Abstract Highlights

Citation: EMJ Hepatol. 2024;12[1]:46-57. https://doi.org/10.33590/emjhepatol/ZHNU8747.

The following highlights spotlight the latest research in hepatology, featuring studies presented at this year's European Association for the Study of the Liver (EASL) Congress. Ranging from a deep dive into clinical trial eligibility amongst steatotic liver disease patients, to complication predictors after biopsy, these highlights demonstrate the latest cutting edge developments and most talked-about topics in the field today.

Cirrhosis and Bacterial Infections: A Deadly Duo

DECOMPENSATED cirrhosis poses a major public health issue in Latin America, with bacterial infections potentially worsening both morbidity and mortality rates according to a study presented at the 2024 EASL Congress.

The presence of multidrug-resistant (MDR) bacteria complicates the management and prognosis of these infections. This study's objective was to examine the current epidemiology and prognostic significance of MDR bacterial infections in patients with cirrhosis throughout Latin America.

> **The presence of multidrug-resistant (MDR) bacteria complicates the management and prognosis of these infections**

A multicentre prospective study was conducted between 2018–2020, involving 1,274 non-elective hospitalised patients with acutely decompensated cirrhosis. The study spanned 44 centres across seven Latin American countries: Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Paraguay.

Among the 1,274 patients, 524 (41.1%) experienced a total of 619 bacterial infections, with 41.7% of these being culture-positive. Acute-on-chronic liver failure (ACLF) developed in 47.1% of cases, and septic shock occurred in 26.9%. Higher rates of both conditions were observed in Mexico (ACLF: 62.5%; septic shock: 45.7%) and Peru (ACLF: 53.3%; septic shock: 37.8%), with respective p-values of 0.042 and <0.001. Gram-negative bacteria were the most commonly isolated (67.8%; *Escherichia coli*: 34.8%). MDR bacteria were found in 29.4% of culture-positive infections, with higher rates in Mexico (41.7%), Argentina (35.1%), and Peru (33.3%). Extended spectrum beta-lactamases (ESBL)-producing *Escherichia coli* was the most prevalent MDR strain (27.6%). There were notable differences in MDR bacteria types among countries. ESBL- and Amp-C producing *Enterobacteriaceae* were most common in Mexico (36.1%), followed by Colombia and Paraguay (25% each), Peru (22.2%), Chile (18.2%), Argentina (16.2%), and Brazil (12.1%). Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* were mainly found in Argentina (5.4% and 2.7%, respectively). Carbapenem-resistant *Klebsiella pneumoniae* was prevalent in Argentina (5.4%), and Carbapenem-resistant *Pseudomonas* was prevalent in Brazil (2%). MDR infections were more frequently linked to septic shock (40%) and ACLF (57.4%). The 28-day mortality rate for infected patients was 29.4%, with a higher rate in Mexico (47.1%; p<0.001). This rate increased to 47.8% for patients infected with MDR, with no significant difference between countries.

The study concludes that MDR bacterial infections are common and linked to poor outcomes in patients with decompensated cirrhosis in Latin America. The predominant resistant strains differ significantly between countries.

The Key to Tailored Hepatocellular Carcinoma Treatment

THE VESSELS that encapsulate tumour (VETC) phenotype is predictive of the effectiveness of anti-angiogenic drugs in patients with advanced hepatocellular carcinoma (HCC).

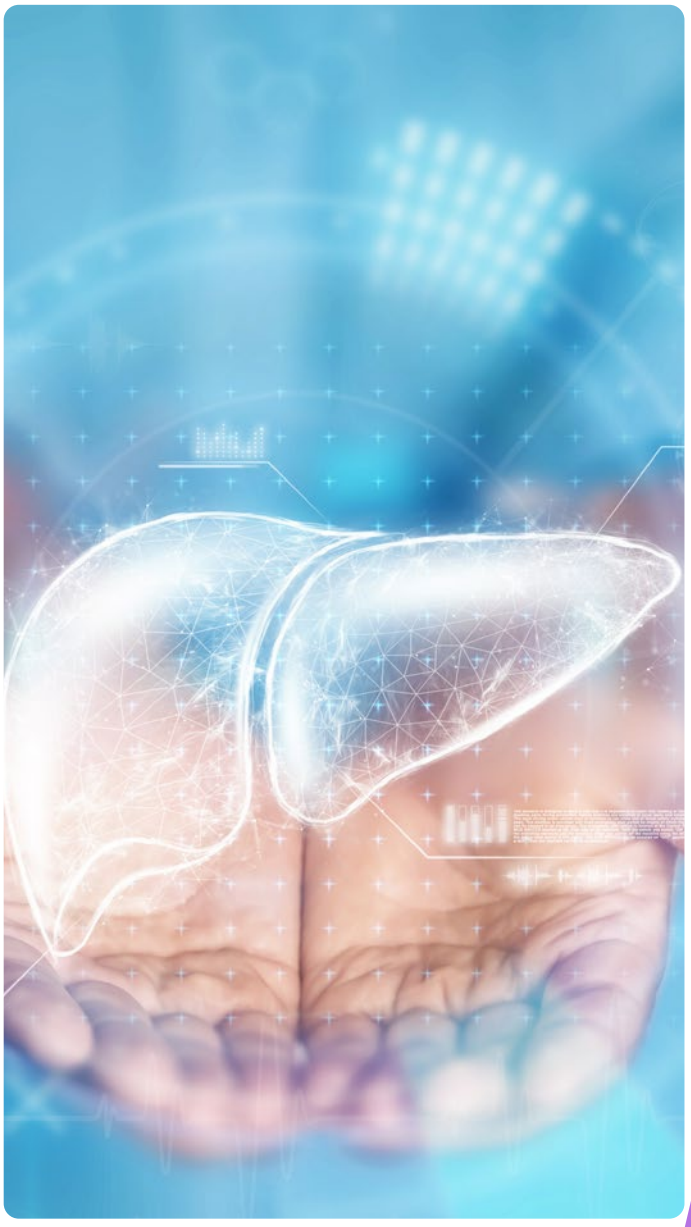
VETC, a distinctive vascular feature associated with a worse prognosis for patients with HCC, has previously shown promise in predicting responses to chemoembolisation and sorafenib. A new study, presented at the EASL Congress 2024, aimed to assess VETC's predictive value for patients undergoing systemic treatment for advanced HCC.

The research was conducted utilising a retrospective, mono-institutional analysis of 81 patients with advanced HCC (the study cohort), which was later validated in an external, retrospective series of 83 patients (the validation cohort). Each patient's VETC status was determined from liver biopsy samples taken just before initiating systemic treatment. Results from both the study and validation cohorts indicated that patients

> **Identifying patients who are VETC-positive can guide clinicians in selecting the most effective systemic therapies**

with the positive VETC phenotype exhibited a significantly better response to anti-angiogenic therapies, including tyrosine kinase inhibitors (TKI) and bevacizumab. In the combined total of 163 patients, those with the positive VETC phenotype treated with TKI or bevacizumab demonstrated a notably longer overall survival (OS) compared to those receiving immune checkpoint inhibitors (ICI). Specifically, the OS for patients treated with TKI and/or bevacizumab was 19.2 months versus 10.2 months for those treated with ICIs (hazard ratio: 0.4; 95% CI: 0.24–0.70; P=0.0012). Similar trends were observed for patients treated with sorafenib versus ICIs, with OS of 16.3 months compared to 8.7 months, respectively (hazard ratio: 0.4; 95% CI: 0.25–0.93; P=0.03). Conversely, no significant benefit from anti-angiogenic drugs was observed in patients negative for the VETC phenotype.

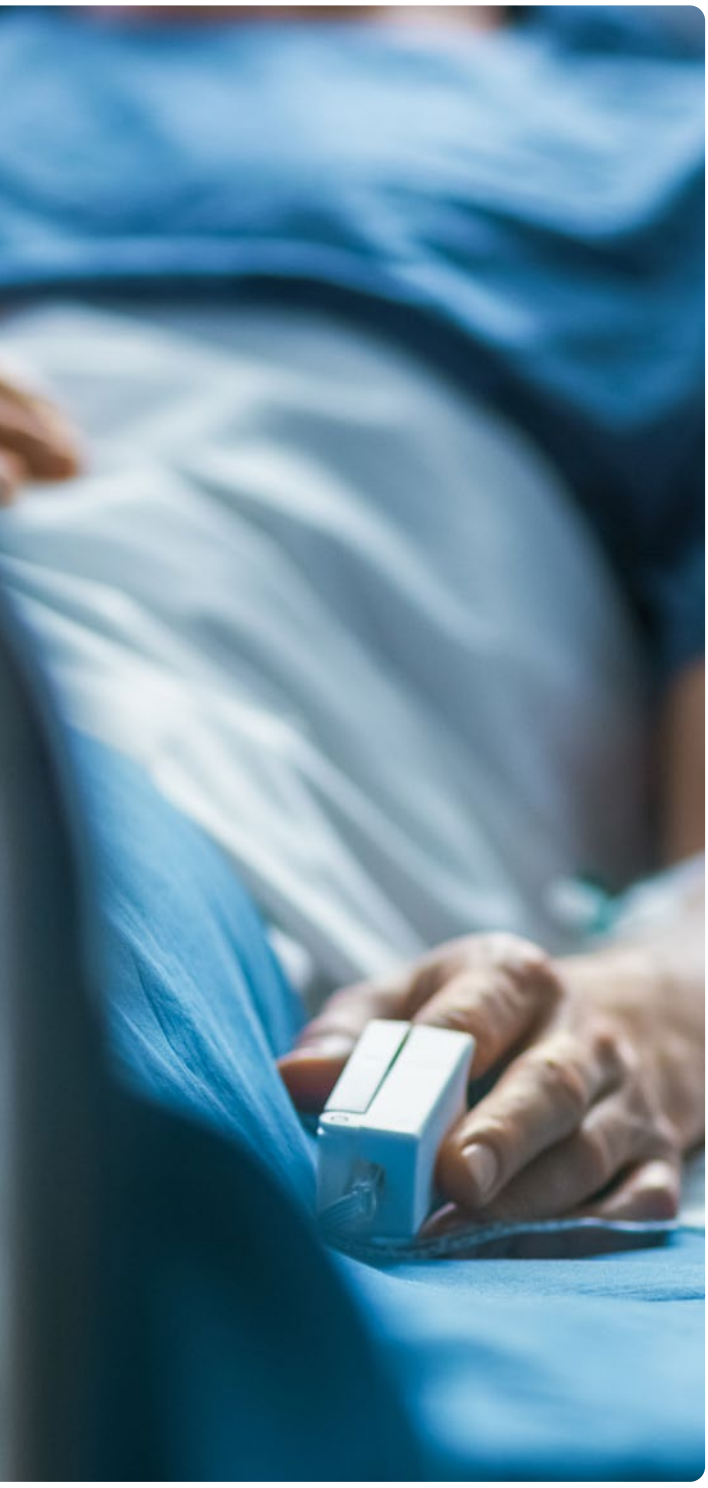
The findings underscore the importance of the VETC phenotype as a predictive marker for treatment response in patients with advanced HCC. Identifying patients who are VETC-positive can guide clinicians in selecting the most effective systemic therapies, potentially improving patient outcomes. This study highlights the potential for tailored treatment strategies based on individual tumour characteristics, marking a significant step forward in the personalised treatment of HCC.



Patients with the positive VETC phenotype exhibited a significantly better response to anti-angiogenic therapies

Inadequate Organ Allocation in Acute-on-Chronic Liver Failure

LIVER transplantation (LT) improves survival of patients with acute-on-chronic liver failure (ACLF), which is characterised by a high risk of short-term mortality. However, current worldwide organ allocation systems are primarily based on the model for end-stage liver disease (MELD) scores, or its variations.



They do not consider risk of death due to failure of extrahepatic organs. Because of this, many patients die on the waiting list.

A study presented at the 2024 EASL Congress aimed to assess the clinical outcomes of patients with ACLF Grade 2 or 3 undergoing LT in the current allocation systems. Among 823 patients (80% of the overall study cohort), 376 patients with ACLF Grade 2 or 3 were listed for LT (Group 1), 313 patients with ACLF Grade 0 or 1 and MELD>20 were listed for LT (Group 2), and 134 patients with ACLF Grade 2 or 3 were referred to the waiting list evaluation but not listed (Group 3). Patients were recruited from 62 liver transplant centres across Asia, Europe, Latin America, and North America between July 2021–October 2023. ACLF was defined by the EASL-Chronic Liver Failure (CLIF) criteria. The rate of delisting/death was presented according to ACLF Grade and MELD-sodium at study inclusion, and by geographical distribution.

> **Delisting/death on the waiting list occurred in 28% of patients in Group 1, compared with 16% in Group 2**

Delisting/death on the waiting list occurred in 28% of patients in Group 1, compared with 16% in Group 2 (P<0.001); while 85% of non-listed patients (Group 3) died. For Groups 1 and 2, 68% and 79% received LT (P<0.001), respectively, and time to death/delisting was 38.5 days (interquartile range [IQR]: 13–85), while time to LT was 14 days (IQR: 5–47; P<0.001). Significant differences in death/delisting on the waiting list were observed across continents (Asia: 13%; Europe: 18%; Latin America: 40%; North America: 20%), which were associated with significantly greater time (in days) on the waiting list for Latin America, compared to Asia (47.5 [19–68]); Europe (10 [4–30]); Latin America (50 [10–79]); and North America (10 [4–22]); P<0.001. The higher rate of delisting/death for patients with ACLF Grade 2 or 3 was observed across all MELD-sodium ranges (<25 [50%], 25–29 [35%], 30–34 [22%], >35 [29%]) compared to patients without ACLF 2 or 3 (<25 [12%], 25–29 [19%], 30–34 [15%], >35 [17%]; P<0.001).

These findings suggest that current worldwide allocation systems are inadequate for patients with ACLF Grade 2 or 3, leading to an excess of waiting list mortality. The authors strongly argue for a change in the organ allocation system for patients with ACLF, given the efficacy of LT.

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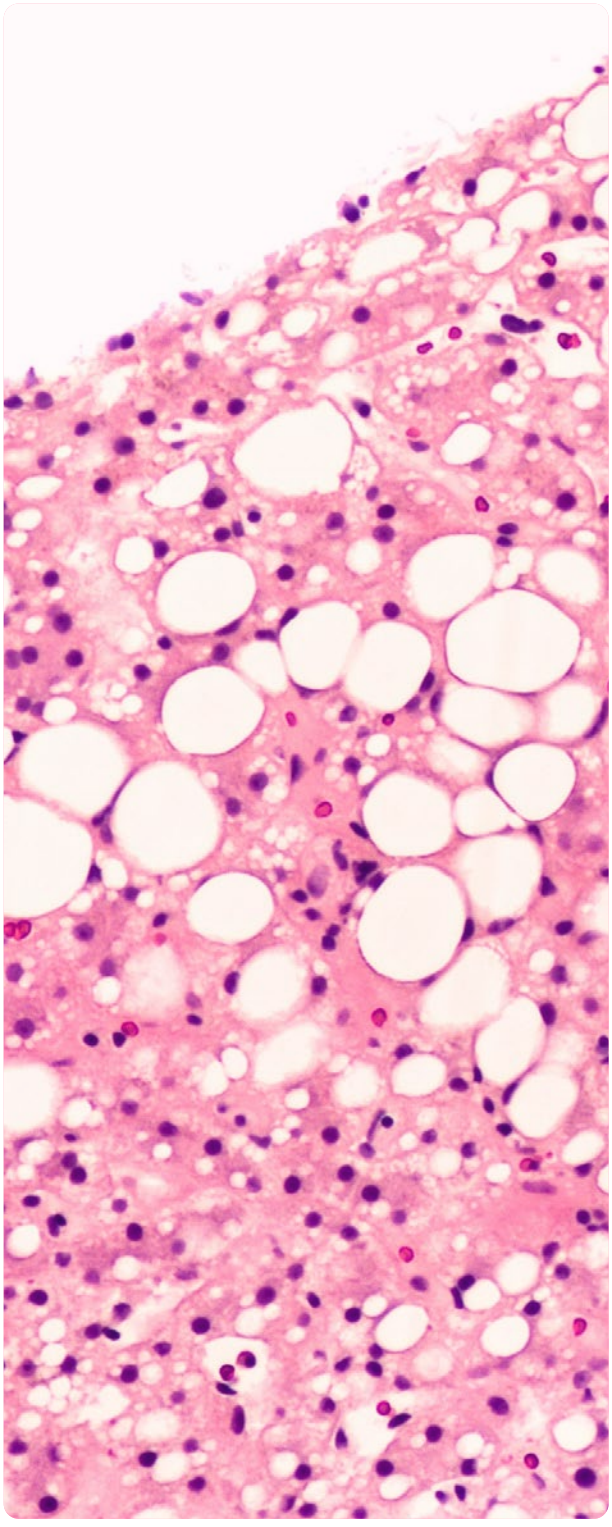
Steatotic Liver Disease Severity Predicts Mortality and Cardiovascular Disease

NEW findings presented at EASL 2024 showed that the severity of steatotic liver disease (SLD) is associated with increased all-cause mortality and cardiovascular disease (CVD) events, most pronounced in individuals aged 50+ years.

SLD, the most common chronic liver disease worldwide, has been linked to heightened mortality in patients. A recent longitudinal cohort study conducted as part of the Busselton Health Study in Western Australia examined the relationship between hepatic steatosis severity and subsequent mortality and CVD events.



> **Analysis revealed a nonlinear association between FLI and all-cause mortality, evident in both sexes**

The study included 4,382 participants (56% female) with a mean age of 51 years. Participants were followed for up to 20 years, from the survey dates in 1994–1995 until death or the end of the study period in 2014. The study utilized the fatty liver index (FLI) to diagnose SLD, calculated based on body mass index (BMI), waist circumference, serum triglycerides, and gamma-glutamyl transferase levels. Cox proportional hazards models explored the relationships between FLI and A) all-cause mortality, B) CVD mortality, and C) CVD-related events. Nonlinear relationships between FLI and outcomes were analyzed using restricted cubic splines.

The study underscores the importance of monitoring hepatic steatosis severity in older adults to mitigate mortality and long-term health risks

Over the follow-up period, there were 974 deaths (22.2%), 408 CVD-related deaths (9.3%), and 1,018 CVD events (23.2%). Analysis revealed a nonlinear association between FLI and all-cause mortality, evident in both sexes. After adjusting for multiple variables, participants in the lowest FLI quintile had a 28% lower risk of all-cause mortality compared to those in the highest quintile (hazard ratio [HR]: 0.72; 95% CI: 0.55–0.94). CVD deaths and events initially increased with higher FLI in Model A, though this association weakened after further adjustments in Models B and C. No significant association was observed between FLI and mortality or CVD outcome in participants younger than 50 years. Conversely, in individuals aged 50+ years, there was a notable increase in all-cause mortality in the third and fourth FLI quintiles (HR: 1.30 and HR: 1.26, respectively) and an increased risk of CVD-related events in the third quintile (HR: 1.29).

The study underscores the importance of monitoring hepatic steatosis severity in older adults to mitigate mortality and long-term health risks. Further research is warranted to explore interventions that could reduce these risks.

Early Pain Predicts Complications after Percutaneous Liver Biopsy

MONITORING of patients after an ultrasound-guided percutaneous liver biopsy (US-PLB) can be safely discontinued if no pain develops within the first hour post-procedure, according to findings presented at EASL 2024.

This research, conducted in three tertiary centres in Lombardia, Italy, analysed complications associated with the procedure and identified pain within 1 hour as the sole significant predictor of major issues.

The study retrospectively assessed 1,838 patients who underwent either parenchymal or lesion-targeted PLB between January 2018–December 2023. The cohort had an average age of 55.1 years, with 46.1% females and a mean body mass index of 25.1 kg/m^2. Notably, 13.7% of the biopsies were performed on patients with previous liver transplants. The patients had a mean platelet count of 209.7±80.74 ×10^3/mm^3 and a mean Prothrombin Time International Normalized Ratio value of 1.04±0.12. Needle aspiration was the predominant technique used (92%), mostly employing 18G (59.5%) and 16G (22.1%) needles. The study also considered various clinical, biochemical, and procedural features, including the use of anticoagulant/antiplatelet therapy, which was relatively rare (4.2%/16.2%).

> **Future guidelines could consider these results to streamline post-procedure care**

Over an average observation period of 5.4±2.0 hours, pain was reported in 7.4% of patients. Major complications were infrequent, occurring in only 1.4% of cases, with transient hypotension being the most common (0.8%). Bleeding events were observed in 0.5% of patients, typically within the first hour. Hospitalisation was required in 0.7% of cases, primarily for managing bleeding, although most cases resolved spontaneously. Pain, especially within the first hour post-procedure, was significantly associated with major complications. However, no other baseline or procedural variables, such as heart rate, mean arterial pressure, or haemoglobin values, were linked to severe outcomes.

The findings suggest that if pain does not develop within 1 hour after a US-PLB, patient monitoring can be safely discontinued, reducing the need for prolonged hospital stays and repeated blood counts. Future guidelines could consider these results to streamline post-procedure care, emphasising the importance of immediate pain assessment to identify patients at risk for complications. Further studies could help refine these recommendations to improve patient management and resource allocation in clinical settings.

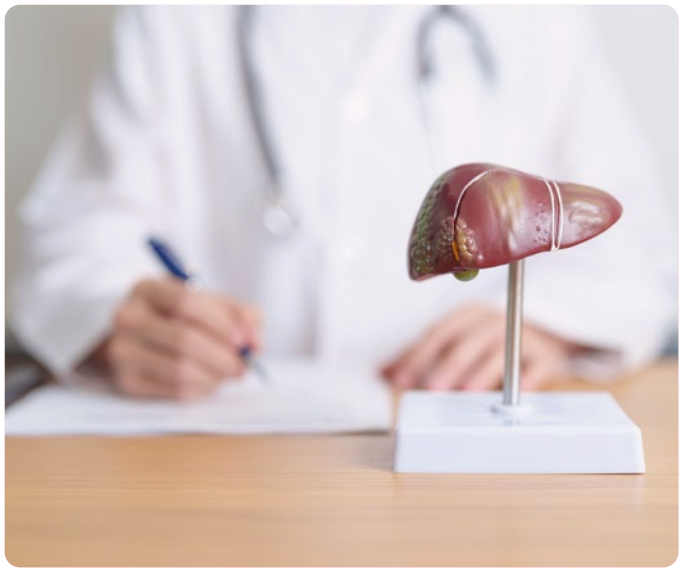
Machine Learning Advances Liver Fibrosis Prediction

METABOLIC dysfunction-associated steatotic liver disease (MASLD) impacts around 30% of the global adult population.

It significantly increases the risk of disease progression, especially in those with moderate to advanced fibrosis (Stage 2–3). Following the FDA's approval of resmetirom for treating metabolic dysfunction-associated steatohepatitis (MASH) at these fibrosis stages, a surrogate marker is needed to enhance the selection process for liver biopsy candidates. The ALADDIN study, presented at the 2024 EASL Congress, has introduced an innovative web-based calculator, employing machine learning, to estimate the likelihood of Stage ≥2 fibrosis in patients with MASLD using routine laboratory parameters, both with and without vibration-controlled transient elastography (VCTE).

A total of 3,708 patients from six global centres with biopsy-confirmed MASLD were split evenly into derivation and internal validation cohorts. Additionally, 1,289 patients from nine centres were included for external validation. The ALADDIN models were created to assess moderate fibrosis (Stage ≥F2).

In external validation, the VCTE model achieved an area under the curve (AUC) of 0.800 (95% CI: 0.773–0.827), significantly surpassing the FAST (AUC: 0.707; 95% CI: 0.674–0.739; p<0.0001) and Agile-3 (AUC: 0.764; 95% CI: 0.735–0.793; p=0.001) models. The model using only routine laboratory parameters, without VCTE, achieved an AUC of 0.757 (95% CI: 0.730–0.783), performing comparably to FAST and Agile-3. Additionally, the VCTE model



demonstrated superior results in decision curve analysis, calibration, and classification accuracy using a dual cut-off approach, and outperformed existing models in predicting moderate fibrosis.

The researchers conclude that the ALADDIN study, through an international consortium, has successfully developed and externally validated machine learning models with high accuracy for predicting moderate fibrosis. The authors' VCTE model has shown statistical superiority, while the model using routine laboratory parameters without VCTE has demonstrated comparable performance to traditional models such as Agile-3 and FAST. These algorithms will aid in the targeted selection of patients for liver biopsy, aligning with the recent FDA approval of resmetirom treatment.

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Classification of Steatotic Liver Disease and Clinical Trial Eligibility

IN NEW research presented at EASL Congress 2024, a team based in Denmark has found that the highly dynamic classification of steatotic liver disease (SLD) impacts eligibility for clinical trials and subclass-specific interventions.

SLD includes several subclasses including metabolic-dysfunction associated steatotic liver disease (MASLD), metabolic and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD). Classification is based on the presences of hepatic steatosis, cardiometabolic risk factors (CMRF) and current alcohol use. However, these criteria may be sensitive to spontaneous changes in lifestyle, making the SLD diagnoses dynamic.

> The team concluded that SLD and its subclassification are highly dynamic

The team conducted a prospective cohort study among individuals from the general population and individuals at risk of SLD (obesity, Type 2 diabetes or, a history of excessive alcohol use). Presence of steatosis was defined as controlled attenuation parameter (CAP) >275 dB/m and presence of advanced fibrosis as transient elastography (TE) >12 kPa. Subclassification of SLD was based on the presence of at least one CMRF and self-reported current alcohol use (MASLD <20/30 (female/male) g/day; MetALD 20–50 / 30–60 (female/male) g/day; ALD >50/60 (female/male) g/day). The SLD classification was assessed at baseline and after 2 years follow-up. In total, 994 patients were included (mean age: 57 years; 64% male). Of this group, 54 had advanced fibrosis.

At baseline, 551 (55%) patients had SLD (CAP >275 dB/m and/or TE >12 kPa) while 443 (45%) did not have SLD. Among the patients with SLD, 337 (61%) met the criteria for MASLD, 133 (24%) for MetALD, 79 (14%) for ALD, and two (0.4%) were classified as cryptogenic SLD. Median time between baseline and follow up visit was 25 months (IQR: 25–31). At follow-up, 382 (38%) of the 994 participants were reclassified. Among the 443 participants that did not have SLD at baseline, 113 (26%) met the criteria for SLD at follow-up. Among the 551 participants classified as having SLD at baseline, 269 (49%) were reclassified, of which 186 (69%) did not meet the criteria for SLD at follow up and 83 (31%) changed SLD subclass. For the 382 participants reclassified, 299 (78%) were due to changes in steatosis, 83 (22%) due to changes in alcohol use, and zero due to changes in presences of CMRFs.

The team concluded that SLD and its subclassification are highly dynamic, especially driven by changes in alcohol use and steatosis. This in turn affects eligibility for clinical trials, and the team reported that patients with SLD should be reassessed regularly to ensure correct subclass diagnosis and management.