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Introduction: In 2011, the Latin-American DILI-Network (LATINDILI-N) set up under the guidance of the Spanish DILI Registry a network of hepatologists to prospectively identify and characterize DILI patients.

Aim: To evaluate the drugs more frequently associated with DILI in LA, clinical phenotype and outcome.

Methods: Demographics, clinical and biochemical parameters of all cases included in the LATINDILI Network were analysed according to the type of liver injury (hepatocellular, Hep; cholestatic, Chol and mixed, Mix).

Results: 404 DILI cases were included. Anti-infectives (31%), musculoskeletal system drugs (13%) and herbal products (9.2%) were the main causative therapeutic drug classes. Mean age was 49 years (female sex, 61%). Hep injury predominated (62%) whereas Chol and Mix patterns were 24% and 15% of cases, respectively. Chol patients (mean age 56y) were older than Hep and Mix cases (47 and 50, $p < 0.05$). Jaundice was more prevalent in Chol and Mix injury than in Hep cases (65% vs 75% vs 58%, respectively, $p = 0.062$), though no differences in hospitalization rates were observed (Hep 43%, Chol and Mix 46%, $p = 0.867$). Of note, 12 cases, mostly Hep, had a positive rechallenge. Positive autoantibodies were more common in Hep cases (25% vs Chol 9.1% vs Mix 19%, $p = 0.010$), with nitrofurantoin/herbal products as the most common causative agents. Hep cases showed a higher risk of severe/fatal injury (18% vs 6.0% and 1.8% in Chol and Mix cases, respectively, $p < 0.001$). The new Hy's law performed as expected, with 14% of ALF/Tx cases. Hep cases more frequently died from liver-related death (3.5%) compared with Chol (1.1%) and Mix (0) cases.

Conclusions: In Latin-American DILI cases with Hep pattern predominated, showing a higher severity and most frequent inadvertent re-exposition. The LATINDILI Network is proving as an important tool for the characterization of DILI singularities in this world region, and improvement of Public Health.

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OP-1 GUT METATRSCRIPTOMICS AND METABOLOMICS REVEAL ASSOCIATION OF CYSTEINE AND PURINE METABOLISMS WITH METABOLIC ASSOCIATED FATTY LIVER DISEASE (MAFLD)

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Background: The gut microbiome represents a niche for biomarkers discovery to risk-stratify MAFLD patients. However, each population may have unique microbiome signatures and studies are needed in Latin America where MAFLD prevalence and severity are high.

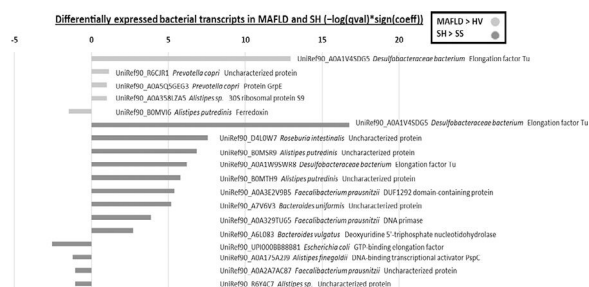
Aims: To identify gut metatranscriptome and metabolome signatures associated with MAFLD and steatohepatitis (SH) in Argentina.

Methods: Stool samples, diet, demographic and clinical data were obtained from 33 biopsy-proven patients (12 simple steatosis -SS- and 21 SH) and 19 healthy volunteers (HV). PNPLA3 rs738409 SNP was genotyped. HPLC, flow injection analysis with MS/MS in tandem and MetaboAnalyst-v4.0 were used for metabolomics. RNA-seq was performed in NovaSeq6000[®]. bioBakery-v1.8 and MaaSLIN2-v1.2.0 were used for data analysis.

Results: BMI was higher in MAFLD patients, particularly in SH ($q = 4.49e-06$). After adjusting for BMI, 89 and 53 gene family clusters were differentially expressed between HV and MAFLD and between SS and SH, respectively ($q < 0.1$). Pathways related to sulfur oxidation, short-chain fatty acid metabolism, purine metabolism and lipopolysaccharide synthesis were enriched in MAFLD patients when compared with HV and in SH when compared with SS, whereas folate synthesis was enriched in SS patients ($q < 0.1$). Gene expression associated with Desulfobacteraceae bacteria harbored most of the functional features of MAFLD patients when compared with HV, and of SH patients within the case group (Figure). The PNPLA3 GG genotype was related to decreased hydrolysis of glycerolipids, high expression of *Clostridium cadaveris* and low expression of Desulfobacteraceae bacteria associated genes ($q < 0.1$).

Higher concentrations of xanthine, implicated in purine metabolism, and of the sulfur amino acid cysteine were detected in the stool of MAFLD patients when compared with HV, and of SH patients within the case group (BMI-adjusted $q < 0.1$).

Conclusion: Cysteine and purine metabolisms are strongly related to MAFLD and SH in Argentinian patients. Cysteine and xanthine could be useful as potential biomarkers.



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