HYPERFERRITINEMIA PREDICTS LONG-TERM MORTALITY IN PATIENTS WITH NAFLD.

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INTRODUCTION:

Hyperferritinemia is common in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and correlates with the severity of liver fibrosis. Our aim was to assess the impact of ferritin on long-term outcomes and survival in a large cohort of NAFLD patients.

METHODS:

We included 1247 patients with biopsy-proved NAFLD from tertiary centers in Italy (Turin, Milan, Rome, Palermo), Australia (Sydney), UK (Newcastle) and Spain (Seville). Clinical and biochemical data were collected at the time of liver biopsy (**Table 1**). Ferritin levels of 300 ug/L for men and 200 ug/L for women were considered as the upper limit of normal (ULN). Clinical outcomes, including liver-related events (ascites, encephalopathy, variceal bleeding), hepatocellular carcinoma (HCC) and survival, were collected after a median follow-up of 90 months.

RESULTS:

The median age of the study cohort was 48 [IQR 38-57] years and 814 (65.3%) patients were male. The overall prevalence of obesity and type 2 diabetes was 45.0% and 28.1%. Overall, hyperferritinemia was found in 373 (29.9%) patients; severe fibrosis (F3-4) was found at liver biopsy in 272 (21.8%) patients. NASH was diagnosed in 756 (60.6%) cases and was similarly distributed between those with normal and high ferritin levels. Serum ferritin > 2 x ULN (32.2% of the total population with hyperferritinemia), significantly associated with F3-4 (OR = 2.10 [95% CI 1.40-3.14], p < 0.001) (**Figure 1**).

After a median follow-up of 90 months, 24 patients (2.3%) died, while 57 (4.8%) and 18 (1.5%) developed liver-related events and HCC. At univariate analysis, the incidence of liver-related events and mortality varied significantly according to serum ferritin values > 2 x ULN (log-rank test: p = 0.004 and p = 0.001, respectively) (**Figures 2 and 3**).

However, at multivariate Cox regression analysis adjusted for age, body mass index, diabetes and fibrosis, ferritin levels > 2 x ULN independently predicted mortality (HR = 3.04 [95% CI 1.16-7.93], p = 0.023) but not liver-related events (HR = 1.67 [95% CI 0.90-3.11], p = 0.105).

CONCLUSIONS:

Ferritin levels higher than 2 x ULN are associated with severe liver fibrosis in NAFLD patients and are able to predict long-term mortality.

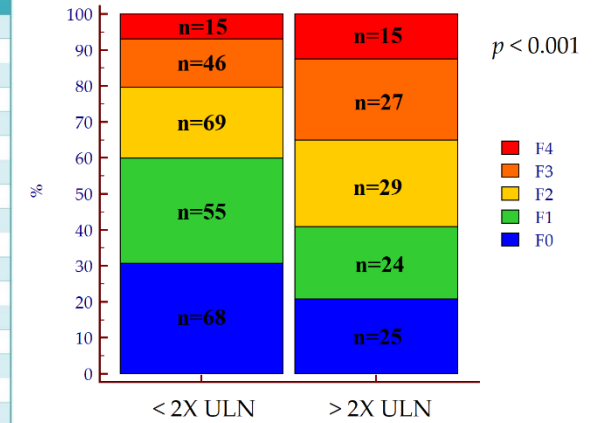| Total population (n=1247)	Low ferritin (n=874)	High ferritin (n=373)	p
Age (years), median [IQR]	46 [37-56]	51 [40-59]	<0,001
Gender (M), n (%)	544 (62,2)	270 (72,4)	<0,001
BMI (Kg/m²), median [IQR]	29,6 [26,2-34,9]	29,4 [26,5-32,8]	0,231
Waist circumference (cm), median [IQR]	100 [92-110]	102 [95-108]	0,351
ALT (U/L), median [IQR]	56 [39-80]	69 [43-101]	<0,001
AST (U/L), median [IQR]	35 [27-48]	41 [29-64]	<0,001
GGT (U/L), median [IQR]	65 [37-122]	61 [33-118]	0,322
ALP (U/L), median [IQR]	83 [65-110]	71 [59-93]	<0,001
Albumin (g/L), median [IQR]	45 [43-48]	46 [43-49]	0,078
Total bilirubin (mmol/L), median [IQR]	10,3 [7,9-14,9]	12,0 [8,0-15,4]	<0,001
Platelets (10⁹/L), median [IQR]	234 [196-280]	215 [180-253]	<0,001
Hemoglobin (g/dL), median [IQR]	14,6 [13,3-18,0]	15,0 [14,0-16,0]	<0,001
Creatinin (mg/dL), median [IQR]	0,8 [0,7-1,0]	0,8 [0,7-1,0]	0,989
Blood glucose (mmol/L), median [IQR]	5,3 [4,8-6,2]	5,3 [4,8-6,3]	0,630
HDL (mmol/L), median [IQR]	1,3 [1,1-1,5]	1,2 [1,0-1,4]	<0,001
Triglycerides (mmol/L), median [IQR]	1,5 [1,1-2,1]	1,7 [1,1-2,2]	<0,001
Diabetes , n (%)	238 (27,2)	113 (30,3)	0,272

***Table 1**. Population characteristics*

***Figure 1.** Association between different grades of hyperferritinemia and fibrosis stages.*
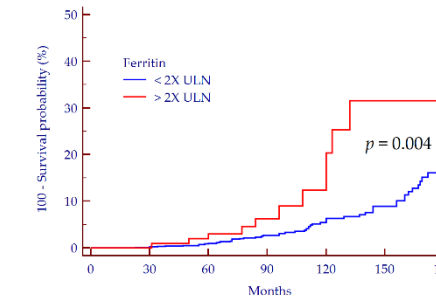
***Figure 2.** Cumulative incidence of liver-related events.*
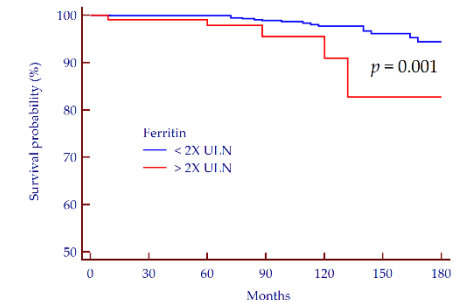
***Figure 3.** Cumulative incidence of mortality.*