**Massimo Colombo**

Past Professor of Gastroenterology at the University of Milan, Italy; and Director of the Department of Medical Specialties, Gastroenterology and Hepatology Policlinic Hospital Milan, Italy

**Citation:** EMJ Hepatol. 2025;13[1]:82-85. https://doi.org/10.33590/emjhepatol/SKDT5302

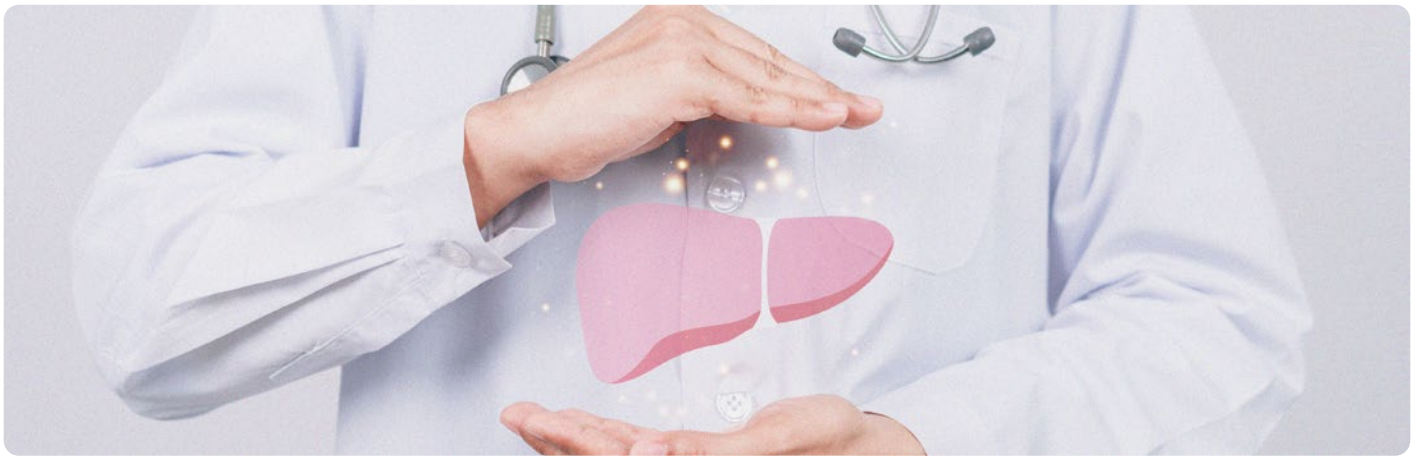
**To break the ice with bench work, I started practising techniques of immunohistopathology, an approach that helped me gain confidence with autoimmune liver diseases**

**Q1 What inspired you to transition from specialising in gastroenterology to focusing on hepatology, and how did your time as a researcher at Mount Sinai Hospital shape this shift in your career?**

The incipit of my academic career was navigating liver diseases in the years subsequent to the discovery of the aetiologic agent of hepatitis B and a kind of fatal attraction for the elusive hepatitis non A, non B, later reclassified as hepatitis C. In the 90s, I focused on liver cancer as it was a relevant cause of liver morbidity and mortality in my country. In an era devoid of clinically impactful non-invasive techniques for the diagnosis and prognostication of liver diseases, I felt it necessary to refine my professional skills through high-profile training in liver histopathology due to the fact that liver biopsy had been emerging as the ultimate guidance for the management of liver patients. With this in mind, I joined the Department of Pathology at Mount Sinai Hospital in New York, USA, confident that the group led by Hans Popper, one of the founders of modern hepatology, could represent a unique opportunity for feeding both my clinical and scientific curiosity. To break the ice with bench work, I started practising techniques of immunohistopathology, employed in the routine detection of serum tissue antibodies, an approach that helped me gain confidence with autoimmune liver diseases, which at that time was an unrecognised risk factor of liver morbidity in my country. The next steps were developing research programmes in immunopathology of the liver, that, once back home, led me and my coworkers to establish productive collaborations with colleagues in many parts of the world, including the National Institute of Health (NIH), Pasteur Institute in Paris, BCLC group in Barcelona, and with the Nobel Prize awardee Michael Houghton, Alberta, Canada, the discoverer of the aetiologic agent of non A, non B hepatitis.

**Q2 Having previously been appointed as Editor-in-Chief of the Journal of Hepatology, the official journal of the European Association for the Study of the Liver (EASL), and lately as the Chairman of the EASL International Liver Foundation, what actions did you take in your role to shape the organisation's approach to liver disease research, and how did the goals of EASL influence the advancement of liver disease research on a larger scale?**

To gain readership among clinicians, the journal embraced the policy of prioritising the publication of robust, well-structured multicentre clinical studies that, together with the periodic release of updated evidence-based recommendations (Clinical Practice Guidelines) for the management of liver diseases, significantly contributed to expanding the outreach of the journal beyond the European borders. No surprise, the impact factor of the journal almost doubled at the end of our term, thus paving the way for the next



editors to further increase it up to the current amazing score of 26.8.

The EASL Foundation was activated in 2017 with the aim of flanking EASL in promoting both educational and philanthropic activities while enhancing fundraising to promote science. One major engagement was promoting research and disseminating educational programmes in Eastern Europe and the Middle East and North Africa (MENA), where European hepatology, for many reasons, undisputedly holds a relevant credit. A European registry of the national interventions and programmes of management of MASLD was generated by the Vice President of the Foundation, Jeff Lazarus, in Barcelona, which highlighted the lack of national programmes and preparedness to fight the impact of MAFLD in terms of public health, therefore emphasising the need for funding campaigns of awareness among the healthcare institutional providers in Europe. One major achievement was the establishment of an EASL Centre of Excellence for Viral Hepatitis Elimination in Tbilisi, Georgia, that was meant to flank the local authorities partnering with the CDC in Atlanta in what later turned out to be a very successful programme of hepatitis C elimination, as recently outlined by the WHO. In collaboration with the University of Tashkent, Uzbekistan, the Foundation sponsored a programme for the analysis of morbidity and mortality of the hepatitis delta virus (HDV) in an endemic area for hepatitis B infection that was carried out under the guidance of Mario Rizzetto, University of Torino, Italy, the discoverer of HDV. The Foundation was also active in other fields like funding the educational activity for physician assistants engaged in the rehabilitation programmes of people who inject drugs and in the release of bursaries to sustain educational and research programmes in Europe, with special attention to liver regeneration.

**Q3 How do you think immune checkpoint inhibitors (ICI) like atezolizumab and bevacizumab enhance the body's immune response to target and fight cancer cells in advanced hepatocellular carcinoma (HCC), and what are your thoughts on the future potential of combining ICIs with other therapies, such as targeted therapies, to further improve treatment efficacy in hepatology?**

For almost 15 years, systemic treatment of advanced HCC relied on monotherapy with oral tyrosine kinase inhibitors (TKI), whose effectiveness and tolerability turned out to be unsatisfactory. The advent of ICIs-based combination regimens heralded a new dawn in the pharmacological treatment of HCC as it proved to increase the survival of patients with such a lethal condition as advanced HCC. This was the case for four ICIs-based regimens that have been validated as effective first-line therapies for patients with advanced HCC which develops in compensated liver (Child-Pugh A status): the anti-PD-L1 atezolizumab plus the anti-VEGF bevacizumab and the anti-PD-L1 durvalumab plus the anti-CTL4 tremelimumab, both recommended by the FDA and EMA; the anti-PD-1 camrelizumab plus the TKI anti-VEGFr2 rivoceranib; and the biosimilar anti-PD-1 sintilimab plus the anti-VEGF bevacizumab. More recently, in a preplanned interim analysis of a Phase III RCT, the combination of anti-PD1 nivolumab plus the anti-PD-L1 ipilimumab was shown to provide more survival benefits than monotherapy with the TKI lenvatinib or sorafenib. Emerging data suggest that ICI-based regimens are effective and well-tolerated even in certain groups of patients with HCC who have more impaired liver function, such as those with Child-Pugh B status. Additionally, ICI combinations are being explored beyond first-line treatment for advanced HCC. These

investigations include their use in second-line therapy, as part of pretransplant downstaging for HCC exceeding the Milan criteria, and as adjuvant therapy following hepatic resection or tumour ablation.

**Q4 In terms of emerging therapies, how do you see CAR-T cell therapies offering new potential angles for the treatment of hepatocellular carcinoma (HCC)?**

No doubt, CAR-T cell therapy, together with therapeutic cancer vaccines, is among the most promising areas of cancer treatment. However, adoptive cell therapies to treat unresectable HCC are still in their infancy, as they are confronted with major barriers like the molecular and immunologic heterogeneity of HCC while exposing patients with impaired liver function to potentially life-threatening side effects like cytokine release syndrome, neurotoxicity, and infections. As a matter of fact, CAR-T cell therapy is currently approved by the FDA for the treatment of refractory blood cancers only.

**Q5 A recent paper you co-authored entitled "Hepatocellular Carcinoma Prevention in the Era of Hepatitis C Elimination", discussed the persistent risk of HCC even after the successful treatment of HCV. Given the ongoing risk of HCC in cured patients, especially those with additional co-morbidities such as diabetes, obesity, and alcohol consumption, what do you think are the most important steps to take in terms of risk-stratified surveillance and early detection in this growing population?**

Owing to the fact that the risk of neoplastic transformation of the liver stays lifelong even after pharmacological eradication of HCV and that the number of patients with a cured hepatitis C is restlessly growing, the implementation of cost-effective, risk-stratified screening aimed at optimising both early diagnosis and cure of liver cancer, is imperative.

Working against this goal, however, is the histological and molecular heterogeneity of HCC, not to speak of the time dependence of the outcomes in patients with HCC, the lack of calibration studies of the currently available biomarkers, and their nonlinear trajectory over time, which conflicts with the linearity of the models utilised for assessing the predictive power of such biomarkers. That said, EASL recommends semi-annual examination with abdominal ultrasound of patients with cirrhosis and advanced liver fibrosis as they can be identified with vibration-controlled transient elastography (FibroScan®) or share wave elastography, whereas screening of patients with advanced fibrosis but lacking cirrhosis is not endorsed by the American Association for the Study of Liver Diseases (AASLD). As screening with ultrasound may yield poor visualisation of the liver in certain patients, like individuals who are obese and those with decompensated cirrhosis, in those individuals a user-friendly diagnostic approach like abbreviated MRI and low-dose CT scan might better serve the purpose. In one controlled study of an ordinary population with cirrhosis, a screening programme based on alternating MRI and ultrasound every 6 months led to an increased yield of early-stage HCC identification compared to the delivery of ultrasound alone.

> **"The implementation of cost-effective, risk-stratified screening aimed at optimising both early diagnosis and cure of liver cancer, is imperative"**

**Q6 What are the most promising advancements in hepatitis B treatment, such as long-acting injectable therapies or gene-editing approaches, and how do they compare in terms of efficacy and accessibility to current standard treatments like daily antivirals?**

According to the WHO report, last year >900,000 people died from hepatitis B worldwide, >80% of the 250 million people living with chronic HBV infection were unaware of their status, and 3% had been put only on antiviral treatment. As the advent of nucleot(s)ide analogues (NUC) did not impact global mortality rates from HBV, more efforts are deemed necessary to curb the epidemics of hepatitis B worldwide, with an eye to support operational research into simplified care pathways needed to identify and treat as many as possible infected individuals. There are, however, barriers to the elimination of serum HBsAg with NUCs (the so-called functional cure) related to the persistence of occult HBV infection expressed by the accumulation of covalently closed circular DNA (cccDNA) of HBV in the liver cell nuclei and chromosomal integrations of viral DNA that are resistant to NUCs and interferon while being prone to transcribing potentially carcinogenetic viral genes. On the other hand, the achievement of a

functional cure for HBV is hindered by the impaired immune system of the infected host, whose integrity is essential for clearing infected hepatocytes. However, this is compromised due to defective responses from CD8 T cells, B cells, and innate immunity. With this as a background, research in HBV therapy has been directed at exploring the clinical efficacy of different antiviral agents administered alone and in combination with other agents, spanning from the inhibitors of virus entry (one of these, bulevirtide, has been marketed for the treatment of chronic hepatitis D) to inhibitors of translation, capsid assembly, and HBsAg secretion. The other pocket of the therapeutic toolkit includes immune modulators, i.e., activators of innate and adaptive immunity, as well as the recently developed, engineered therapeutic viral vaccines. While the latter lag behind in Phase I and II studies, more advanced studies are available to tell us that, depending on the number and the turnover of infected liver cells, the combination of two or three inhibitors and/or immunologic agents accelerates the decay of cccDNA and increases the rates of functional cure. Of note, interferon alfa, which in the 80s pioneered the treatment of HBV, still retains a pivotal role in some of the newly developed therapeutic regimens of HBV.

**Q7 With the advancements in targeted medicine, bioengineering, and personalised treatments for HCC, how do you envision the future of HCC therapies evolving, particularly with the integration of biomarkers and genetic testing to improve patient outcomes?**

The future of HCC therapy looks bright; however, let me pinpoint that a pragmatic approach to reduce HCC-related mortality stands on the prevention grounded on the identification and neutralisation of the dominant risk factors for liver cancer, like viral hepatitis, metabolic syndrome complications, and alcohol abuse. For the populations already carrying HCC risk like those with MASLD, viral hepatitis, and cirrhosis of any aetiology, risk-stratified algorithms are recommended by the professional societies for HCC screening that currently are grounded on liver disease severity. Unfortunately, this stands as a hurdle given the difficulty of identifying liver patients within the general population and the limited accessibility of the general population to non-invasive tests required for assessing liver disease severity. The initial enthusiasm of utilising genetic markers in the risk stratification algorithms did not meet the expectations of improving cost-effectiveness of screening programmes for liver cancer even when they were incorporated into algorithms built on the usual demographic and clinical predictors of HCC. All in all, data gathered in the last years suggests that genetic variants act more as a disease modifier rather than as a disease driver.

Another barrier to the implementation of cost-effective programmes of HCC screening is the lack of high-precision tests for HCC, given the fact that comprehensive tumour molecular data remain elusive due to the infrequency of tissue biopsy in patients with an early-stage tumour. Liquid biopsies analysing tumour components such as DNA, RNA, circulating tumour cells, and extracellular vesicles are promising, but they are associated with challenges related to sensitivity, cost, and accessibility. Preliminary data highlighting the sensitivity of metabolomics in the prediction of HCC need to be validated by further studies aiming to solve the issue of the possible association between cancer risk and liver disease aetiology. As a matter of fact, the molecular profile of metabolic-related liver cancer differs substantially from that observed in patients with viral or autoimmune-related HCC.

**“Data gathered in the last years suggests that genetic variants act more as a disease modifier rather than as a disease driver”**