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BIOMARKER STRATEGIES FOR SIGNIFICANT AND ADVANCED LIVER DISEASE AT THE PRIMARY AND SECONDARY HEALTH CARE LEVELS

Dr Quetin Anstee, UK

Metabolic dysfunction-associated steatotic liver disease (MASLD), is a chronic, asymptomatic, progressive condition affecting about 38% of the global population. It is characterized by substantial interpatient variability in disease severity and outcomes. MASLD is caused by a build-up of fat in the liver and includes a range of disease states, from isolated lipid accumulation or steatosis (metabolic dysfunction-associated steatotic liver, MASL) to its active inflammatory form, metabolic dysfunction-associated steatohepatitis (MASH).

Some points should be noted while setting the goal for diagnostic tests for advanced liver disease at the primary and secondary health care levels, such as:

- In primary care, there is a low prevalence of advanced (F3-4) diseases. So, severe cases should be excluded.
- On the other hand, the prevalence of advanced disease is increasing in secondary care.
- Hence, it is important to identify patients with ≥F2 for therapy and monitoring.
- Patients with F(3)4 should be identified for intensive therapy and surveillance.

Diagnosis and identification of the patients at different stages of the disease can be done with the help of biomarkers, which can be categorized into two groups, i.e., indirect and direct serum biomarkers and imaging biomarkers.

For example, in the enhanced liver fibrosis (ELF) test in MASLD, three direct markers of fibrosis are combined, such as procollagen III N-terminal peptide, hyaluronic acid and tissue inhibitor of metaproteinase 1 (TIMP1). Some other key biomarker strategies that can help in diagnosing are:

- At present, the staged application of available 'simple panel' biomarkers, such as NFS, and FIB-4 followed by noninvasive tests, such as fibroscan, ELF and MR elastography helps to rule out cases that are unlikely to have significant disease.
- The biomarker field is developing rapidly, therefore, the objective assessment of biomarker performance for specific predefined context of use is important to understand their utility. There is an urgent need for more sensitive and specific, independently validated, and qualified biomarkers for use in MAFLD.
- Promising experimental biomarkers, include direct biomarkers related to extracellular matrix turnover, metabolomic profiling and miRNAs. However, they all require further validation.

HCC STAGING: WHAT IS NEW IN INASL GUIDELINES (2023)

Dr Subrat K Acharya, Bhubaneswar

INASL modification provides improvement over the previous Barcelona-Clinic Liver Cancer (BCLC) staging in terms of:

- ALBI (Albumin-Bilirubin) score: It is the further clinical assessment of liver reserve which had documented to influence outcome (prognostication to therapy)—transarterial radioembolization (TARE) for BCLC-A (option) - single lesion >5 cm.
- Categorizing BCLC-B: into three groups (B1, B2, B3) based on results of therapeutic response- included expanded criteria for transplant in B1 (more burden than A).
- Defined treatment stage migration and UTP: to allocate further treatment with a possibility of further benefit.
- Down staging in BCLC-B an option: end point successful - Transplant.
- Systemic therapy: for BCLC B3/ALL BCLC-C - 1st line/2nd line/3rd line.

MANAGEMENT OF LEAN PATIENTS WITH NAFLD (MASLD)

Dr Arka De, Chandigarh

- Lean nonalcoholic fatty liver disease (NAFLD) can progress to clinically significant liver disease without becoming obese.

- Lean NAFLD patients have an improper lifestyle with more sedentary hours and higher dietary intake of free sugars and fructose. Exercise improves insulin resistance in these patients. A healthy diet with curtailed free sugars is advised. It is difficult to recommend specific calorie restrictions in this group due to the scarcity of data.
- Weight loss is the central pillar of NAFLD management in general, however, lean patients have normal body mass index (BMI). They need a lesser degree of weight loss to attain NAFLD remission compared to obese patients.
- Indications for pharmacotherapy in lean NAFLD (MASLD) is likely similar to non-lean ones. Drugs like vitamin E, pioglitazone and saroglitazar can be used.

OUTCOMES AND FOLLOW-UP AFTER HEPATITIS C ERADICATION WITH DAAs

Dr Fransesco Paolo Russo, Italy

EASL Guidelines advise hepatitis C virus (HCV) RNA in PW1bs or men who have sex with men with ongoing risk behavior (A1). Current direct-acting antivirals (DAAs)-based regimens are highly effective and safe. Early treatment halt the progression to cirrhosis and allow for a decrease in health care costs. HCV eradication can prevent the complications of liver cirrhosis and extrahepatic manifestations. Noninvasive tests can predict the onset of complications. Ideal follow-up after sustained virologic response in patients with advanced liver disease and cirrhosis is still debated.

RIFAXIMIN ALONE VS. COMBINATION WITH NORFLOXACIN FOR SECONDARY PROPHYLAXIS OF SPONTANEOUS BACTERIAL PERITONITIS WITH HEPATIC ENCEPHALOPATHY: RANDOMIZED CONTROLLED TRIAL

Dr Tarana Gupta, Rohtak

Gut dysbiosis is the emerging concept that has been linked with complications of cirrhosis, such as spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HE). These events portend a poor prognosis for the patients.

Several studies have shown that rifaximin can reduce the oralisation of the gut microbiome and mucin degradation species in the gut. This helps in improving the gut microenvironment by reducing systemic inflammation caused by neutrophils and downregulation of TLR4 expression. On the other hand, due to the emergence of multidrug-resistant organism (MDRO), gut-selective antibiotics with minimal systemic effects are needed.

Therefore, in this study, the effect of rifaximin vs. a combination of rifaximin with norfloxacin for secondary prophylaxis of patients of cirrhosis presenting with SBP and HE was evaluated. The primary outcomes of the study included recurrent episodes of SBP and HE at 6-month and 28-day, 90-day and 6-month mortality. Secondary outcomes included the number of rehospitalizations, new episodes of upper gastrointestinal (UGI) bleed, acute kidney injury and child-turcotte-pugh (CTP) and model for end-stage liver disease (MELD) over 6 months.

The key results and conclusion drawn from this study were: The mortality rates at 28 days, 90 days, and 6 months were comparable between the two groups. Rehospitalization was higher in the combination group. Patients of cirrhosis with SBP and HE have a high in-hospital mortality rate of up to 40%. Both the groups showed no significant difference in the recurrence rate of SBP and HE. Rifaximin has similar efficacy as a combination of rifaximin and norfloxacin for secondary prophylaxis of patients with SBP and HE.

PATIENTS WITH ACLF SHOULD RECEIVE PRIORITY ON THE LIVER TRANSPLANT WAITING LIST

Dr Sanjiv Saigal, New Delhi

There is a lack of specific drug for a comprehensive medical treatment for acute-on-chronic liver failure (ACLF). Moreover, the novel treatment options are in premature stage. There is no cure for ACLF on the background of high short-term mortality, making liver transplantation (LT) desirable in this group. Balance between the dynamics of ACLF and the allocation of the organs has not been found in the actual clinical practice. Timely evaluation and admission to the LT waiting list and prioritization of patients with ACLF within the narrow window of opportunity improves outcome and reduces futility. Careful selection of patients and timely LT saves precious life. Hence, ACLF patients should receive priority on LT wait list.

DIGITAL HEALTH INTERVENTIONS IN THE MANAGEMENT OF MASLD

Prof Jeffrey V Lazarus, Spain

Globally, the use of digital health interventions (DHIs) is expanding, along with growing scientific evidence of their effectiveness to help in caring for people with or at risk of liver diseases, such as metabolic dysfunction-associated liver disease and MASH. However, this

shift in caregiving is not uniform among all health care providers.

For instance, a survey showed that despite a high level of familiarity with DHIs among physicians, most of them do not recommend these tools for patient care management. In the survey, it was seen that out of 295 participant physicians, 56% of physicians never recommend DHIs to their patients. It was also seen that although, 91% of the physicians understood the functioning of DHIs, only 25% of them received DHI education/training. Additionally, 51% of the participant commented that they will recommend DHIs to their patients if they have evidence of their utility.

When we look at artificial intelligence (AI), it has several applications in MASLD, or liver disease in general, such as: Potential to augment the exploitation of massive multiple parametric data; Creating models that enable machines to learn from data, recognize patterns, make decisions and solve complex problems; Enhance accuracy compared to traditional methods; Personalized clinical decisions for patients; Streamline patient care.

However, there are some challenges in applying AI, such as: Need for good quality datasets for algorithm development; Data availability: address the need for large and diverse datasets for training reliable AI models; A flawed algorithm can cause harm. Hence, systemic amendments, extensive simulation and validation are required; Need for randomized controlled trials to compare AI-based approaches with non-AI-based approaches.

NONINVASIVE TESTS FOR HEPATIC FIBROSIS (NITS)

Dr Meena B Bansal, New York

- For screening high risk-populations FIB-1 is the First-line of Defense. Sequential or combination testing can be done to address the Grey Zone.
- For identification of at-risk NASH, use the FibroScan-AST (FAST), MRI-aspartate aminotransferase (MAST), MR elastography combined with FIB-4 (MEFIB) or Agile 3t (F3 fibrosis).
- To assess response to Resmetirom - check for a 30% reduction in MRI proton density fat fraction (MRI-PDFF), Pro-C3/C3M ratio and vibration-controlled transient elastography (VCTE). For evaluating progression to cirrhosis check for VCTE >16.6 kPa, ELF >9.75.
- For predicting MALO check if ELF >11.27, VCTE >30.7 kPa, cT1 >875 ms, MAST >0.24, ME-FIB + (MRE ≥3.3 and FIB-4 ≥1.6). Longitudinal changes over time are more important than a single cross-sectional view. Use FIB-4, VCTE and MR elastography.

DIAGNOSTIC AND PROGNOSTIC ROLE OF BIOMARKERS IN PATIENTS WITH CIRRHOSIS AND AKI

Dr Paolo Angeli, Italy

Patients with cirrhosis have a high prevalence of renal dysfunction. The susceptibility to renal dysfunction is due to both the severe splanchnic arterial vasodilation and the systemic inflammation observed in these patients. An accurate assessment of renal function is recommended in all patients with cirrhosis.

Meanwhile, despite its limitations, serum creatinine is still the most used biomarker for the estimation of glomerular filtration rate (GFR) and the assessment of acute kidney injury (AKI) in patients with cirrhosis. New renal biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), IL-18, TIMP-2, etc. can improve the assessment of GFR and the prognostic stratification in these patients.

AKI is a life-threatening complication and needs timely management. AKI can be further categorized into four types in patients with cirrhosis and ascites, including: Acute tubular necrosis (ATN-AKI) - 41.7%.; Prerenal failure (Prerenal-AKI) - 38%; Hepatorenal syndrome (HRS-AKI) - 20%; Post-renal failure (Post-renal AKI) - 0.3%.

The differential diagnosis between HRS and ATN is tricky in clinical practice. The nature of HRS can be predominantly functional or associated with some degree of parenchymal damage in a continuum spectrum of kidney injury from prerenal-AKI to ATN-AKI. New biomarkers of kidney injury, such as neutrophil gelatinase-associated lipocalin and IL-18, represent useful tools in refining the discrimination between HRS and ATN.

A study has shown that the sensitivity and specificity of IL-18 and NGAL for the diagnosis of ATN were 0.8, 0.86 and 0.88, 0.82, respectively.

Due to its higher sensitivity, NGAL is seen as a promising tool in phenotyping AKI and predicting its evolution in patients with cirrhosis.

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