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Markers of Inflammation and Mortality in a Cohort of Patients With Alcohol Dependence

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Abstract: Inflammation and intestinal permeability are believed to be paramount features in the development of alcohol-related liver damage. We aimed to assess the impact of 3 surrogate markers of inflammation (anemia, fibrinogen, and ferritin levels) on mid-term mortality of patients with alcohol dependence.

This longitudinal study included patients with alcohol dependence admitted for hospital detoxification between 2000 and 2010. Mortality was ascertained from clinical charts and the mortality register. Associations between markers of inflammation and all-cause mortality were analyzed with mortality rates and Cox proportional hazards regression models.

We also performed a subgroup analysis of mortality rates in patients with anemia, based on their mean corpuscular volume (MCV).

We included 909 consecutive patients with alcohol dependence. Patients were mostly male (80.3%), had a median age of 44 years (interquartile range [IQR]: 38–50), and upon admission, their median alcohol consumption was 192 g/day (IQR: 120–265). At admission, 182 (20.5%) patients had anemia; 210 (25.9%) had fibrinogen levels >4.5 mg/dL; and 365 (49.5%) had ferritin levels >200 ng/mL. At the end of follow-up (median 3.8 years [IQR: 1.8–6.5], and a total of 3861.07 person-years), 118 patients had died (12.9% of the study population). Cox regression models showed that the presence of anemia at baseline was associated with mortality (hazard ratio [HR]: 1.67, 95% confidence interval [CI]: 1.11–2.52, $P < 0.01$); no associations were found between mortality and high fibrinogen or high ferritin levels.

A subgroup of patients with anemia was analyzed and compared to a control group of patients without anemia and a normal MCV. The mortality ratios of patients with normocytic and macrocytic anemia were 3.25 (95% CI: 1.41–7.26; $P < 0.01$) and 3.39 (95% CI: 1.86–6.43; $P < 0.01$), respectively.

Patients with alcohol dependence admitted for detoxification had an increased risk of death when anemia was present at admission. More accurate markers of systemic inflammation are needed to serve as prognostic factors for poor outcomes in this subset of patients.

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Abbreviations: ALT = alanine amino-transferase, ARLD = alcohol-related liver disease, AST = aspartate amino-transferase, AUD = alcohol use disorder, CI = Confidence Interval, CRP = C-reactive protein, HBcAb = Hepatitis B core antibody, HBsAg = Hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HR = hazard ratio, ICD-10 = International Classification of Diseases, version 10, IQR = interquartile range, MVC = mean corpuscular volume, p-y = person-years.

INTRODUCTION

Alcohol consumption is widespread in western countries.[1] Alcohol abuse is one of the leading causes of preventable death and alcohol-related liver disease (ARLD). ARLD continues to be an important cause of death in individuals with alcohol use disorder (AUD).[2,3] In Spain, 4.4% of the general population between the ages of 15 and 64 years consumes alcohol in excess (ie, hazardous drinking).[4]

Alcohol-related mortality disproportionately affects younger individuals; it results in 2.3 million years of potential life lost, or around 30 years of life lost per alcohol-associated death.[5] The causal association between alcohol intake and ARLD has been well demonstrated,[3,6] but only a small proportion of individuals that drink heavily develop liver cirrhosis.[7] AUD confers an elevated risk of premature death, particularly in young and middle-aged adults.[2] Epidemiological and clinical data have indicated that the prognosis of alcohol dependence is negatively impacted by medical comorbidity,[3,8] but early markers of poor survival are scarce.

In animal models, systemic inflammation has been linked to increased intestinal permeability; this finding is paramount in the development of ARLD.[9,10] In humans, the majority of studies on inflammation and intestinal permeability have analyzed patients with cirrhosis of the liver,[11,12] but little is known about patients with less advanced liver disease. Also, we lack information about factors involved in intestinal permeability and systemic inflammation that might correlate to liver disease. Individuals with AUD at different stages of ARLD and/or medical comorbidity may represent a key population for studying the interplay between intestinal permeability, immune activation, and inflammation, mortality, and other disease-specific outcomes.

Proinflammatory cytokines, like C-reactive protein (CRP) and interleukin (IL)-6 have been associated with all-cause mortality in some subsets of patients,[13,14] including patients with AUD.[15] A prior study from our group found that patients with alcohol dependence admitted to detoxification had high mid-term mortality.[8] In fact, 11% of the cohort died after 3 years

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of follow-up, and mortality was highest in those with the greatest comorbidity (measured with the Cumulative Illness Rating Scale-Substance Abuse score).[8] It is unknown whether elevated systemic inflammation and elevated intestinal permeability might form the link between medical comorbidity and increased mortality in patients with AUD.

Chronic inflammation and intestinal permeability can be detected by measuring the levels of several biomarkers and cytokines.[12] However, those tests are associated with issues regarding cost and standardization, which limit their utility in daily clinical practice.[15] Therefore, there is a need for surrogate markers of inflammation that might serve as early prognostic factors of poor outcomes in patients with AUD.

In the present study, we aimed to assess the association between baseline markers of inflammation (presence of anemia[16] and levels of ferritin[17] and fibrinogen[18]) and all-cause mortality in a cohort of patients with AUD admitted for hospital detoxification at 2 hospitals in the Barcelona metropolitan area.

PATIENTS AND METHODS

This longitudinal study included a cohort of patients with alcohol dependence that were admitted for detoxification to 2 hospital units located in metropolitan Barcelona, Spain from 2000 to 2010. One hospital was the Hospital Universitari de Bellvitge in L'Hospitalet de Llobregat, and the other was the Hospital Universitari Germans Trias i Pujol in Badalona.

All patients provided written informed consent before entering the study. The present study was approved by the Ethics Committee at the Hospital Universitari Germans Trias i Pujol. Methods used for conducting this study complied with the ethical standards for medical research and the principles of good clinical practice in accordance with the World Medical Association's Declaration of Helsinki.

At admission, we recorded the sociodemographic characteristics, use of alcohol or other drugs, and routine laboratory parameters for all patients. The laboratory parameters included, among others, hemoglobin levels, mean corpuscular volume (MCV), leukocyte and lymphocyte counts, platelet count, general biochemistry parameters from two liver enzyme tests (aspartate amino-transferase [AST] and alanine amino-transferase [ALT]), and bilirubin levels. In addition, we analyzed blood samples to rule out infections from human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV; tested with HBsAg and HBcAb).

Additional information about the admission protocol can be found elsewhere.[8,19]

Independent Variables

Three different surrogate markers of systemic inflammation were chosen, anemia, fibrinogen, and ferritin. The values were treated as dichotomous; thus, we assigned thresholds based on normal values of hemoglobin, fibrinogen, and ferritin to distinguish inflammatory status from normal status. The thresholds for anemia were based on the World Health Organization definition of normal levels (hemoglobin <12 g/dL for women and <13 g/dL for men).[20] The thresholds for high fibrinogen and ferritin levels were >4.5 mg/dL and >200 ng/mL, respectively, based on the upper limits of normal.

Other Covariates

For the purpose of this study, ARLD was diagnosed for patients that met ≥ 2 of the following criteria upon admission:[3,21] AST levels were between 74 and 300 IU/L; the ratio of AST/ALT was ≥ 2; and total bilirubin was >1.2 mg/dL

Outcomes During Follow-up

The dates and causes of death were ascertained by reviewing clinical charts and crosschecking with the mortality register through December 31, 2010. Causes of death were classified according to the International Classification of Diseases, version 10 (ICD-10).[22] We recodified causes of death according to the ICD-10 codes with an algorithm described elsewhere.[23]

Statistical Analysis

When patients were admitted more than once during the study period, we analyzed only the data from their first admission. Data from the 2 hospitals were controlled to exclude duplicates.

Descriptive statistics were expressed as the median and interquartile range (IQR) for quantitative variables and as absolute frequencies and percentages for qualitative variables.

The main baseline characteristics were stratified according to the presence of surrogate markers of inflammation to compare groups. Differences among groups were analyzed with the chi-square test for qualitative variables and with the *t* student test for quantitative variables.

Mortality rates were calculated in person-years (p-y). Mortality ratios were calculated with the reference category defined as the absence of anemia or normal levels of ferritin and fibrinogen.

Cox proportional hazards regression models were used to analyze the predictors of death. The 3 markers were included as potential predictors of death. Age and sex were among the predictors of death explored in our adjusted analysis. Also, other covariates, like viral infections or the presence of ARLD, were chosen as potential predictors a priori because they had been associated with mortality in prior studies with the same cohort.[23] The proportional hazards assumption was checked for all variables. The covariates used for multivariate analysis were identified as statistically significant variables in the univariate analysis.

In addition, to assess the mortality rates in patients with anemia, we assigned patients to subgroups based on their MCV; this approach allowed us to disentangle the impact of normocytic anemia on mortality. For this purpose, MCVs <80 fL were defined as microcytic anemia; MCVs between 80 and 95 fL were defined as normocytic anemia; and MCVs >95 fL were defined as macrocytic anemia.

Statistical tests were 2-sided, and P values <0.05 were considered statistically significant. Analyses were performed with SPSS 15.0 (SPSS, Chicago, IL, USA).

RESULTS

The present study included 909 consecutive patients with alcohol dependence. Table 1 shows the baseline characteristics of the study population. Patients were predominantly male (80.3%), with a median age of 44 years (IQR: 38–50). The median daily alcohol intake at admission was 192 g (IQR: 120–265); 18.3% of patients had prior injected drug use, 9.4% were on methadone treatment, and 8.9% reported cocaine use. More than 20% of patients were infected with HCV, 25.1% had been exposed to HBV (HBcAb-positive), but only a very small proportion had active HBV infections (HBsAg-positive); 8.3% were infected with HIV.

Regarding markers of inflammation, 25.9% of patients had serum fibrinogen levels >4.5 mg/dL and almost half the study

TABLE 1. Baseline Characteristics of 909 Patients With AUD Admitted for Hospital Detoxification in Metropolitan Barcelona, Spain 2000–2010

	Total (N = 909)
Male sex, n (%)	730 (80.3)
Age (years), median (IQR)	44 (38–50)
Alcohol consumption at admission (g/day), median (IQR) (n = 869)	192 (120–265)
Comorbidities	
HIV infection, n (%) (n = 903)	75 (8.3)
HCV infection, n (%) (n = 896)	194 (21.7)
HBsAg, n (%) (n = 832)	14 (1.7)
Presence of ARLD, n (%) (n = 864)	126 (14.6)
Surrogate markers of inflammation	
Hemoglobin (g/dL), median (IQR) (n = 889)	14 (12.9–15.1)
<12 g/dL in females and <13 gr/ dL in males, n (%)	182 (20.5)
Fibrinogen (mg/dL), median (IQR) (n = 812)	3.6 (2.8–4.5)
>4.5, n (%)	210 (25.9)
Ferritin (ng/mL), median (IQR) (n = 738)	198.4 (105.5–394.4)
>200, n (%)	365 (49.5)

ARLD = alcohol-related liver disease, HBsAg = Hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IQR = interquartile range.

population had ferritin levels >200 ng/dL. Anemia was present in 20.5% of patients.

Regarding liver enzyme tests, the median AST and ALT levels were 42 IU/L (IQR: 24–78) and 36 IU/L (IQR: 22–66), respectively; the median bilirubin level was 0.7 mg/dL (IQR: 0.5–1.1). The median MCV was 98.1 fL (IQR: 94.0–102.9); the median leukocyte, lymphocyte, and platelet counts were 6.6×10^9 cells/L (IQR: 5.3–8.1), 1.9×10^9 cells/L (IQR: 1.4–2.4), and 195×10^9 cells/L (IQR: 143–249), respectively.

We also performed a stratified analysis to assess disease correlates of the 3 surrogate markers of inflammation, as shown in Table 2. Of note, compared with patients without anemia, patients with anemia were more likely to be older (46 vs 43 years, $P < 0.01$), infected with HIV (11.6% vs 7%, $P < 0.04$), and exhibit ARLD (29% vs 10.9%, $P < 0.01$). In addition, those with anemia had higher ferritin levels, but lower leukocyte (5.3×10^9 vs 6.9×10^9 cells/L, $P < 0.01$), lymphocyte (1.5×10^9 vs 2.0×10^9 cells/L, $P < 0.01$), and platelet counts (164×10^9 vs 199×10^9 cells/L, $P < 0.01$) than those with normal hemoglobin levels.

Table 2 shows that patients with fibrinogen >4.5 mg/dL were less likely to be infected with HCV (10.6% vs 24%, $P < 0.01$), had lower alcohol consumption levels (160 vs 200 g/day, $P < 0.01$), and were less likely to harbor ARLD (9.5% vs 15.6%, $P = 0.03$) than those with lower fibrinogen levels. In addition, patients with high fibrinogen were less likely than those with low fibrinogen to have a drug use history; for example, methadone treatment (4% vs 9.7%, $P = 0.01$), prior injected drug use (9.1% vs 21.6%, $P < 0.01$), and prior cocaine use (3.8% vs 9%, $P = 0.02$). Those with high fibrinogen also had a higher platelet count (223×10^9 vs 187×10^9 cells/L, $P < 0.01$) than those with fibrinogen ≤4.5 mg/dL.

Patients with ferritin levels >200 ng/dL were more often male (86.6% vs 74.8%, $P < 0.01$), had a greater daily alcohol intake at admission (200 vs 175 g, $P = 0.04$), and more frequently exhibited ARLD (21.2% vs 6.8%, $P < 0.01$) compared with those with low ferritin. Also, patients with high ferritin levels had higher MCVs (means 100 vs 95.8 fL, $P < 0.01$) and lower platelet counts (172×10^9 versus 205×10^9 cells/L, $P < 0.01$) than patients with normal ferritin levels.

Outcomes at the End of Follow-up

The median follow-up was 3.8 years (IQR: 1.8–6.5), and the total follow-up was 3861 p-y. At the end of the study, 118 patients had died (12.9%); the mortality rate was 3.06 × 100 p-y (95% confidence interval [CI]: 2.54–3.65).

The mortality rates were 5.65 × 100 p-y (95% CI: 4.07–7.63) for participants with anemia, and 2.41 × 100 p-y (95% CI: 1.89–3.05) for those without anemia; thus, the mortality ratio was 2.34 (95% CI: 1.59–3.41, $P < 0.01$). The mortality rates were 3.70 × 100 p-y (95% CI: 2.44–5.38) for patients with fibrinogen levels >4.5 mg/dL, and 2.90 × 100 p-y (95% CI: 2.30–3.61) for those with fibrinogen ≤4.5 mg/dL; thus, the mortality ratio was 1.27 (95% CI: 0.82–1.96; p = 0.27). Mortality rates were 3.57 × 100 p-y (95% CI: 2.69–4.66) for patients with ferritin levels >200 ng/dL, and 2.73 × 100 p-y (95% CI: 1.95–3.72) for patients with ferritin levels ≤ 200 ng/dL; thus, the mortality ratio was 1.31 (95% CI: 0.87–1.99; $P = 0.20$).

The main causes of death in the total study group were liver-related (37.4%), cancer-related (21.2%), and cardiovascular (13.3%). Of interest, liver-related deaths were not evenly distributed among groups; they comprised 8.1% of deaths in those with fibrinogen levels >4.5 mg/dL and 46.3% of deaths in participants with anemia.

Table 3 shows the Cox proportional hazards model results. In the unadjusted analysis, age, HIV infection, HCV infection, ARLD, and anemia were associated with mortality. However, fibrinogen and ferritin levels were not associated with mortality. In the multivariate analysis, the presence of anemia was associated with mortality. The hazard ratio (HR) was 1.67 (95% CI: 1.11–2.52, $P < 0.01$).

Of note, in the fully adjusted model, among the covariates, age at admission (HR: 1.04; 95% CI: 1.02–1.06; $P < 0.01$), HCV infection (HR: 1.89; 95% CI: 1.18–3.04; $P < 0.01$), and the presence of ARLD (HR: 1.61; 95% CI: 1.01–2.58; $P = 0.05$) were also associated with an increased risk of death. In addition, the association between HIV infection and mortality was borderline significant (HR: 1.79; 95% CI: 0.98–3.28; $P = 0.06$).

Subgroup Analysis of Patients With Anemia

Out of the 182 patients with anemia, 10 (5.5%) had MCVs <80 fL, 44 (24.2%) had MCVs between 80 and 95 fL, and 128 patients (70.3%) had MCVs >95 fL, consistent with microcytic, normocytic, and macrocytic anemia, respectively. At the end of follow-up, none of the patients in the microcytic anemia group had died; there were 10 deaths in the normocytic anemia group (mortality rate: 5.8 × 100 p-y [95% CI: 2.95–10.34]), and 32 deaths in the macrocytic anemia group (mortality rate: 6.05 × 100 p-y [95% CI: 4.21–8.44]).

When those without anemia and normal MCVs were used as the reference group, the mortality ratios of patients with normocytic and macrocytic anemia were 3.25 (95% CI: 1.41–7.26; $P < 0.01$) and 3.39 (95% CI: 1.86–6.43; $P < 0.01$), respectively (Figure 1). Figure 1 also shows that patients

TABLE 2. Characteristics of Patients With AUD Admitted for Detoxification Stratified by Markers of Inflammation

	Hemoglobin			Fibrinogen			Ferritin		
	No Anemia (n = 785)	Anemia* (n = 182)	*P*	≤4.5 mg/dL (n = 602)	>4.5 mg/dL (n = 210)	*P*	≤200 ng/mL (n = 373)	>200 ng/mL (n = 365)	*P*
Male sex, n (%)	574 (81.2)	141 (77.5)	0.26	488 (81.1)	164 (78.1)	0.35	279 (74.8)	316 (86.6)	<0.01
Age median (years), median (IQR)	43 (37–50)	46 (40–52)	<0.01	43 (37–49)	41 (36–49)	<0.01	43 (37–50)	45 (39–51)	0.17
Alcohol consumption at admission (g/day), median (IQR)	192 (120–275)	200 (100–250)	0.21	200 (120–200)	160 (120–200)	<0.01	175 (100–275)	200 (120–300)	0.04
HIV infection, n (%)	49 (7.0)	21 (11.6)	0.04	51 (8.5)	9 (4.3)	0.04	26 (7)	25 (6.9)	0.96
HCV infection, n (%)	137 (19.7)	46 (25.4)	0.09	143 (24)	22 (10.6)	<0.01	71 (19.3)	79 (21.8)	0.41
HBsAg-positive, n (%)	12 (1.9)	2 (1.1)	0.82	10 (1.8)	3 (1.5)	0.79	7 (1.9)	6 (1.7)	0.81
Presence of ARLD, n (%)	75 (10.9)	51 (29.0)	<0.01	92 (15.6)	19 (9.5)	0.03	25 (6.8)	75 (21.2)	<0.01
Hemoglobin (g/dL), median (IQR)				13.9 (13–15.1)	14.2 (13.1–15.6)	0.44	14 (12.9–15)	13.8 (12.8–14.9)	0.87
MCV (fL), median (IQR)	97 (94–102)	100 (93.8–105)	<0.01	98 (94–103)	98.6 (94.6–102.6)	0.423	95.8 (91.8–99.9)	100 (96.8–105.2)	<0.01
Fibrinogen (mg/dL), median (IQR)	3.6 (2.9–4.5)	3.4 (2.7–4.6)	0.38				3.65 (2.9–4.5)	3.50 (2.8–4.5)	0.10
Ferritin (ng/mL), median (IQR)	195.9 (109.8–377.4)	243.9 (83.8–551.0)	0.02	206 (108–411)	149 (71–266)	0.11			
Leukocyte count (10^9 cells/L), median (IQR)	6.9 (5.7–8.4)	5.3 (4.2–6.9)	<0.01	6.5 (5.1–7.9)	6.4 (5.1–8.3)	<0.01	6.8 (5.6–8.4)	6.2 (4.9–7.7)	<0.01
Lymphocyte count (10^9 cells/L), median (IQR)	2.0 (1.5–2.5)	1.5 (1.2–2.0)	<0.01	1.9 (1.4–2.4)	1.9 (1.5–2.4)	0.84	2.0 (1.5–2.5)	1.8 (1.4–2.2)	<0.01
Platelet count (10^9 cells/L), median (IQR)	199 (154–251)	164 (102–228)	<0.01	187 (136–235)	223 (165–270)	<0.01	205 (167–264)	172 (122–225)	<0.01

ARLD = alcohol-related liver disease, HBsAg = Hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IQR = interquartile range, MCV = mean corpuscular volume.

* Anemia: hemoglobin <12 g/dL in females and <13 g/dL in males.

TABLE 3. Univariate and Multivariate Cox Regression Models for the Association Between Inflammatory Markers and Mortality in 909 Patients With AUD Admitted for Detoxification in Metropolitan Barcelona, Spain 2000–2010

	Univariate Analysis		Multivariate Analysis	
Variable	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Male sex	0.70 (0.43–1.15)	0.16		
Age at admission	1.03 (1.01–1.05)	<0.01	1.04 (1.02–1.06)	<0.01
HIV infection	2.56 (1.61–4.07)	<0.01	1.79 (0.98–3.28)	0.06
HCV infection	2.20 (1.51–3.21)	<0.01	1.89 (1.18–3.04)	<0.01
HBsAg-positive	0.86 (0.29–4.73)	0.83		
Presence of ARLD	1.96 (1.25–3.06)	<0.01	1.61 (1.01–2.58)	0.05
Anemia	2.33 (1.59–3.41)	<0.01	1.67 (1.11–2.52)	<0.01
Fibrinogen >4.5 mg/dL	1.27 (0.82–1.97)	0.28		
Ferritin >200 ng/mL	1.32 (0.87–2.00)	0.19		

ARLD = alcohol-related liver disease, AUD = alcohol use disorder, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus.

without anemia and MCVs >95 fL had a mortality rate of 2.76×100 p-y (95% CI: 2.01–3.44). When this group was used as the reference group, the mortality ratio of those with macrocytic anemia was 2.28 (95% CI: 1.46–3.52; $P < 0.01$).

DISCUSSION

In this cohort study of patients with alcohol dependence admitted for detoxification, the presence of anemia was associated with an elevated risk of mortality. However, we were unable to find an association between fibrinogen or ferritin levels and mid-term mortality.

The association between anemia and mortality remained significant in the model after adjusting for other markers of poor clinical outcomes, such as age, HIV infection, HCV infection, and the presence of ARLD. Of interest, HCV infection was also associated with overall mortality in the adjusted Cox regression model; this finding was consistent with prior findings in the same cohort.[23] Among the studied covariates, other predictors of death were age and the presence of ARLD, and there was also a borderline-significant association between HIV infection and all-cause mortality.

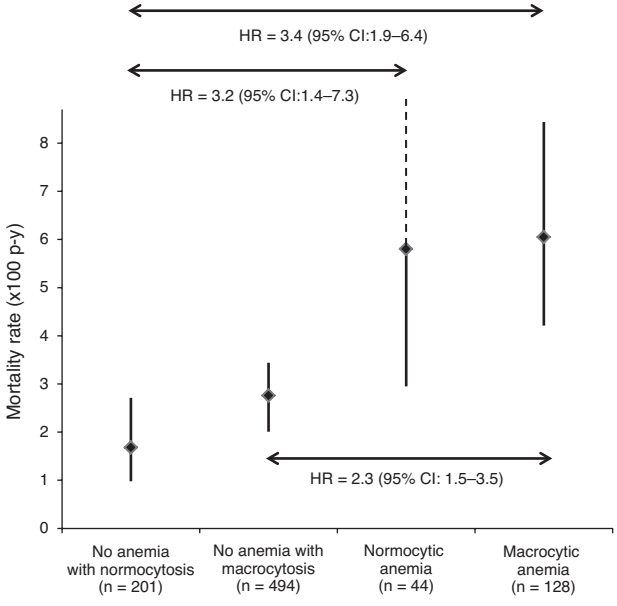

FIGURE 1. Unadjusted mortality rates and hazard ratios (HRs) of death according to anemia status in patients with AUD admitted for detoxification treatment.

Anemia has been regarded to indicate increased risk of mortality in different settings, including heart failure,[24] acute ischemic stroke,[25] bacteremia,[26] myocardial infarction at advanced age,[27] surgery,[28] and severe alcoholic hepatitis.[29] We are not aware of any previous studies that have analyzed the prognostic value of anemia in patients with alcohol dependence admitted for detoxification.

In addition to its value as a surrogate marker of chronic inflammation, anemia may also arise from multiple factors in patients with AUD.[16,30] The differential diagnosis of anemia in patients with alcohol dependence includes hemolytic anemia, megaloblastic anemia due to folate and/or vitamin B12 deficits, or syderoblastic anemia.[31] In our study group, a significant number of patients with anemia had normal MCV values. Normocytic anemia is most commonly associated with inflammation and chronic diseases.[16] In the subgroup analysis that we performed, after excluding patients with abnormal MCV values, those with normocytic anemia had increased risk of death, with a mortality ratio of 3.25 (95% CI: 1.41–7.26).

It is important to note that patients with macrocytic anemia also had a very high mortality rate, and when compared with patients with macrocytosis, but without anemia, they had a significantly higher risk of death, with a mortality ratio of 3.39 (95% CI: 1.86–6.43). Therefore, anemia had a higher impact on mortality than alcohol-driven bone marrow toxicity. Given that an etiologic study of anemia in those with AUD is not always feasible, there may be other markers of inflammation that could more effectively stratify patients with alcohol dependence to analyze risk of death. Those markers might include IL-6 and CRP,[15,32] which were previously associated with inflammation and mortality in some subsets of patients. Also, sCD14, a marker of intestinal permeability,[33] has been shown to be associated with mortality in different populations.[33–34]

Our finding that high fibrinogen levels were not associated with mortality in this cohort merits some discussion. Other researchers have proposed that low fibrinogen levels in individuals with moderate alcohol intake were associated with

reduced cardiovascular mortality.[35,36] Interestingly, in our study population, among the patients with AUD, those with the highest fibrinogen levels had the lowest alcohol consumption levels at admission. In addition, compared with those with low fibrinogen levels, those with higher fibrinogen levels had a lower prevalence of other markers of poor prognosis, like HCV infection, or presence of ARLD. Therefore, it is possible that the potential benefit that moderate alcohol intake and low fibrinogen levels have on some cardiovascular outcomes may be lost in individuals who consume unhealthy amounts of alcohol or have alcohol dependence.

Ferritin acts as an acute-phase reactant; therefore, ferritin levels might reflect the levels of iron, which is a cofactor in the progression of liver disease in individuals with AUD.[37,38] In our study, the group of patients with higher ferritin levels tended to be male and they tended to drink more heavily (at admission) than those with lower ferritin levels. Nevertheless, we found that ferritin levels >200 ng/dL had no impact on mid-term mortality. Of interest, in our cohort, male sex and baseline alcohol intake were not associated with an increased risk of death. A potential explanation for our finding that ferritin levels could not discriminate patients at high risk of death was the high prevalence of hyperferritinemia. Nearly half of our population had ferritin levels >200 ng/mL, and two-thirds of the population had ferritin levels >100 ng/mL.

Of note, in the 3 different groups of fibrinogen, ferritin, or hemoglobin levels, there was an uneven distribution of ARLD. However, ARLD did not have an impact on mortality, except in the group with anemia. In the fully adjusted Cox regression, both the presence of ARLD and anemia were independently associated with mortality. Therefore, our definition of ARLD might be used as a tool for detecting patients with alcohol dependence that are at increased risk of death.

Also, among the groups of patients with different markers of inflammation, there was an uneven distribution of liver-related deaths. Liver-related deaths accounted for almost half the deaths in the group of patients with anemia.

In our cohort of patients with alcohol dependence, cardiovascular death was the third cause of death, after liver-related and cancer-related deaths. It was surprising that a group of patients in their mid 40s had such high mid-term cardiovascular mortality. This finding emphasized the importance of inflammation in patients with alcohol dependence.

The present study had several limitations. First, we only conducted one determination of surrogate markers of inflammation at admission. Indeed, the evolution of those markers could have had a greater impact on mortality than a single determination. Also, we were not able to adjust the analysis for the presence of alcohol abstinence over time, after hospital discharge; this factor is a known marker of prognosis.[3] In addition, as we previously mentioned, we did not have sufficient laboratory information for a full characterization of the anemia in patients with low hemoglobin levels. Finally, we could not adjust our analysis for other markers of poor outcomes in middle-aged adults, such as smoking or the presence of hypertension.

The present study had important strengths. We recruited a large study population with a relatively long follow-up, the mortality data included causes of death, and we had a wide range of patient-level data.

In summary, in this study of surrogate markers of inflammation in a cohort of patients with alcohol dependence, we showed that the presence of anemia was associated with all-cause mortality. Future research should focus on exploring other markers of inflammation and intestinal permeability that might be used for the prognosis of patients with alcohol dependence.

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