLF were European American or African American. A higher percentage of patients with ACLF than patients without ACLF were from a low socioeconomic level; had preexisting heart failure; had cirrhosis caused by autoimmune liver disease or nonalcoholic fatty liver disease; had at least 1 recent episode of decompensation during the 3 months before admission; were referred from another hospital or admitted to the intensive care unit; and presented with inflammatory precipitants, such as proven bacterial infection with sepsis or alcoholic hepatitis. A lower percentage of patients with ACLF than patients without ACLF had recently received (ie, during the 2 weeks before admission) a biguanide (including metformin or another biguanide), were at home before admission, or presented with gastrointestinal hemorrhage. Table 1 also shows the short-term outcomes in the 2 groups. A higher percentage of patients with ACLF at enrollment than patients without ACLF underwent an early liver transplantation or died without liver transplantation within 28 days after enrollment.

Short-term deaths. Table 1 summarizes the characteristics at enrollment of the 243 patients who died within 28 days after enrollment and the 1031 who survived. Compared with patients who survived, those who died were older, had a higher median percentage of Native American genetic ancestry, and had a lower median percentage of European genetic ancestry. The median percentage of African genetic ancestry did not differ between the 2 groups. A higher percentage of patients who died than patients who survived were Native American. A lower percentage of patients who died than patients who survived were European American or African American, had cirrhosis caused by nonalcoholic fatty liver disease, and had recently received a biguanide. A higher percentage of patients who died than patients who survived were referred from another hospital; had been admitted to a public hospital or had been admitted to the intensive care unit; and had presented with bacterial infection and sepsis, alcoholic hepatitis, ascites, hepatic encephalopathy, ACLF-2, or ACLF-3. A lower percentage of patients who died than patients who survived had presented with gastrointestinal hemorrhage. When compared with patients who survived, those who died had presented with lower mean arterial pressure; lower SpO_2/FiO_2 ratio; lower levels of serum albumin or serum sodium; higher Model for End-Stage Liver Disease–sodium scores; higher levels of serum bilirubin, international normalized ratio, serum creatinine, aspartate aminotransferase or C-reactive protein; or higher white blood cell counts.

Factors Associated With Acute-on-Chronic Liver Failure at Enrollment

Table 2 shows the unadjusted and adjusted odds of ACLF at enrollment. In the adjusted analysis using genetic ancestry (model 1), a 10% increase in the percentage of Native American ancestry was associated with an 8% increase in the odds of ACLF (odds ratio, 1.08; 95% CI, 1.03–1.13). In contrast, the percentage of African ancestry was not associated with changes in odds of ACLF. In the adjusted analysis using race (model 2), Native American race was associated with approximately 2.6 times the odds of ACLF as European American race (odds ratio, 2.57; 95% CI, 1.84–3.58). In contrast, the other races were not associated with increased odds of ACLF vs European American race.

In model 1 and model 2, variables that were associated with increased odds of ACLF were heart failure as comorbidity; any episode of decompensated cirrhosis during the 3 months before enrollment; referral from another hospital; enrollment with proven bacterial infection and sepsis (vs absence of proven bacterial infection), alcoholic hepatitis, or ascites. In model 1 and model 2, gastrointestinal hemorrhage at enrollment was associated with lower odds of ACLF. Running these analyses on a complete-case basis, we obtained results similar to those obtained after multiple imputations (sensitivity analyses; Supplementary Table 4).

Factors Associated With Short-Term Death

Table 3 shows the unadjusted and adjusted HRs for short-term death. In the adjusted analyses, neither genetic ancestry (model 1) nor race (model 2) was associated with the risk of short-term death.

In model 1 and model 2, variables that were associated with higher short-term mortality were increasing age,

admission to public hospital (vs private hospital), and enrollment with proven bacterial infection and sepsis or alcoholic hepatitis; lower arterial pressure or lower SpO_2/FiO_2 ratio; higher blood levels of creatinine, or international normalized ratio; lower blood levels of albumin; or higher white blood cell counts. Running these analyses on a complete-case basis, our results were similar to those obtained after multiple imputations (sensitivity analyses; Supplementary Table 5).

Unlike multivariable analyses described above, univariable analyses showed that increasing percentage of Native American ancestry and Native American race were associated with higher short-term mortality (Tables 3 and Supplementary Table 3). We hypothesized that Native American ancestry and race were not among the variables associated with short-term mortality in multivariable analyses because these included confounders, such as variables assessing organ system functions. To address this hypothesis, we performed post-hoc multivariable analyses of factors associated with short-term mortality without including organ function–related variables (ie, without both the categorical variable of hepatic encephalopathy and continuous variables, including mean arterial pressure, SpO_2/FiO_2 ratio, and blood levels of creatinine, international normalized ratio, and albumin) (Supplementary Table 7). In model 1 (genetic ancestry), increasing percentage of Native American ancestry was associated with higher short-term mortality (subdistribution HR, 1.06; 95% CI, 1.01–1.12). In model 2 (race), Native American race (vs European American race) was associated with short-term mortality (subdistribution HR, 1.67; 95% CI, 1.24–2.23). These findings, therefore, support the hypothesis that the association of genetic ancestry and race with short-term mortality may be hidden by the inclusion of variables assessing organ system functions in multivariable models.

Post-Hoc Analysis of Admission to Public Hospitals, Genetic Ancestries, and Races

Because admission to public hospital was the only social factor independently associated with higher short-term mortality, we compared the 963 patients (75.6%) admitted to 31 public hospitals with the 311 (24.4%) admitted to 13 private hospitals (Supplementary Table 8). Patients admitted to public hospitals were characterized by younger age, higher mean percentages of Native American and African genetic ancestries, lower percentages of European genetic ancestry, overrepresentation of Native Americans and African Americans, higher percentages of patients with low educational levels, and higher percentages of patients with low socioeconomic levels. The percentage of participating centers that performed early liver transplantation was similar in private and public hospitals (38.5% [n = 5 of 13] and 35.5% [n = 11 of 31], respectively). However, a lower percentage of patients admitted to public hospitals than patients admitted to private hospitals received early transplantation (3.6% and 10.0%, respectively). Moreover, the percentage of patients who were enrolled with ACLF-2 or ACLF-3 and then received early liver transplantation was lower at public hospital than at private hospital (9.1% and 25.0%, respectively). Finally, a higher percentage of patients admitted to public hospitals than patients admitted to private hospitals died without undergoing liver transplantation by 28 days (20.5% and 14.8%, respectively).

Supplementary Table 9 shows characteristics and outcomes according to the 3 genetic ancestries, the percentages of each genetic ancestry being divided into 3 categories of low genetic ancestry (<25%), intermediate genetic ancestry (25%–50%), and elevated genetic ancestry (>50%). We focused on the categories of elevated genetic ancestries that included 622 patients for European ancestry, 58 patients for African ancestry, and 247 patients for Native American genetic ancestry. A higher percentage of patients with elevated Native American genetic ancestry than patients with elevated European or African genetic ancestry had ACLF of any grade (38.9% and 27.2% or 36.2%, respectively). Moreover, a higher percentage of patients with elevated Native American genetic ancestry than patients with elevated European or African genetic ancestry had ACLF-2 or ACLF-3 (ie, severe ACLF; 23.9% and 10.6% or 17.2%, respectively). A higher percentage of patients with elevated Native American genetic ancestry than patients with elevated European or African genetic ancestry died by 28 days (25.1% and 15.6% or 19.0%, respectively). The cumulative incidence of death by 28 days was lower in patients with elevated European genetic ancestry than in those with intermediate or low European genetic ancestry (Figure 3*A*). The cumulative incidence of death by 28 days was lower in patients with intermediate African genetic ancestry than in those with elevated or low African genetic ancestry (Figure 3*B*). The cumulative incidence of death by 28 days was higher in patients with elevated percentages of Native American genetic ancestry than in those with low or intermediate Native American genetic ancestry (Figure 3*C*). Of note, multivariable models for ACLF and short-term death after categorizing the genetic ancestries have been included in Supplementary Tables 10 and 11, respectively, offering results similar to those presented in Tables 2 and 3, respectively.

Table 4 provides characteristics and outcomes across the different reported races. We focused on the 670 European American, 173 African American, and 291 Native American patients. A higher percentage of Native American than European American or African American patients had ACLF of any grade (43.3% and 26.6% or 26.6%, respectively). A higher percentage of Native American than European American or African American patients had severe ACLF (ACLF-2 or ACLF-3; 26.8% vs 10.3% or 8.1%). A higher percentage of Native American than European American or African American patients died by 28 days (28.5% and 17.3% or 15.0%, respectively). The cumulative incidence of death by 28 days differed across races (Figure 3*D*); the cumulative incidence of death was higher in Native American vs European American patients, whereas there were no differences in cumulative incidence of death

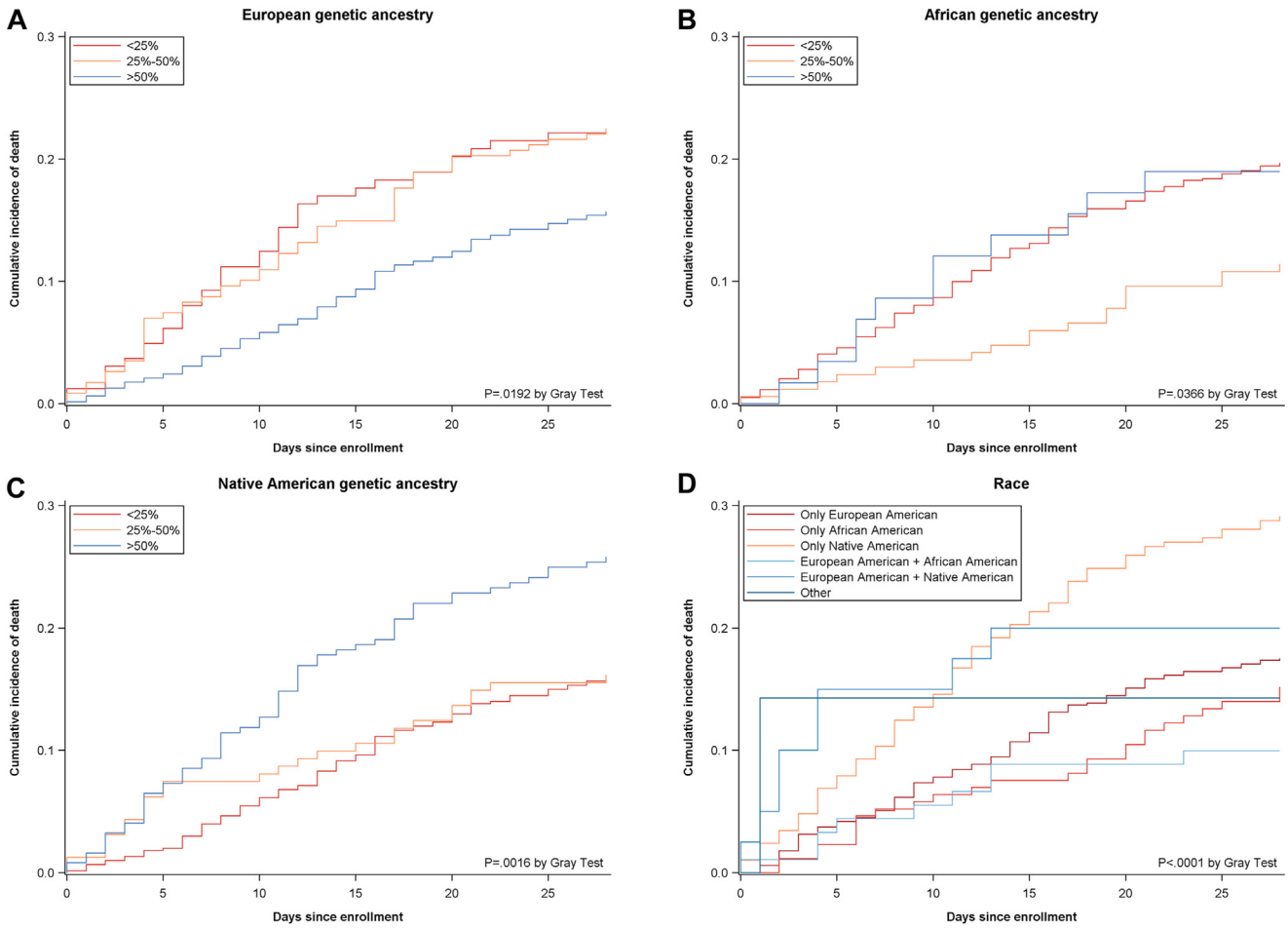

Figure 3. Cumulative incidence of death by 28 days according to genetic ancestries and across races. (*A*) Cumulative incidence of death according to percentages of European genetic ancestries divided into 3 categories (<25% [163 patients], 25% to 50% [229 patients], and >50% [622 patients]). (*B*) Cumulative incidence of death according to percentages of African genetic ancestries divided into 3 categories (<25% [787 patients], 25% to 50% [169 patients], and >50% [58 patients]). (*C*) Cumulative incidence of death according to percentages of Native American genetic ancestries divided into 3 categories (<25% [606 patients], 25% to 50% [161 patients], and >50% [247 patients]). (*D*) Cumulative incidence of death across reported races, including European American patients (n = 670), African American patients (n = 173), Native American patients (n = 291), mixed-race European American and African American patients (n = 93), mixed-race European American and Native American patients (n = 40), and others (7 patients). All *curves* depict the cumulative incidence of death during the 28 days after enrollment.

between African American vs European American patients (Supplementary Tables 2 and 3).

Discussion

To our knowledge, this study is the first in the field to show that in a continent with elevated racial admixture, differences in genetic ancestry and race are associated with disparities in presentation with ACLF, in particular severe ACLF (ACLF-2 and ACLF-3), and death by 28 days. Native American genetic ancestry or Native American race were represented more in specific groups of patients (ie, among patients with ACLF of any grade at enrollment, among those with severe ACLF [ACLF-2 and ACLF-3] at enrollment, and among those who died by 28 days) relative to their representation in the entire study population.

As far as we know, there are only 2 studies that considered race as well as prevalence and severity of ACLF, and death among patients with decompensated cirrhosis admitted to hospitals in United States.[15,16] Because both used the US Department of Veterans Affairs database, we will only comment on the study by Hernaez et al,[16] which included the highest number of patients (n = 72,316). The study by Hernaez et al, which was retrospective and did not assess genetic ancestry and major confounders, such as socioeconomic differences, assessed differences in races (European American vs African American) among patients with ACLF and among those without. The main finding of their study was that African American race was overrepresented relative to European American race among patients with ACLF of any grade, but underrepresented among patients with the most severe forms of the syndrome (ie, ACLF-2 and ACLF-3). Consistent with these findings, the

Table 4. Characteristics of Enrolled Patients According to Reported Races

Characteristic	European American (n = 670)	African American (n = 173)	Native American (n = 291)	Mixed (European American and African American) (n = 93)	Mixed (European American and Native American) (n = 40)	Other (n = 7)
Age, *y*, median (IQR)	59 (52–67)	55 (48–64)	57 (49–64)	59 (51–66)	58 (51–65)	64 (54–74)
Female sex, n (%)	229 (34.2)	62 (35.8)	124 (42.6)	32 (34.4)	16 (40.0)	5 (71.4)
Genetic ancestry, % of genetic makeup[a]						
European						
Mean ± SD	70.6 ± 20.6	51.2 ± 23.7	27.4 ± 21.7	65.0 ± 17.4	55.9 ± 20.1	—
Median (IQR)	73.5 (56.0–87.0)	51.8 (36.6–67.7)	25.3 (9.0–42.9)	65.3 (53.6–78.7)	53.2 (42.0–70.8)	—
African						
Mean ± SD	10.6 ± 11.6	37.6 ± 24.3	5.5 ± 11.9	26.9 ± 16.2	10.2 ± 11.3	—
Median (IQR)	6.0 (2.3–16.1)	35.2 (19.4–52.3)	1.5 (0.0–4.4)	25.6 (13.1–39.3)	5.7 (2.5–13.0)	—
Native American						
Mean ± SD	18.8 ± 20.8	11.2 ± 8.8	67.2 ± 25.5	8.1 ± 5.8	33.9 ± 21.5	—
Median (IQR)	10.1 (3.8–28.8)	8.8 (5.2–15.4)	70.0 (49.3–89.0)	7.1 (3.4–12.5)	34.9 (14.6–43.4)	—
Missing data, n (%)	183 (27.3)	16 (9.2)	38 (13.1)	14 (15.1)	2 (5.0)	7 (100.0)
Educational level, n (%)[b]						
None	20 (3.0)	19 (11.0)	13 (4.5)	3 (3.2)	2 (5.0)	0 (0.0)
Primary school or equivalent	318 (47.5)	126 (72.8)	71 (24.4)	43 (46.2)	13 (32.5)	4 (57.1)
High school or equivalent	218 (32.5)	24 (13.9)	126 (43.3)	36 (38.7)	18 (45.0)	1 (14.3)
University or higher	114 (17.0)	4 (2.3)	81 (27.8)	11 (11.8)	7 (17.5)	2 (28.6)
Socioeconomic level, n (%)[b]						
Low	189 (28.2)	109 (63.0)	102 (35.1)	25 (26.9)	11 (27.5)	2 (28.6)
Medium	435 (64.9)	62 (35.8)	171 (58.8)	67 (72.0)	27 (67.5)	5 (71.4)
High	46 (6.9)	2 (1.2)	18 (6.2)	1 (1.1)	2 (5.0)	0 (0.0)
Family or social support, n (%)[b]						
Insufficient/absent	13 (1.9)	10 (5.8)	7 (2.4)	1 (1.1)	1 (2.5)	0 (0.0)
Limited	141 (21.0)	56 (32.4)	57 (19.6)	13 (14.0)	12 (30.0)	1 (14.3)
Adequate	516 (77.0)	107 (61.8)	227 (78.0)	79 (84.9)	27 (67.5)	6 (85.7)
Smoking, n (%)						
Never	448 (66.9)	114 (65.9)	232 (79.7)	73 (78.5)	27 (67.5)	7 (100.0)
Former	150 (22.4)	45 (26.0)	45 (15.5)	12 (12.9)	7 (17.5)	0 (0.0)
Current	72 (10.7)	14 (8.1)	14 (4.8)	8 (8.6)	6 (15.0)	0 (0.0)
Comorbidity, n (%)						
Diabetes mellitus	255 (38.1)	60 (34.7)	82 (28.2)	35 (37.6)	9 (22.5)	2 (28.6)
Arterial hypertension	221 (33.0)	43 (24.9)	76 (26.1)	31 (33.3)	13 (32.5)	3 (42.9)
Chronic kidney disease not requiring hemodialysis	34 (5.1)	7 (4.0)	12 (4.1)	4 (4.3)	1 (2.5)	1 (14.3)
Coronary artery disease	33 (4.9)	6 (3.5)	3 (1.0)	1 (1.1)	0 (0.0)	0 (0.0)

Table 4. Continued

Characteristic	European American (n = 670)	African American (n = 173)	Native American (n = 291)	Mixed (European American and African American) (n = 93)	Mixed (European American and Native American) (n = 40)	Other (n = 7)
Cerebrovascular disease or other neurologic disease	23 (3.4)	2 (1.2)	2 (0.7)	2 (2.2)	1 (2.5)	0 (0.0)
Chronic obstructive pulmonary disease	22 (3.3)	3 (1.7)	1 (0.3)	1 (1.1)	0 (0.0)	0 (0.0)
Heart failure	19 (2.8)	4 (2.3)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other chronic systemic disease	94 (14.0)	24 (13.9)	51 (17.5)	12 (12.9)	2 (5.0)	3 (42.9)
Cause of cirrhosis, n (%)						
Alcoholic	311 (46.4)	82 (47.4)	99 (34.0)	42 (45.2)	20 (50.0)	2 (28.6)
Nonalcoholic fatty liver disease	181 (27.0)	35 (20.2)	100 (34.4)	23 (24.7)	7 (17.5)	2 (28.6)
Hepatitis C	102 (15.2)	28 (16.2)	24 (8.2)	11 (11.8)	3 (7.5)	2 (28.6)
Autoimmune liver disease	64 (9.6)	25 (14.5)	47 (16.2)	10 (10.8)	5 (12.5)	0 (0.0)
Cryptogenic	55 (8.2)	14 (8.1)	38 (13.1)	10 (10.8)	4 (10.0)	1 (14.3)
Other causes	48 (7.2)	14 (8.1)	12 (4.1)	13 (14.0)	3 (7.5)	1 (14.3)
Recent treatments, n (%)[c]						
Diuretics	255 (38.1)	93 (53.8)	136 (46.7)	34 (36.6)	16 (40.0)	1 (14.3)
Beta-blockers	247 (36.9)	80 (46.2)	96 (33.0)	44 (47.3)	18 (45.0)	2 (28.6)
Proton pump inhibitor	128 (19.1)	34 (19.7)	37 (12.7)	12 (12.9)	9 (22.5)	3 (42.9)
Metformin or other biguanide	95 (14.2)	22 (12.7)	32 (11.0)	17 (18.3)	2 (5.0)	1 (14.3)
Insulin	78 (11.6)	26 (15.0)	24 (8.2)	9 (9.7)	1 (2.5)	0 (0.0)
Antibiotic prophylaxis	57 (8.5)	16 (9.2)	17 (5.8)	9 (9.7)	6 (15.0)	0 (0.0)
Any immunosuppressive drug	27 (4.0)	19 (11.0)	26 (8.9)	7 (7.5)	2 (5.0)	0 (0.0)
Glucagon-like peptide 1 analogue	23 (3.4)	4 (2.3)	7 (2.4)	0 (0.0)	1 (2.5)	0 (0.0)
Any episode of decompensated cirrhosis during the last 3 mo before enrollment, n (%)	484 (73.4)	138 (80.2)	197 (67.9)	61 (67.8)	27 (67.5)	4 (66.7)
No. (%) of patients according to their location before admission to the participating center						
Home	560 (83.6)	132 (76.3)	260 (89.3)	83 (89.2)	37 (92.5)	7 (100.0)
Another hospital	96 (14.3)	31 (17.9)	29 (10.0)	10 (10.8)	2 (5.0)	0 (0.0)
Location different from home or another hospital	14 (2.1)	10 (5.8)	2 (0.7)	0 (0.0)	1 (2.5)	0 (0.0)
Enrollment in public hospital, n (%)	459 (68.5)	166 (96.0)	247 (84.9)	60 (64.5)	25 (62.5)	6 (85.7)
Time between hospital admission and enrollment, *d*, median (IQR)	1.38 (0.79–2.42)	1.58 (0.75 2.42)	1.17 (0.75–2.17)	1.54 (0.79–2.50)	1.73 (0.92–2.60)	0.88 (0.54–0.96)
Intensive care unit as location of enrollment, n (%)	97 (14.5)	10 (5.8)	49 (16.8)	37 (39.8)	0 (0.0)	1 (14.3)

Table 4. Continued

Characteristic	European American (n = 670)	African American (n = 173)	Native American (n = 291)	Mixed (European American and African American) (n = 93)	Mixed (European American and Native American) (n = 40)	Other (n = 7)
Clinical data at enrollment						
Body mass index, *kg/m²*, median (IQR)	26.7 (23.4–30.6)	25.8 (22.6–29.7)	26.6 (23.6–30.3)	25.2 (23.0–27.7)	27.0 (23.7–30.0)	30.3 (27.3–31.7)
Missing data, n (%)	154 (23.0)	38 (22.0)	23 (7.9)	20 (21.5)	5 (12.5)	1 (14.3)
Mean arterial pressure, *mm Hg*, median (IQR)	83 (73–91)	83 (77–91)	75 (70– 3)	83 (77–93)	80 (73–90)	82 (75–83)
Missing data, n (%)	5 (0.7)	0 (0.0)	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Ascites, n (%)	475 (70.9)	137 (79.2)	190 (65.3)	67 (72.0)	27 (67.5)	4 (57.1)
Hepatic encephalopathy, n (%)	303 (45.2)	73 (42.2)	156 (53.6)	29 (31.2)	16 (40.0)	2 (28.6)
Proven bacterial infection, n (%)						
Absent	445 (66.4)	110 (63.6)	188 (64.6)	59 (63.4)	27 (67.5)	6 (85.7)
Present without sepsis	164 (24.5)	47 (27.2)	50 (17.2)	24 (25.8)	9 (22.5)	1 (14.3)
Present with sepsis	61 (9.1)	16 (9.2)	53 (18.2)	10 (10.8)	4 (10.0)	0 (0.0)
Alcoholic hepatitis, n (%)	161 (24.0)	47 (27.2)	64 (22.0)	22 (23.7)	14 (35.0)	1 (14.3)
Gastrointestinal hemorrhage, n (%)	159 (23.7)	28 (16.2)	98 (33.7)	32 (34.4)	13 (32.5)	2 (28.6)
Laboratory values at enrollment						
Serum bilirubin, *mg/dL*, median (IQR)	2.1 (1.2–5.1)	2.1 (1.1–5.3)	3.4 (1.7–9.0)	2.7 (1.2–6.0)	3.3 (1.7–12.1)	1.6 (0.7–7.2)
Missing data, n (%)	5 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
International normalized ratio, median (IQR)	1.52 (1.33–1.83)	1.53 (1.34–1.84)	1.70 (1.37–2.20)	1.57 (1.36–2.11)	1.81 (1.48–2.49)	1.49 (1.26–1.64)
Missing data, n (%)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Serum albumin, *g/dL*, median (IQR)	2.82 (2.50–3.30)	2.78 (2.40–3.10)	2.64 (2.28–3.15)	2.90 (2.50–3.30)	2.62 (2.30–3.00)	3.10 (2.90–3.30)
Missing data, n (%)	16 (2.4)	5 (2.9)	4 (1.4)	4 (4.3)	2 (5.0)	0 (0.0)
Serum creatinine, *mg/dL*, median (IQR)	1.00 (0.75–1.56)	1.04 (0.80–1.67)	1.17 (0.73–1.92)	1.04 (0.75–1.51)	1.15 (0.79–1.76)	1.35 (1.00–1.80)
SpO_2/FiO_2 ratio, median (IQR)	457 (448–467)	462 (452–467)	452 (375–462)	462 (457–467)	457 (440–467)	457 (428–462)
Missing data, n (%)	22 (3.3)	1 (0.6)	7 (2.4)	3 (3.2)	0 (0.0)	0 (0.0)
White blood cell count, *10^9 cells/L*, median (IQR)	5.90 (4.03–9.00)	5.51 (3.35–8.25)	6.35 (4.20–10.40)	5.99 (4.33–8.50)	7.80 (4.81–12.50)	6.91 (5.75–7.57)
Missing data, n (%)	16 (2.4)	10 (5.8)	0 (0.0)	3 (3.2)	1 (2.5)	0 (0.0)
Serum C-reactive protein, *mg/L*, median (IQR)	25.1 (12.1–50.0)	28.5 (11.5–50.3)	33.5 (16.2–60.8)	38.3 (17.1–60.2)	29.2 (19.1–52.6)	47.1 (16.3–73.6)
Missing data, n (%)	72 (10.7)	4 (2.3)	18 (6.2)	5 (5.4)	3 (7.5)	0 (0.0)
Aspartate aminotransferase, *U/L*, median (IQR)	49 (34–85)	54 (36–86)	56 (36–99)	50 (38–89)	72 (48–140)	57 (24–86)
Missing data, n (%)	21 (3.1)	10 (5.8)	5 (1.7)	4 (4.3)	2 (5.0)	1 (14.3)
Serum sodium, *mEq/L*, median (IQR)	136 (132–139)	135 (131–138)	135 (130–138)	137 (133–140)	137 (133–138)	137 (133–137)
Missing, n (%)	2 (0.3)	2 (1.1)	1 (0.3)	1 (1.1)	1 (2.5)	0 (0.0)
Severity scores at enrollment[b]						
MELD-sodium score, median (IQR)	20.0 (15.0–26.0)	21.0 (16.0–26.0)	24.0 (18.0–31.0)	21.0 (16.0–26.0)	23.0 (17.0–28.0)	17.0 (15.0–31.0)
Missing, n (%)	7 (1.0)	3 (1.7)	2 (0.7)	1 (1.1)	1 (2.5)	0 (0.0)

Table 4. Continued

Characteristic	European American (n = 670)	African American (n = 173)	Native American (n = 291)	Mixed (European American and African American) (n = 93)	Mixed (European American and Native American) (n = 40)	Other (n = 7)
Chronic Liver Failure Consortium Organ failure score, median (IQR)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	8.0 (7.0–10.0)	7.0 (6.0–8.0)	7.5 (7.0–9.0)	7.0 (6.0–8.0)
Missing, n (%)	10 (1.5)	1 (0.6)	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
ACLF at enrollment[b]						
ACLF of any grade, n (%)	178 (26.6)	46 (26.6)	126 (43.3)	29 (31.2)	14 (35.0)	2 (28.6)
Grade of ACLF, n/N (%)						
ACLF-1	107/176 (60.8)	32/46 (69.6)	48/126 (38.1)	20/29 (69.0)	5/14 (35.7)	1/2 (50.0)
ACLF-2	40/176 (22.7)	9/46 (19.6)	40/126 (31.7)	5/29 (17.2)	4/14 (28.6)	0/2 (0.0)
ACLF-3	29/176 (16.5)	5/46 (10.9)	38/126 (30.2)	4/29 (13.8)	5/14 (35.7)	1/2 (50.0)
Missing, n (%)	2/178 (0.3)	0/42 (0.0)	0/126 (0.0)	0/29 (0.0)	0/14 (0.0)	0/2 (0.0)
Type of organ system failure, n (%)						
Liver failure	66 (9.9)	15 (8.7)	55 (18.9)	10 (10.8)	10 (25.0)	1 (14.3)
Missing	5 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney failure	115 (17.2)	31 (17.9)	70 (24.1)	15 (16.1)	7 (17.5)	1 (14.3)
Cerebral failure	45 (6.7)	9 (5.2)	47 (16.2)	4 (4.3)	5 (12.5)	1 (14.3)
Coagulation failure	57 (8.5)	10 (5.8)	50 (17.2)	14 (15.1)	9 (22.5)	1 (14.3)
Missing	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Circulation failure	35 (5.2)	7 (4.0)	42 (14.4)	3 (3.2)	3 (7.5)	0 (0.0)
Respiratory failure	20 (3.0)	3 (1.7)	31 (10.7)	2 (2.2)	2 (5.0)	0 (0.0)
Clinical outcomes, n (%)						
Newly developed sepsis during index hospitalization	34 (5.1)	14 (8.1)	22 (7.6)	5 (5.4)	2 (5.0)	0 (0.0)
Newly developed ACLF during index hospitalization	54 (11.0)	18 (14.2)	14 (8.5)	10 (15.6)	3 (11.5)	0 (0.0)
Liver transplantation within 28 d after enrollment	34 (5.1)	7 (4.0)	18 (6.2)	6 (6.5)	1 (2.5)	0 (0.0)
Death within 28 d after enrollment	116 (17.3)	26 (15.0)	83 (28.5)	9 (9.7)	8 (20.0)	1 (14.3)

NOTE. Race was reported by the attending physician and the study coordinator.
MELD, Model for End-Stage Liver Disease.
[a]Genetic data were available from 1014 patients (79.6%).
[b]See Supplementary Material.
[c]Recent treatment is defined as treatment received during the 2 weeks before admission to hospital.

risk of death at 28 days and 90 days was significantly lower in African American patients than in European American patients.[16] These data are completely different from those of our study in which the prevalence of ACLF of any grade were identical among African American and European American patients (26.6% in both; Table 4). The differences between the study by Hernaez et al and our study may have 2 potential explanations. First, the percentage of African genetic ancestry among African American people in the United States has been reported to be of approximately 80%,[17] whereas it was approximately 38% in our African American patients (Table 4). Higher percentages of African genetic ancestry might be associated with higher predisposition to develop ACLF. Second, the different geographical origin of African ancestors may be associated with differences in genetic ancestry between African American people living in the United States and those living in Brazil (that was the main recruiting country in our study). It is surprising that the study by Hernaez et al did not consider the Mexican population living in the United States,[16] which represents 6% of the total population living in this country. In our study, patients from Mexico had the highest prevalence of ACLF of any grade (41.9% [n = 78 of 186; Supplementary Table 12] vs 31% [n = 395 of 1274] in the whole study population [Supplementary Table 6]) and the highest percentage of patients with severe ACLF among patients with ACLF (65.4% [n = 51 of 78; Supplementary Table 12] vs 45.8% [n = 180 of 393] in the whole study population [Supplementary Table 6]).

One of the 2 major objectives of this study was to assess the association of genetic ancestry and race with ACLF of any grade at enrollment using multivariable models. Because genetic ancestry and race were correlated, we had to develop 2 different multivariable models, 1 using genetic ancestry with additional covariates (model 1) and 1 using race with additional covariates (model 2). Our multivariable models showed that increasing percentage of Native American genetic ancestry and Native American race (vs European American race) were independently associated with increased odds of ACLF. The 2 models shared the following covariates that were also independently associated with ACLF: preexisting heart failure; referral from another hospital; complications of cirrhosis, such as antecedence of an episode of decompensated cirrhosis, enrollment with clinically apparent inflammatory disorders (proven bacterial infection with sepsis, or alcoholic hepatitis); or ascites. Of note, the association between Native American genetic ancestry or Native American race and ACLF was not mediated by differences in socioeconomic levels (Supplementary Table 2).

The current understanding of pathophysiology of ACLF emphasizes the primary role of acute systemic inflammation in driving the development of ACLF.[3] Proven bacterial infection with sepsis, alcoholic hepatitis, or both simultaneously, are the major inducers of acute systemic inflammation and subsequent ACLF.[5,6,18] Our multivariable models, however, indicated that the association between Native American genetic ancestry (and race) with ACLF was not mediated by proven bacterial infection with sepsis or alcoholic hepatitis, findings indicating that Native American genetic ancestry (and race) are crucial contributors per se to the development of ACLF. The recent evidence presented in the literature suggesting that genetic ancestry may cause excessive acute inflammatory responses to pathogen-associated molecular patterns (PAMPs) and poor health outcomes[9] is important in this context. Indeed, circulating PAMPs resulting from increased intestinal permeability have been found in patients with cirrhosis without features of ongoing infection or alcoholic hepatitis.[3] The hypothesis that higher percentages of Native American genetic ancestry (or Native American race) may contribute to ACLF by promoting more frequent PAMP translocation or more intense PAMP-induced inflammatory responses, or both, should therefore be tested.

The significant correlation found between Native American race and Native American genetic ancestry indicated that Native American race is a proxy of Native American genetic ancestry (see also Supplementary Figure 3). It was therefore not surprising to see that, like the increasing percentage of Native American genetic ancestry, Native American race was independently associated with increased odds of ACLF.

The second major objective of this study was to investigate the association of genetic ancestry and race with short-term mortality using 2 multivariable models (1 using genetic ancestry with additional covariates [model 1] and 1 using race with additional covariates [model 2]). Contrary to what was observed for ACLF, neither increasing percentage of Native American genetic ancestry nor Native American race (vs European race) were independently associated with higher short-term mortality after adjustment for social and clinical characteristics (in particular, those that define organ system failures), all at enrollment. However, the inclusion of variables that define organ system failures at enrollment (see below), and ultimately those used to define ACLF, may be behind these results, absorbing the variability related to genetic ancestry or race. This explanation was reinforced by the results of additional multivariable analyses (Supplementary Table 7), which revealed that increasing percentage of Native American genetic ancestry and Native American race (vs European American race) were independently associated with higher short-term mortality, when these analyses were performed without using variables assessing individual organ functions. Our findings suggest the existence of a cascade of events in which elevated percentages of Native American genetic ancestry and being of Native American race may increase the risk of short-term death by promoting the development of ACLF.

It is noteworthy that the 2 multivariable models for short-term death identified the same independent factors, including sociodemographic factors (increasing age or admission to public hospital) and clinical factors (enrollment with proven bacterial sepsis, alcoholic hepatitis, lower arterial pressure, or lower SpO_2/FiO_2 ratio), as well as several biomarkers at enrollment (higher white blood cell counts, higher blood creatinine levels or international normalized ratio, or lower albumin levels). Four points deserve comments. First, markers of the perturbed function

of 5 major organ systems considered for the definition of ACLF, including the kidneys (higher creatinine), liver (lower albumin), coagulation (higher international normalized ratio), circulation (lower mean arterial pressure), and respiration (lower SpO_2/FiO_2 ratio) were each independent predictors of short-term mortality. This indicates that any impairment in the function of each of these organ systems is associated with an increased risk of short-term death among patients with acutely decompensated cirrhosis. Therefore, early correction of each organ dysfunction could be translated into a decrease in the risk of death in patients with acutely decompensated cirrhosis. The second point of interest is that although hepatic encephalopathy was associated with higher short-term mortality in univariable analyses, this variable was not among the variables associated with short-term mortality in multivariable analyses. The reasons explaining these findings should be elucidated in future studies. The third point that deserves comments was that serum bilirubin (the biomarker usually used to assess liver function)[1] was not included in the multivariable models because of its strong correlation with international normalized ratio. Nevertheless, liver function was captured in our multivariable models because they included serum albumin. The fourth point of interest was the association between increased risk of short-term death and admission to public hospital (vs private hospital) that was explained, at least in part, by the lower percentage of patients enrolled with ACLF-2 or ACLF-3 who received early liver transplantation in public hospitals. This is a relevant finding, considering that the percentage of study centers that performed liver transplantation was similar between public and private hospitals (38.5% and 35.5%, respectively).

The observation that prevalence and severity of ACLF was higher in Native American patients than in European American and African American patients hospitalized for acutely decompensated cirrhosis and that these differences in prevalence and severity of ACLF were related to differences in the percentage of Native American genetic ancestry but not to socioeconomic disparities is important from a medical perspective not only in Latin America but also in United States and Europe. Sixty-five million Latino people live in the United States and 6 million live in Europe, including 3.5 million in Spain. Therefore, hepatologists and transplantation surgeons should be aware that Native American patients with acutely decompensated cirrhosis are at high risk of developing severe ACLF and should receive any effective prophylactic treatment against ACLF development. For example, there is a randomized clinical trial that found that long-term norfloxacin therapy reduced the incidence of hepatorenal syndrome, which is a form of ACLF, and improved survival.[19] Furthermore, there is universal agreement that liver transplantation must be prioritized to those patients with lower probability of survival. Therefore, if the results of our study are confirmed by other investigations, patients of Native American race should be prioritized in the waiting list relative to the other patients populations with similar Model for End-Stage Liver Disease scores.

Additional results are discussed in the Supplementary Material.

This study has several limitations. A major limitation of this study is that our models were built following data-driven approaches, which may limit the external validity of the interpretations offered in this article. Moreover, because most of the enrolled patients were living in urban area, and because 65% of patients were from medium or high socioeconomic levels, our findings may have limited external generalizability to patients living in rural area or to those from low socioeconomic levels in Latin America. Although our study collected information on several sociodemographic factors, a limitation may be confounding by unmeasured or unrecognized social determinants of health and access to health care. The fact that data for genetic ancestry is missing in 20% of patients, leading us to use multiple imputation, may be considered as a limitation. However, sensitivity analyses restricted to complete cases (Supplementary Tables 4 and 6) found that our estimates were robust to our assumptions around missing data. Moreover, a strength of this study was the assessment of genetic ancestry with the use of autosomal markers of ancestry, and not by parental indicators of ancestry (Y-single nucleotide polymorphisms and mitochondrial DNA could provide a limited characterization of the genetic admixture of a given population). Notwithstanding these limitations, this study, which used 2 independent approaches (ie, 1 using genetic ancestries and 1 using reported races) sheds light on Native American genetic ancestry and race, which are underrepresented in the ACLF medical literature and should therefore be emphasized in future interventional studies that aim to prevent or treat ACLF.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.05.033.

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Data Availability

The individual participant data collected will be available after deidentification, as well as the study protocol. The data will be available 3 months after article publication and with no particular end date. Researchers who provide a methodologically sound proposal can apply for the data, as long as the proposal is in line with the research consented by the patient. A sample and data use committee will evaluate the proposal. These proposals should be requested through www.datahub.clifresearch.com. Data requestors will need to sign a data transfer agreement.