Differential effect of the allele G ADRB2 (rs1042714) and allele C ADRB3 (rs4994) and its association with metabolic-associated steatotic liver disease (MASLD) risk factors in Mexican population.

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Introduction and Objectives: Adrenergic receptors (ADR) regulate adipocyte energy expenditure. G ADRB2 and C ADRB3 alleles are associated with fat deposition and metabolic alterations. The distribution of these polymorphisms and their influence on liver disease in Western Mexico are unknown.

Materials and Patients: In this cross-sectional study, we evaluated 919 unrelated adults with Caucasian ancestry (Villa Purificación, Los Altos, Cuquio), Native population (Nahuas, Huicholes), and Mestizo (admixed) (Guadalajara, Nayarit). Genomic ADN was extracted from leukocytes using the salting out method. ADRB2 and ADRB3 genotyping was performed using a Real-Time PCR system (TaqMan, Applied Biosystems, rs1042714 and rs4994). Body composition was assessed by bioelectrical impedance with an InBody analyzer (Inbody Co, Seoul, Korea). Biochemical tests included glucose, total cholesterol (TC), triglycerides (TG), high-density cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (C- VLDL). Insulin resistance (IR) was calculated as fasting plasma glucose (mg/dL) × fasting serum insulin (μU/mL)]/405 and defined as HOMA-IR ≥ 2.5. Statistical differences for quantitative and qualitative variables were analyzed using Student's t-test and Chi-square, respectively, with R study software. Hardy-Weinberg equilibrium (HWE) was obtained using Arlequin software (version 3.01).

Results: The Natives had the lowest frequency of the G ADRB2 allele (2.9%), while the Caucasians showed the highest frequency (21.2%). In the general population, the CG/GG genotypes were associated with a higher risk for increased VLDL [OR 1.98 (1.25-3.09 p=0.003)] and hyperglycemia [OR 1.91 (1.19-3.04 p=0.007)] than CC genotype carriers. Among the Caucasians, the CG/GG genotype was protective against increased LDL [OR 0.22 (0.05-0.81 p=0.023)]. The C ADRB3 allele was highest in native populations (23.7%), while the Caucasians showed the lowest frequencies (12.8%). In Natives, the C ADRB2 allele and C ADRB3 allele were associated with a higher risk of hypertriglyceridemia [OR 2.99 (1.16-9.37 p=0.036)] and hyperinsulinemia [OR 9.93 (1.68-189 p=0.035)] respectively. In the mestizo population, TC/CC genotype patients showed a higher risk of body fat [OR 2.26 (1.4-3.7 p=0.001)].

Conclusions: The frequency of allele G ADRB2 is higher than in those with Caucasian ancestry, while allele C ADRB3 is higher in the Native population. The G ADRB2 and allele C ADRB3 confer the risk of having higher body fat without metabolic alterations in Caucasian populations. The C ADRB2 allele and C ADRB3 allele confer risk for hyperinsulinemia and hypertriglyceridemia in Native populations, metabolic alterations that have been associated with MASLD.

Ethical statement: The Institutional Review Board approved this study, and participants signed a written informed consent before entry.

Declaration of interests: None.

Funding: University of Guadalajara-Programa de Fortalecimiento de Institutos, Centros y Laboratorios.

https://doi.org/10.1016/j.aohep.2025.101872

Assessment of MELD Scores as Predictors of Mortality in Patients with Decompensated Chronic Liver Disease with Variceal Hemorrhage at a third-level care center.

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Introduction and Objectives: The variceal hemorrhage is the most common cause of decompensation in patients with chronic liver disease. Hemoglobin level has been used to classify severity; however, it is unreliable. This study aims to evaluate MELD scores as predictors of mortality in patients with variceal hemorrhage.

Materials and Patients: An observational, retrospective, comparative, and longitudinal study was conducted on patients hospitalized in the Gastroenterology department for one year, who were admitted with a diagnosis of variceal hemorrhage and met the criteria for applying the MELD score within the first 48 hours of hospitalization. Descriptive and inferential statistics were performed using ROC curves. Demographic variables, MELD, MELD Na, and MELD Lactate scores were evaluated. The initial and follow-up hemoglobin levels were assessed. Additionally, hospitalization days and discharge reasons were considered.

Results: A total of 96 patients were analyzed (60 women and 36 men) with an average age of 62 ± 8 years. Regarding the etiology of cirrhosis, Alcohol: 48, MASLD: 18, METALD: 8, Viral: 4, Unspecified: 6, Autoimmune: 16. In the analysis of ROC curves, it was found that there was a significant mortality prediction for the MELD, MELD Na, and MELD Lactate models. The MELD cutoff of 21.5 points presented an AUROC of 0.866 (95% CI: 0.71-1.00, p= <0.001), MELD Na of 20.5 had an AUROC of 0.848 (95% CI: 0.67-1.00, p= <0.001), and the MELD Lactate cutoff of 20.5 had an AUROC of 0.791 (95% CI: 0.644-0.939, p= 0.003)

Conclusions: In the analysis of ROC curves, the MELD, MELD Na, and MELD Lactate models demonstrated a significant predictive capacity for mortality. The AUROC values were 0.866, 0.848, and 0.791 respectively, confirming their utility in clinical practice for patients with chronic liver disease admitted in the context of decompensation due to variceal bleeding.

Ethical statement: Data confidentiality and participant protection are guaranteed.

Declaration of interests: None.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

https://doi.org/10.1016/j.aohep.2025.101873

Characteristics of overlap syndrome in Mexican patients.

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Introduction and Objectives: The overlap syndrome combines two or more autoimmune liver diseases such as: autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis, in Mexico there is little information about this disease. Objective: To

describe the characteristics of the Mexican population with overlap syndrome treated at the liver clinic of the General Hospital of Mexico.

Materials and Patients: This is a retrospective, observational and analytical study in which records of patients with ADHD who met overlapping criteria (two or more hepatic autoimmune diseases) between 2020 and 2024 were reviewed to evaluate demographic variables and their presentation. Descriptive statistics with measures of central tendency and dispersion were used using SPSS 25.0. Liver enzymes AST, ALT, GGT, in addition to BT and FA of EHAI, CBP and CEP compared to CEP+EHAI were compared with Student's t-test for independent groups. Values are expressed as means and standard deviations. The Z test for contingency tables for difference of proportions with Bonferroni correction was used to compare the percentages of the degree of fibrosis among the four groups (EHAI, CBP, CEP and CEP+EHAI). A significance level of less than 5% was considered in all tests.

Results: A total of 256 patients with AHD were evaluated, of whom 55 (21.4%) were found to be compliant for overlap syndrome. Of these, 93.6% were female and 7.3% male, with a mean age of 51.89 ± 12.72 years (range: 50.34-53.44). The most common phenotype was CBP/HAI (73.2%). The most frequent autoimmune comorbidities were hypothyroidism, rheumatoid arthritis, Sjögren's syndrome and systemic sclerosis. 32.1% had grade F3 fibrosis and 16.3% cirrhosis, Child A 12.5%, Child B 62.5% and Child C 25%. A higher proportion of fibrosis was observed in F2 and F3 for overlap syndrome compared to EHAI. Regarding enzymatic tests, significant differences were found in GGT (183.5±254.5 vs. 318.5±232.8) and AF between EHAI and overlap syndrome. The most frequent decompensation was variceal gastrointestinal bleeding in 62.5%, and three patients were transplanted.

Conclusions: Overlap syndrome is an uncommon entity, frequent in women, which is usually associated with other autoimmune pathologies. It is associated with more severe results in liver biochemical tests, especially in GGT and AF levels, as well as with a higher degree of fibrosis.

Ethical statement: the research was carried out in accordance with the Helsinki Declaration of the World Assembly 2013.

Declaration of interests: None.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

https://doi.org/10.1016/j.aohep.2025.101874

High Prevalence of the *FTO* T allele (rs9939609 T>A) and its association with a high risk of Type 2 diabetes or metabolic-associated steatotic liver disease (MASLD) in the Mexican population

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Introduction and Objectives: The *FTO* rs9939609 (T>A) polymorphism has been associated with obesity and metabolic disorders, including type 2 diabetes and MASLD. This study examined the distribution of the *FTO* (T>A) polymorphism in Native and admixed populations and its impact on an admixed Mexican cohort's anthropometric and metabolic profiles.

Materials and Patients: In this cross-sectional study, we evaluated 684 unrelated adults from various regions of West Mexico, categorizing them into Native, Mestizo (admixed), and Mestizo-Caucasian groups based on ancestry. Genotyping for the *FTO* rs9939609 polymorphism was performed using an allele discrimination assay via Real-Time PCR. Given the low prevalence of the A allele among the Mestizo subjects (n=333), the biochemical and anthropometric measurements were adjusted by genotypes AA+AT vs. TT. Anthropometric measurements were assessed using body circumferences and electrical bioimpedance. Metabolic profiles were evaluated by measuring glucose, insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Metabolic abnormalities were defined as follows: hypercholesterolemia (HCL) with TC ≥200 mg/dL, high LDL-c (H-LDL) with LDL-c ≥130 mg/dL, hypoalphalipoproteinemia (HALP) with HDL-c <40 mg/dL, hypertriglyceridemia (HTG) with TG ≥150 mg/dL, hyperglycemia (HGL) with fasting glucose ≥100 mg/dL, hyperinsulinemia (HINS) with insulin >9 μUI/dL, and insulin resistance (IR) with HOMA-IR ≥2.5. Principal Component Analysis (PCA) was used to visualize genetic divergence focusing on the TT genotype. Univariate and multivariate logistic regression analyses were conducted to assess the risk association between the TT genotype and metabolic abnormalities. Statistical analyses were performed using R Studio and SPSS software.

Results: The Huicholes Native population exhibited the highest T allele frequency and TT genotype frequency (94% and 89%), followed by Mestizos from Guadalajara (74% and 56%). In contrast, Mestizo-Caucasians from Cuquio had the lowest T allele frequency (28.1%) and the highest A allele frequency (32.4%) within the Mestizo-Caucasian population of Villa Purificación. Genetic distance analysis using PCA based on *FTO* TT genotype prevalence revealed that the Mestizo-Caucasian population formed a distinct cluster, while Native populations displayed the highest genetic divergence among groups. When analyzing the Mestizos by genotype (AA+AT vs. TT), no significant differences were found in BMI or body fat percentage. However, metabolic profiles of TT genotype carriers showed higher waist-to-height ratios (0.49±0.08 vs. 0.52±0.07, p<0.001), insulin levels (8.8±5.2 vs. 10.8±7.3 μUI/dL, p<0.041), TG (125.8±65.3 vs. 141.8±66.5 mg/dL, p<0.017), and VLDL-c (25.6±14.2 vs. 29.1±14.8 mg/dL, p<0.015). Univariate analysis indicated that the TT genotype was associated with a higher risk of HTG (OR=1.7, 95%CI:1.07-2.73, p<0.027), IR (OR=1.79, 95%CI:1.06-3.07, p<0.031), and HGL (OR=2.77, 95%CI:1.5-5.36, p<0.002) compared to AA+AT genotypes. Multivariate logistic regression further confirmed that TT genotype carriers had a higher risk of HGL compared to AA+AT genotype carriers (OR=2.50, 95%CI:1.213-5.152, p<0.013).

Conclusions: The T allele of the *FTO* (rs9939609 T>A) is more prevalent in Native and Mestizo populations and is associated with higher risks of IR, HTG, and HGL, all of which are linked to type 2 diabetes and MASLD. These results highlight a genetic predisposition to metabolic diseases in populations with significant Amerindian ancestry, particularly in hepatopathogenic environments.

Ethical statement: The Institutional Review Board approved this study, and participants signed a written informed consent form prior to entry.

Declaration of interests: None.

Funding: Supported by the University of Guadalajara, Guadalajara, Mexico – Programa de Fortalecimiento de Institutos, Centros y Laboratorios.

https://doi.org/10.1016/j.aohep.2025.101875

Utility of the CLIF-C AD score to assess readmission in patients with acute decompensation of non-ACLF cirrhosis.

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