MICROB-PREDICT

MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response

D9.12 - Updated clinical practice guideline on cirrhosis and translation for layman

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Abbreviations

ACLF	Acute-on-chronic liver failure
AD	Acutely decompensated cirrhosis / Acute decompensation of cirrhosis
AKI	Acute kidney injury
Clif-C	Chronic Liver Failure Consortium score
concentris	concentris research management gmbh
DAMP	Damage-associated molecular pattern
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
EF CLIF	European Foundation for the Study of Chronic Liver Failure
ELPA	European Liver Patients Association
HE	Hepatic encephalopathy
HRS-AKI	Hepatorenal syndrome – Acute kidney injury
IL-6	Interleukin 6
LUMC	Leiden University Medical Center
PICO	Population (patient group or problem), Intervention, Comparison (or control group), and Outcome (framework for phrasing clinical research statements)
PAMP	Pathogen-associated molecular pattern
PV-1	Plasmalemmal vesicle-associated protein-1
R1 / R2	Delphi Round 1 / Delphi Round 2
SBP	Spontaneous bacterial peritonitis
SC	Steering Committee
TAM	Transplantation for ACLF-3 Model (see “TAM prognostic score”)
UM	University of Münster
QR Code	Quick Response Code
UM	University of Münster
uNGAL	Urinary neutrophil gelatinase-associated lipocalin
VIL1	Villin-1
WP	Work Package

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1. Executive Summary

This deliverable "D9.12 - Updated clinical practice guideline on cirrhosis and translation for layman", presents the consortium's **expert recommendations for improving patient stratification and therapeutic decision-making in decompensated cirrhosis and acute-on-chronic liver failure (ACLF)**, together with our efforts to translate key project findings into accessible information for lay people (patients, relatives, and the wider public). The recommendations were developed through a **multidisciplinary, international, two-round Delphi consensus panel** that evaluated a) mechanisms of progression of decompensated cirrhosis and ACLF, and b) biomarkers for better patient stratification and outcome prediction – with the overarching goal of improving the therapeutic approaches used to treat patients with advanced cirrhosis and ACLF.

Delphi Round 1 involved **137 qualified experts from 27 countries**, predominantly clinicians in hepatology/gastroenterology, with more than 70% of panellists having over ten years of professional experience. The results of Round 1 were presented and discussed at the **MICROB-PREDICT Consensus Conference** "Microbiome-based mechanisms and biomarkers for improved patient stratification and prediction of therapeutic response in decompensated cirrhosis and acute-on-chronic liver failure (ACLF)" on Wednesday, 27 May 2026, during EASL Congress in Barcelona, Spain (see **D9.9**). The three-hour-long face-to-face event brought together **more than 100 attendees** (consortium members, hepatology experts, and microbiome researchers). Six expert presentations addressed two overarching themes: 1) Mechanisms and biomarkers of progression of decompensated cirrhosis and ACLF, and 2) Mechanisms and biomarkers of therapeutic response - focusing on albumin, rifaximin, and terlipressin. Of the **31 PICO[1]-style statements** assessed in Round 1, **26 reached the predefined >75% consensus threshold**. The remaining **five statements** were discussed during the conference and subsequently revised and reassessed in **Delphi Round 2**, which was completed by **107 experts (78% response rate)**.

This **two-round Delphi process** resulted in **11 recommendations** for research and clinical practice – summarised in this deliverable. Key recommendations include recognising intestinal barrier failure as a defining organ failure in ACLF; combining gut-barrier-, inflammatory and established clinical markers to better assess patients; and utilising systemic inflammatory and lipid biomarkers, targeted metabolomics, and microbiome-based approaches for risk assessment and outcome prediction. Therapeutic recommendations address improved patient stratification and appropriate use of **albumin, rifaximin-α, and terlipressin**, including biomarker-guided approaches to support earlier diagnosis of Hepatorenal Syndrome – Acute Kidney Injury (HRS-AKI) and better prediction of treatment response. Together, these recommendations aim to save lives of cirrhosis patients via a more precise, biomarker-informed management of acutely decompensated (AD) cirrhosis and ACLF.

To **translate these recommendations to lay people**, a simplified **graphical abstract** has been created. This visual and an accompanying textual **lay summary** will be provided on the MICROB-PREDICT website once the respective scientific manuscript has been published. Beyond the lay summary of these recommendations, the European Liver Patients' Association (ELPA) has also prepared **lay summaries and matching visuals** for seven more key publications of the MICROB-PREDICT consortium (see project website and *Appendix 2*). These summaries translate major outcomes to patients, relatives, and the general public. The are also currently shared via **individual posts on ELPA's social media channels**.

This deliverable thereby supports the uptake of MICROB-PREDICT results into future research and clinical practice while ensuring that key findings are also communicated in an understandable and accessible format to patients, patient organisations, and the wider public.

[1] PICO, Population (patient group or problem), Intervention, Comparison, and Outcome.

2. Deliverable Report

2.1 Title, Abstract, and Keywords of the underlying Consensus Manuscript

Manuscript Title:

Multidisciplinary Delphi Consensus statement on microbiome-based mechanisms and biomarkers for improved patient stratification & therapeutic response prediction in decompensated cirrhosis and ACLF

Abstract:

Acute-on-chronic liver failure (ACLF) is characterised by a high short-term mortality rate. At the same time, however, there is neither a standardised definition of ACLF nor any promising treatment options that have been consistently validated by clinical trials. This may be due to the overlooking of important mechanistic processes or biomarkers of these processes in risk stratification, and to a lack of tools for predicting treatment response, in the context of personalised medicine. As part of the Horizon 2020-funded MICROB-PREDICT consortium, the two-round Delphi survey aimed to reach consensus on key mechanistic processes involved in the development of ACLF and their biomarkers, as well as to promote the targeted, biomarker-guided allocation of treatment options. The process involved 137 scientists and experts worldwide in the first round and 107 experts in the second round, with a 78% participation rate from the first to the second round. Based on the results of the Delphi survey, the MICROB-PREDICT consortium has developed 11 recommendations that could be adopted by the scientific and clinical community to enhance coherence and consistency in the conduct of current and future experimental and clinical trials in decompensated cirrhosis and ACLF.

Keywords:

Delphi survey, ACLF, decompensated cirrhosis, biomarkers, gut barrier, microbiome, patient stratification, rifaximin, terlipressin, albumin

2.1 Methodology

The Delphi consensus process followed a structured, iterative approach over the course of 8 months. (see *Figure 1*). During the **Delphi kick-off meeting** with the MICROB-PREDICT Steering Committee (SC) members in February 2026, the scope and intended outcomes of the consensus process were clearly defined and maintained throughout the study.

- **Scope:** Microbiome-based mechanisms and biomarkers for improved patient stratification & Therapeutic response prediction in decompensated cirrhosis and ACLF
- **Outcome 1:** Consensus Conference during EASL Congress 2026 **(D9.9) -** held on 27 May 2026
- **Outcome 2:** Consensus manuscript & Updated clinical practice guideline on cirrhosis and translation for layman **(D9.12)**

Over the following months, an in-depth **literature review** was conducted by **six topic-specific working groups** (8-12 members per group, with a group leader and a deputy for each group) to identify relevant evidence and inform the development of candidate statements. These were formulated as **clear statements** (closed questions) to minimise ambiguity. Where applicable, questions were structured according to the **PICO framework**, specifying the Population/Patient/Problem (P) of interest, the Intervention (I) under consideration, the relevant Comparator/Control Group (C), and the Outcome (O) of interest. This ensured that the Delphi survey remained focused, scientifically and clinically relevant, and specific enough to support meaningful interpretation by the expert panel. In the meantime, the **SC members collected and provided the contact details** of 270 expert panellists that were to be contacted via email during Delphi Round 1 (R1).

The working groups were organised into the following six topics - three for each theme:

Theme 1: Progression of decompensated cirrhosis and ACLF (basic science)
Topic 1: Mechanisms of progression
Topic 2: Biomarkers of progression
Topic 3: Biomarkers of failure within the gut-liver axis

Theme 2: Mechanisms and biomarkers of therapeutic response (clinical research)
Topic 4: Albumin
Topic 5: Rifaximin
Topic 6: Terlipressin



Figure 1. *Timeline of the entire Delphi process, from the Kick-off meeting in February (T0) to the final manuscript in September 2026 (T0 + 8 months).*

Delphi survey Round 1 (R1) and Round 2 (R2) were conducted using the **online survey platform Alchemer** (Alchemer.com). For each statement, panellists indicated their level of agreement using a **six-point Likert scale** consisting of three positive response options ("strongly agree", "agree", and "slightly agree") and three negative response options ("slightly disagree", "disagree", and "strongly disagree"). The absence of a neutral midpoint required panellists to make a choice and indicate either agreement or disagreement with each statement. However, if a question was deemed outside a respondent's expertise, the panellist could indicate this. See *Figure 2* for an example.

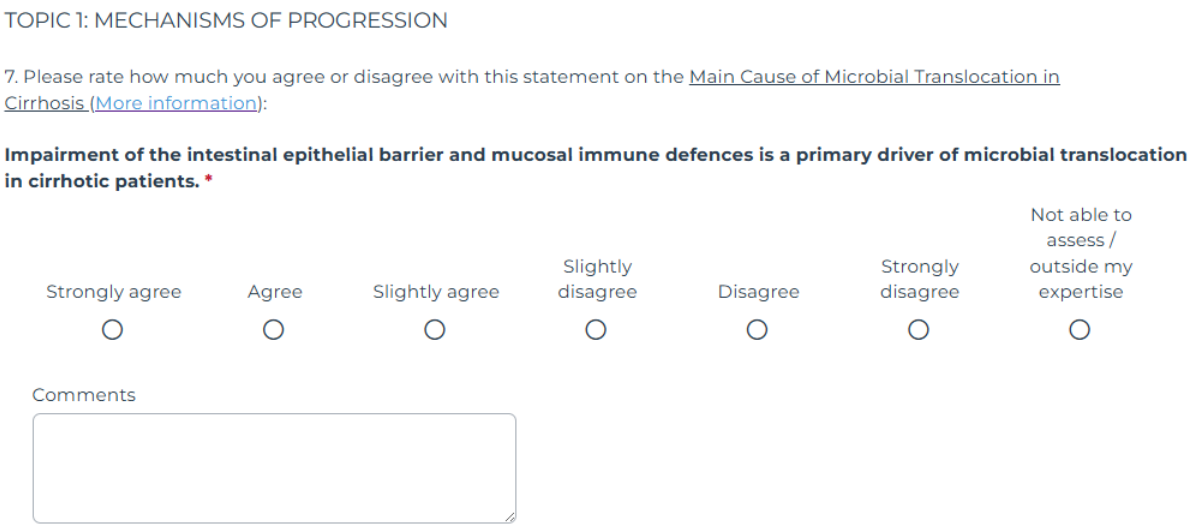


Figure 2. *Screenshot of an exemplary statement (closed question), Likert Scale answer options, and a box for comments under the "Mechanisms of Progression" topic of the survey in Round 1 (R1).*

Consensus was predefined as ≥75% of respondents selecting response options on the same side of the Likert scale. For example, consensus in favour of a statement was reached when at least 75% selected one of the three positive response options.

Following internal review and testing, the **first-round (R1) Delphi questionnaire** was finalised and distributed to the expert panel. Panellists were given **28 days to respond**, with several email reminders sent during the response period. Quantitative responses as well as **qualitative expert comments** were subsequently evaluated.

The **results of R1** were summarised and presented during the 3h-long **MICROB-PREDICT Consensus Conference** (see **Deliverable D9.9**) at EASL Congress on 27 May 2026. Statements that did not reach the predefined 75% consensus threshold were discussed in detail during the face-to-face Consensus Conference, and subsequently revised to make them more precise - based on the panellists' written comments (from survey R1) and the expert comments (from the Consensus Conference).

The **revised statements** were included in the **second-round (R2) questionnaire**. For R2, panellists were given **20 days to respond**, with several email reminders issued during the response period. Following completion of R2, responses were analysed against the predefined consensus criterion.

The results of R1 and R2 were subsequently synthesised and used to derive the final **consensus-based recommendations** for a scientific manuscript and this **Deliverable D9.12**. Structured coordination, management, and conference organisation were maintained by concentris research management gmbh (concentris) throughout all stages of the Delphi process.

2.2 Response Rates and Panel Participation

In Delphi Round 1 (R1), **270 experts** were invited via email (see *Figure 3*) to evaluate **31 questions and PICO-style statements**. In addition, open invitations were circulated via the MICROB-PREDICT (microb-predict.eu) and EASL (easl.eu) websites, via a newsletter by the European Liver Patients Association (elpa.eu), and the consortium's social media accounts on LinkedIn (linkedin.com/company/microb-predict), Bluesky Social (bsky.app/profile/microb-predict.bsky.social), and X (x.com/MicrobPredict).

Of the 270 invited panellists, 116 took part in the survey, while 21 participants were recruited via social media accounts. The **137 panellists** (see *Supplemental Table 2*) completed the questionnaire in R1 and provided 251 comments and suggestions. The results from R1 were presented in an interactive 3h-long **MICROB-PREDICT Consensus Conference** session during EASL Congress 2026 in Barcelona, Spain.

The comments from this session and from R1 were reviewed and taken into account in R2, in which **five revised statements** were put to a vote once again because no consensus had been reached on them in R1. The 137 panellists from R1 were then invited again to take part in Delphi Round 2 (R2). During R2, 107 of the 137 invited panellists **(78% response rate)** completed the survey containing the five revised statements.

2.3 Delphi Panel Characteristics

Panellists from **27 countries** took part in the survey. The majority of the panellists came from **Europe** (81.0%, 19 countries), followed by **North, Central and South America** (13.1%, 6 countries) and **Asia** (2.9%, two countries) – see *Figure 4*. Among the 137 participating experts in the Delphi process, **35% of the panellists were female**, and one panellist did not specify their biological sex, see *Figure 5A*.

The majority of the panellists stated that they were **clinicians working in Hepatology or Gastroenterology (78.8%)**. The second most frequent response was basic scientists (13.9%), followed by patient representatives (1.5%), members of a scientific society (0.7%) and liver transplant surgeons

(0.7%), see *Figure 5B*. One panellist did not provide any details, whilst five panellists stated that they held professional roles other than those mentioned above, including science communication, infectiology, other clinical researchers or PhD students.

Over **two-thirds of the panellists s**tated that **cirrhosis and its complications, as well as ACLF,** are their main areas of expertise. A further quarter or so of the panellists work on other stages of chronic liver disease, including liver cancer and liver transplantation. The remaining panellists have indicated other areas of expertise. Over **70% of the panellists** stated to have **more than 10 years of experience** in their field.

Email Invitation

RE: MICROB-PREDICT Consensus Survey for Hepatology Experts // Invitation to Participate

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Dear Colleague,

We invite you to complete (and share) this short **Consensus Survey** in preparation for the MICROB-PREDICT Consensus Conference on Wednesday, 27 May 2026, during EASL Congress in Barcelona, Spain.

- Survey Scope: **Microbiome-based mechanisms and biomarkers for improved patient stratification and prediction of therapeutic response in decompensated cirrhosis and acute-on-chronic liver failure (ACLF)**
- Survey Link: https://survey.alchemer.eu/s3/91081387/MICROB-PREDICT-Delphi
- Completion Time: **15-20 minutes**

Your expertise in hepatology is highly valued and will contribute to building a structured, evidence-informed Delphi-style consensus in this rapidly evolving field.

Theme 1: Progression of decompensated cirrhosis and ACLF
Topic 1: Mechanisms of progression
Topic 2: Biomarkers of progression
Topic 3: Biomarkers of failure within the gut-liver axis

Theme 2: Mechanisms and biomarkers of therapeutic response
Topic 4: Albumin
Topic 5: Rifaximin
Topic 6: Terlipressin

Responses are fully anonymised and will be analysed in aggregate only.

Thank you in advance for taking a couple of minutes to complete the survey!

Kind regards & See you soon in Barcelona,

Prof Jonel Trebicka (University Hospital Münster EF CLIF)
Prof Minneke Coenraad (Leiden University Medical Center)
Prof Aleksander Krag (Odense University Hospital)

(on behalf of the MICROB-PREDICT Consortium)



Figure 3. *Email invitation sent to 270 selected expert contacts for Delphi Round 1 (R1).*

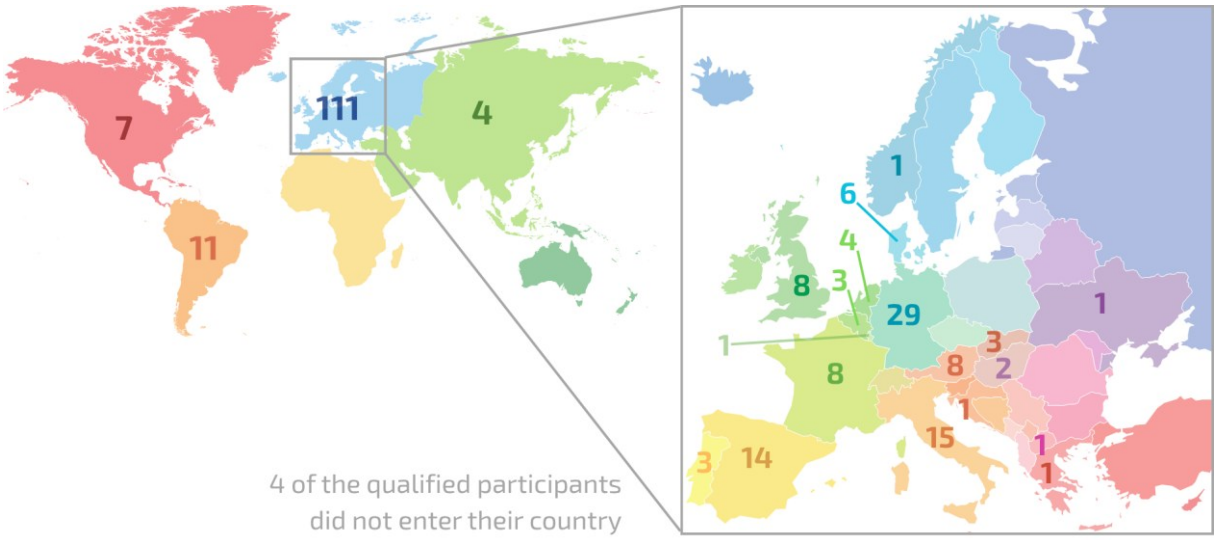


Figure 4. *Geographical Delphi panel characteristics in Round 1 (R1), with the majority of the 137 participants working in Europe.*

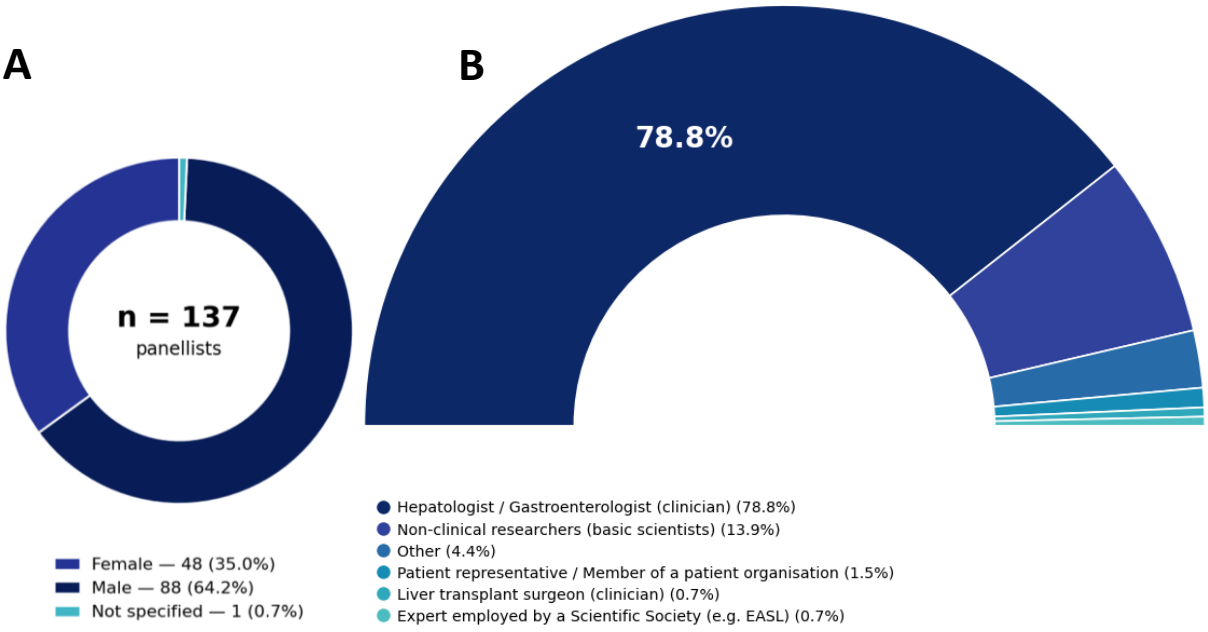


Figure 5. *Delphi panel demographics and characteristics (**A**, gender; **B**, professional role).*

2.4 Recommendations for Basic Research

Below are the **six basic science recommendations** that emerged from the Delphi consensus on how novel basic research approaches may support clinical decision making for cirrhosis patients with acute decompensation (AD) or ACLF. For reference (e.g. the left column listing related statements/PICOs), please consult the ***"Supplemental Information to the Consensus Manuscript"*** *(Appendix 1).*

Table 1: *Basic research recommendations for an improved assessment and characterisation of mechanisms and biomarkers that lead to the progression of advanced cirrhosis towards AD and ACLF.*

Recommendation	Specific actions	Related statements / PICOs
1. Establish intestinal barrier failure as an organ failure defining ACLF.	Impairment of the intestinal epithelial barrier and mucosal immune defences are considered primary drivers of microbial translocation in cirrhosis and might therefore be assessed by intestinal villin-1 (VIL1), secretory immunoglobulin A, or plasmalemmal vesicle-associated protein-1 (PV-1) in patients.	1.1, 3.1, 3.2, 3.3
2. Use multiple biomarkers to define gut barrier failure in acutely decompensated (AD) cirrhosis.	A single biomarker is not sufficient to define gut barrier failure in AD cirrhosis. A combined panel integrating gut barrier markers (see recommendation 1), systemic inflammatory markers, and established severity scores should be used.	3.4
3. Assess systemic inflammation for early diagnosis of infection, risk stratification, organ failure and clinical outcomes.	ACLF progression is driven by a Pathogen- / Damage-associated molecular pattern (PAMP/DAMP)-mediated proteomic shift, signaling a transition to terminal organ failure. The incorporation of immunoassay-based biomarkers – such as interleukin 6 (IL-6), urinary neutrophil gelatinase-associated lipocalin (uNGAL) or lipid biomarkers – into standard clinical assessment should be considered for patients with AD, especially those with suspected infection or organ dysfunction. However, additional validation and simplification are needed for adoption in clinical routine.	1.2, 2.1, 2.2, 2.3, 2.5
4. Perform targeted metabolomics for improved monitoring and prediction of outcome.	Microbial metabolites act as primary accelerators of the systemic inflammatory in ACLF progression. Assessment of metabolites improves the monitoring of patients and the prediction of their outcome. However, this approach needs to be simplified and made accessible for routine use.	1.3, 2.6
5. Consider inclusion of biological sex in clinical scores for risk stratification of ACLF progression and survival.	Current prognostic scores for patients with acute decompensation or ACLF - such as Clif-C AD, Clif-C ACLF, and TAM - lack adjustments for sex. Consideration should be given to incorporating biological sex as a factor in scoring systems used to predict the progression of ACLF and survival.	1.4
6. Enhance clinical prognostic scores through microbiome profiling.	It should be investigated whether the introduction of supplementary profiling of the oral and gut microbiome, in combination with the measurement of circulating bacterial DNA, improves prediction of clinical outcomes and guide therapeutic decisions. To achieve this, experimental findings would need to be translated into routine clinical practice.	R2-2.4

2.5 Recommendations for Clinical Practice

Below are the **five clinical recommendations** that emerged from the Delphi consensus regarding improved patient stratification and treatment approaches for AD or ACLF patients with albumin, rifaximin-α, and terlipressin. For reference (e.g. the left column listing related statements/PICOs), please consult the ***"Supplemental Information to the Consensus Manuscript"*** *(Appendix 1)*.

Table 2: *Clinical recommendations for therapeutic guidance in AD cirrhosis and ACLF.*

Recommendation	Target patient population	Related statements / PICOs
1. Patients with decompensated cirrhosis may benefit from intravenous albumin administration.	In patients with decompensated cirrhosis • undergoing large-volume paracentesis (>5L) • diagnosed with spontaneous bacterial peritonitis (SBP) or • diagnosed with hepatorenal syndrome - acute kidney injury (HRS-AKI) CAVE: Risk of developing pulmonary oedema after larger volumes of albumin, especially in ACLF grade 3 patients	4.1
2. Support therapeutic decisions for albumin using predictive biomarkers.	• Outpatients with acute decompensation and ascites • Patients with decompensated cirrhosis and non-refractory ascites	4.2, 4.3
3. Rifaximin-α might be used to improve the outcomes of hepatic encephalopathy (HE), and to reduce selected markers of systemic inflammation (other than secondary prevention of HE).	• no sufficient evidence for reduction in overall liver-related decompensation events • no sufficient evidence for reduction in liver-related mortality • no sufficient evidence for attenuation of hepatic fibrosis progression • does not lead to a reduction in cirrhosis-related bacterial infections • secondary prevention of hepatic encephalopathy might be associated to reduction in biomarkers of gut barrier damage and to improved outcomes of hepatic encephalopathy • reduces selected markers of systemic inflammation and gut-derived inflammatory signaling	5.1, 5.2, 5.3, R2-5.4, R2-5.7, 5.8
4. Use uNGAL as a biomarker for the diagnosis of HRS-AKI, timely initiation of terlipressin therapy, and improved outcome prediction in response to terlipressin therapy.	In patients with liver cirrhosis, ascites, and acute kidney injury	6.1, 6.2, 6.3
5. Improve the response to terlipressin therapy by biomarker-guided early identification of HRS-AKI patients.	In patients with cirrhosis and suspected HRS-AKI, this • may reduce the time-to-initiation of terlipressin therapy • may facilitate timely and targeted initiation of terlipressin therapy • may improve clinically relevant outcomes	6.3, 6.4, 6.5

3. Translation of Recommendations for Lay People

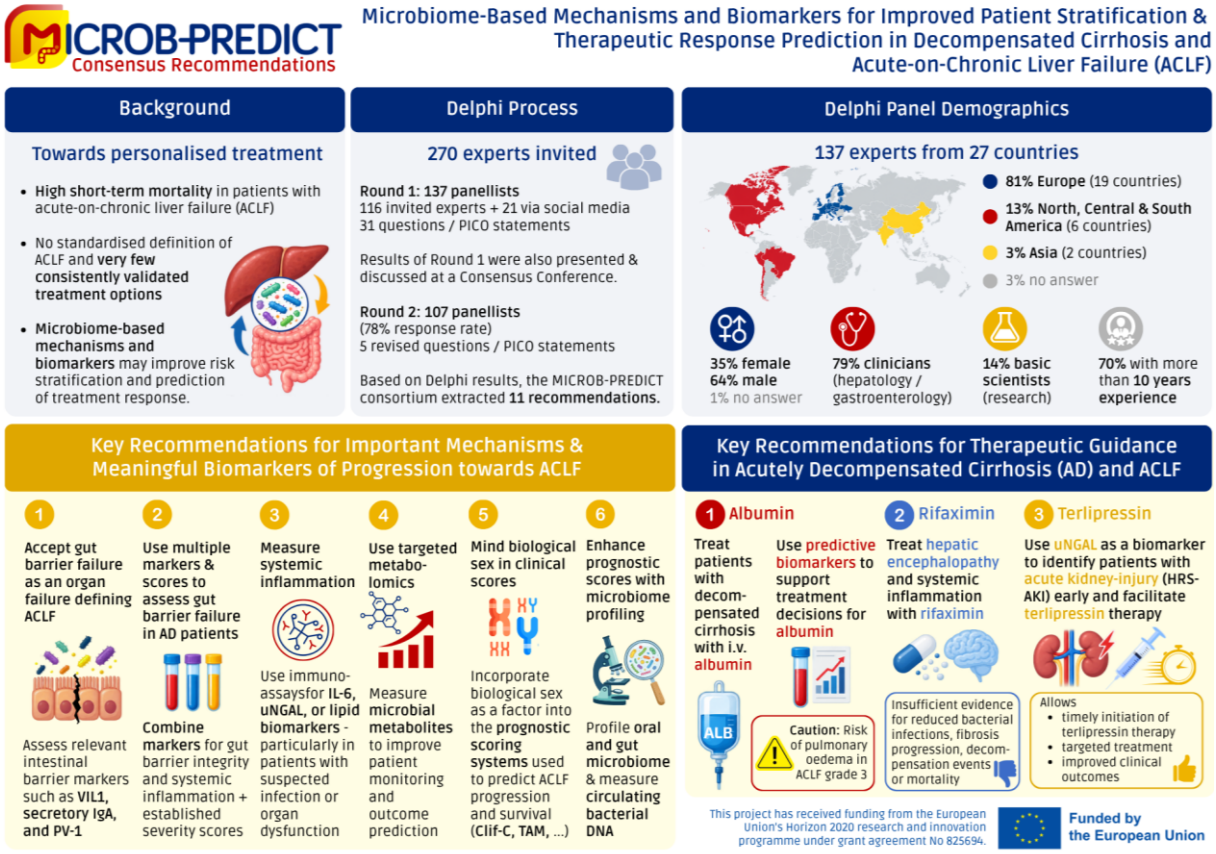


Figure 6. *Graphical abstract of the consensus recommendations for lay people and the general public, especially patients, relatives, and care-takers.*

Textual Lay Summary

Towards more personalised treatment for advanced liver disease

People with **decompensated cirrhosis** suffer from advanced liver disease, meaning the liver can no longer compensate adequately for the damage it has sustained. Some patients develop **acute decompensation (AD)** or even **acute-on-chronic liver failure (ACLF)**, a severe and rapidly progressing condition in which one or more organs begin to fail. When several organs fail at the same time, the risk of death is high. Despite its seriousness, there is still no universally standardised definition of ACLF and only a limited number of consistently validated treatment options.

The EU-funded **MICROB-PREDICT project** therefore asked an international group of experts which biological processes and measurable indicators – also called **biomarkers** - could help doctors identify patients at risk, predict how their disease is likely to progress, and choose treatments more precisely. In a **two-round Delphi consensus process**, 137 experts from 27 countries participated in the first round and 107 in the second. The process ultimately resulted in **11 recommendations for both basic research and clinical practice**. The graphical abstract (see *Figure 6*) provides an overview of both the consensus process and these recommendations.

What do the experts recommend?

A central message is that **the gut plays an important role in the progression of advanced liver disease**. MICROB-PREDICT recommends recognising failure of the intestinal barrier - the protective layer that normally helps prevent harmful substances from passing from the gut into the body - as an important feature of ACLF. Rather than relying on a single laboratory value, several biomarkers should be combined with established clinical scores to obtain a more complete picture of a patient's condition. Markers of **systemic inflammation**, **microbial metabolites**, the **gut and oral microbiome**, and **bacterial DNA** in the blood may further improve the ability to assess a patient's risk and to predict disease progression and treatment outcomes. The experts also recommend incorporating **biological sex** into existing prognostic scores and investigating the **biological differences in disease progression between men and women** in more detail.

The recommendations also address three commonly used treatments used in patients with advanced cirrhosis: **Albumin, rifaximin, and terlipressin**:

- **Intravenous albumin** may benefit specific groups of patients with decompensated cirrhosis, although larger amounts can increase the risk of fluid accumulating in the lungs, particularly in the most severely ill patients. Certain biomarkers that were identified by the MICROB-PREDICT consortium could potentially help identify which patients are most likely to benefit from **albumin treatment** (and which patients may benefit more from standard care).

- **Rifaximin** is used to help **manage hepatic encephalopathy**, a complication in which impaired liver function affects the brain, and may also reduce systemic inflammation. However, the expert panel did not find enough evidence that rifaximin reduces bacterial infections, liver-related decompensation and mortality, or that it halts or improves liver scarring.

- For patients who develop **acute kidney injury associated with hepatorenal syndrome (HRS-AKI)**, a urinary biomarker called **uNGAL** may help identify affected patients and support earlier, more targeted treatment with **terlipressin**. Such biomarker-guided treatment could reduce delays in starting the appropriate therapy and may improve clinically relevant outcomes.

What does this mean for patients?

The overall goal is to move towards **more personalised care**. Instead of assessing patients only through conventional clinical measures, future approaches could combine these with important information about systemic inflammation, status of the gut barrier, microbial activity, and other biomarkers – assessed **in each individual patient**. This can help doctors distinguish between patients with at high or low risk (of developing ACLF or dying), determine biological characteristics and, ultimately, select the most appropriate treatment for a patient at the right time.

These recommendations represent an **expert consensus based on the available evidence**. Some of the proposed biomarkers and microbiome-based approaches still require further validation and simplification before they can become part of routine clinical care.

Nevertheless, the recommendations provide a roadmap for future research and clinical studies aimed at making the management of decompensated cirrhosis and ACLF **more precise, timely, and tailored to the individual patient**.

4. Conclusion

Deliverable D9.12 brings together MICROB-PREDICT's final **consensus-based recommendations for improving patient stratification, outcome prediction, and therapeutic decision-making** for hepatologists and basic researchers working in the field of decompensated cirrhosis and ACLF. Developed through a structured, international two-round Delphi process involving 137 experts from 27 countries in Round 1 and 107 experts in Round 2, the resulting **11 recommendations** aim to translate recently discovered biomarkers and agreed upon disease mechanisms and into future research and clinical practice.

The recommendations emphasise a **multidimensional assessment of patients**, integrating established clinical parameters with information on intestinal barrier dysfunction, systemic inflammation, microbial metabolites, microbiome composition, and other biomarkers. They also identify opportunities for **biomarker-guided therapeutic decision-making**, particularly with respect to treatment with **albumin, rifaximin-α, and terlipressin**.

It is, however, important to note that several proposed biomarkers and microbiome-based approaches still require further validation, simplification, and prospective evaluation before they can be implemented routinely in clinical care.

Importantly, this deliverable extends beyond scientific and clinical recommendations by **translating the key findings into accessible information for lay people** (patients, relatives, caregivers, patient organisations, and the wider public). The **graphical abstract and textual lay summary**, complemented by additional lay summaries of key publications by the MICROB-PREDICT consortium, support **accessibility, transparency, and wide-spread communication** of the project's scientific outcomes beyond the research community.

Overall, D9.12 provides recommendations and guidance towards **more precise, timely, biomarker-informed and personalised management of advanced cirrhosis and ACLF**. By connecting mechanistic research, biomarker development, and clinical decision-making with patient-oriented communication, the deliverable contributes to the long-term uptake and legacy of MICROB-PREDICT. The authors hope that the deliverable serves as a basis for future research and clinical studies aimed at improving outcomes for patients with advanced liver disease.

5. Acknowledgement and Disclaimer



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694. This report reflects only the authors' view and the Commission is not responsible for any use that may be made of the information it contains.

6. Appendices

6.1. Appendix 1 – Supplemental Information to the Consensus Manuscript

Supplemental Table 1: Delphi survey statements or PICO questions and results. The detailed voting ratio is displayed below the summarized voting values. For negative consensus (strongly disagree / disagree / slightly disagree) and for positive consensus (slightly agree / agree / strongly agree).

Section 1 – Mechanisms of progression towards ACLF

Statement	Consensus level	
1.1 Impairment of the intestinal epithelial barrier and mucosal immune defences is a primary driver of microbial translocation in cirrhotic patients.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	0.74 (0.00/0.00/0.74)	**99.26** (5.15/45.59/48.53)

Statement	Consensus level	
1.2 ACLF progression is driven by a PAMP/DAMP-mediated proteomic shift that shuts down hepatic synthesis while simultaneously triggering accelerated hepatic net interstitial collagen accumulation, signalling a transition to terminal organ failure.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	11.20 (1.60/3.20/6.40)	**88.80** (21.60/48.80/18.40)

Statement	Consensus level	
1.3 Microbial metabolites act as primary accelerators of the systemic inflammatory response rather than being a consequence of it.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	10.69 (0.76/6.11/3.82)	**89.31** (16.79/49.62/22.90)

Statement	Consensus level	
1.4 Sex-specific mechanisms of ACLF progression are driven by a complex interplay between hormonal fluctuations and body composition (muscle-to-fat ratio) that are currently not captured in standard clinical scores.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	9.17 (0.83/3.33/5.00)	**90.83** (33.33/38.33/19.17)

Section 2 – Biomarkers of progression towards ACLF

PICO	Consensus level	
2.1 In adult patients with acutely decompensated cirrhosis (AD), especially those with suspected infection or organ dysfunction (P), the incorporation of immunoassay-based biomarkers – such as interleukin 6 (IL-6) or urinary neutrophil gelatinase-associated lipocalin (uNGAL) – into standard clinical assessment (I), compared to conventional scores and routine laboratory tests alone (C), improves early diagnosis of infection (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	21.31 (1.64/9.84/9.84)	**78.69** (30.33/32.79/15.57)

PICO	Consensus level	
2.2 In adult patients with AD, especially those with suspected infection or organ dysfunction (P), the incorporation of immunoassay-based biomarkers – such as IL-6 or uNGAL – into standard clinical assessment (I), compared to conventional scores and routine laboratory tests alone (C), improves risk stratification (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	15.83 (0.83/6.67/8.33)	**84.17** (26.67/38.33/19.17)

PICO	Consensus level	
2.3 In adult patients with AD, especially those with suspected infection or organ dysfunction (P), the incorporation of immunoassay-based biomarkers – such as IL-6 or uNGAL – into standard clinical assessment (I), compared to conventional scores and routine laboratory tests alone (C), improves prediction of short-term mortality, organ failure, and progression to ACLF (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	10.17 (0.85/4.24/5.08)	**89.83** (25.42/42.37/22.03)

PICO	Consensus level	
2.4 In patients with decompensated cirrhosis (P), gut and oral microbiome profiling combined with the quantification of circulating bacterial DNA (I) complement standard prognostic scores (C) to predict clinical outcomes and guide therapeutic decisions (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	27.73 (5.04/10.08/12.61)	72.27 (29.41/32.77/10.08)

PICO	Consensus level	
R2-2.4 In patients with decompensated cirrhosis (P), gut and oral microbiome profiling combined with the quantification of circulating bacterial DNA (I) compared with currently available prognostic tools (C), shows potential to improve outcome prediction, although further validation is required before routine clinical implementation (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	13.64 (1.14/4.55/7.95)	**86.36** (23.86/44.32/18.18)

PICO	Consensus level	
2.5 In patients with decompensated cirrhosis (P), longitudinal monitoring of lipid biomarkers (I) compared with standard clinical follow-up (C), improves the early detection of progression to ACLF and supports clinical decision-making (O). However, additional validation and simplification are needed prior to routine clinical adoption.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	13.51 (0.90/5.41/7.21)	**86.49** (35.14/36.04/15.32)

PICO	Consensus level	
2.6 In patients with decompensated cirrhosis (P), a targeted metabolomics approach (I) improves the monitoring of patients compared to standard clinical and biochemistry follow-up (C) and thus improves the care of cirrhotic patients and the prediction of their outcome (O). However, this approach needs to be simplified and made accessible for routine use.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	19.49 (1.69/7.63/10.17)	**80.51** (22.03/38.98/19.49)

Section 3 – Biomarkers of failure gut-liver axis

Statement	Consensus level	
3.1 In AD cirrhosis, gut barrier failure should be defined in line with the other organ failures in the ACLF paradigm: a biomarker indication of gut barrier injury or dysfunction that is associated with increased risk of short-term mortality.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	14.75 (0.82/8.20/5.74)	**85.25** (20.49/41.80/22.95)

Statement	Consensus level	
3.2 In AD cirrhosis and ACLF, gut barrier failure is a multi-layer disorder that includes structural epithelial injury, gut-vascular barrier damage, mucosal immune barrier disruption, increased permeability, associated with systemic inflammation, and adverse short-term outcome.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	2.46 (1.64/0.00/0.82)	**97.54** (11.48/45.08/40.98)

Statement	Consensus level	
3.3 According to current evidence, villin-1 (VIL1) is the best validated biomarker for acute structural gut barrier injury in acutely decompensated cirrhosis, secretory immunoglobulin A (sIgA) is the most informative biomarker in established ACLF, and plasmalemmal vesicle-associated protein-1 (PV-1) is a promising adjunctive marker of gut-vascular barrier injury. However, before entering clinical routine, these biomarkers require further confirmation and external validation.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	10.38 (1.89/4.72/3.77)	**89.62** (16.04/50.94/22.64)

Statement	Consensus level	
3.4 Due to the acute-on-chronic nature of intestinal injury in AD cirrhosis, a single biomarker is not sufficient to define gut barrier failure in this condition. The most clinically appropriate approach is a combined panel integrating gut barrier markers, systemic inflammatory markers, and established severity scores.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	4.13 (0.00/0.83/3.31)	**95.87** (21.49/46.28/28.10)

Section 4 – Albumin administration in patients with liver cirrhosis and ACLF

PICO	Consensus level	
4.1 In patients with decompensated cirrhosis undergoing large-volume paracentesis (>5L) or diagnosed with spontaneous bacterial peritonitis (SBP) or hepatorenal syndrome–acute kidney injury (HRS-AKI) (P), the administration of specific regimens of intravenous human albumin in addition to standard medical therapy as indicated by the guidelines (I), compared with standard medical therapy alone or alternative plasma expanders (C), is associated with a reduction in adverse outcomes, such as paracentesis-induced circulatory dysfunction, renal failure, and mortality (O). However, especially in acute-on-chronic liver failure (ACLF) grade 3 patients, the risk of developing a pulmonary oedema after larger volumes of albumin should be considered and patients need to be closely monitored.	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being “strongly disagree” and 6 being “strongly agree”, experts voted:	2.59 (0.00/0.86/1.72)	**97.41** (7.76/37.93/51.72)

PICO	Consensus level	
4.2 Outpatients with decompensated cirrhosis and ascites (P), receiving long-term administration of intravenous human albumin in addition to standard medical therapy (I), compared with standard medical therapy alone (C), should be selected using predictive biomarkers, provided such biomarkers are identified, e.g. in the ongoing ALB-TRIAL (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being “strongly disagree” and 6 being “strongly agree”, experts voted:	7.76 (0.00/6.90/0.86)	**92.24** (24.14/50.00/18.10)

PICO	Consensus level	
4.3 In patients with decompensated cirrhosis and non-refractory ascites (P), long-term administration of intravenous human albumin in addition to standard medical therapy (I), compared with standard medical therapy alone (C), reduces liver-related complications and improves survival rates. However, current evidence remains inconsistent, and uncertainties persist regarding the magnitude of the benefit, optimal patient selection, dosing regimens, and cost-effectiveness (O). Identification of biomarkers indicative of the therapeutic response is an unmet need	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	6.72 (0.84/5.04/0.84)	**93.28** (11.76/51.26/30.25)

Section 5 – Rifaximin administration in patients with liver cirrhosis and ACLF

PICO	Consensus level	
5.1 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy (P), outside its established role in the secondary prevention of recurrent hepatic encephalopathy, treatment with rifaximin-α (I), compared to standard of care (C), does not have sufficient evidence to demonstrate a reduction in overall liver-related decompensation events (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	6.14 (0.88/2.63/2.63)	**93.86** (10.53/45.61/37.72)

PICO	Consensus level	
5.2 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy (P), outside its established role in the secondary prevention of recurrent hepatic encephalopathy, treatment with rifaximin-α (I), compared to standard of care (C), does not have sufficient evidence to demonstrate a reduction in liver-related mortality (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	7.89 (0.00/6.14/1.75)	**92.11** (10.53/46.49/35.09)

PICO	Consensus level	
5.3 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy (P), outside its established role in the secondary prevention of recurrent hepatic encephalopathy, treatment with rifaximin-α (I), compared to standard of care (C), does not have sufficient evidence to demonstrate an attenuation of hepatic fibrosis progression (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	13.64 (3.64/6.36/3.64)	**86.36** (8.18/36.36/41.82)

PICO	Consensus level	
5.4 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy, including those with ascites (P), treatment with rifaximin-α (I), compared to standard of care or established prophylactic strategies such as norfloxacin (C), may lead to a reduction in cirrhosis-related bacterial infections (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	32.74 (3.54/18.58/10.62)	67.26 (23.89/34.51/8.85)

PICO	Consensus level	
R2-5.4 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy, including those with ascites (P), treatment with rifaximin-α (I), compared to standard of care (C), does NOT lead to a reduction in cirrhosis-related bacterial infections (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	21.74 (2.90/8.70/10.14)	**78.26** (11.59/44.93/21.74)

PICO	Consensus level	
5.5 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy, including those with ascites (P), treatment with rifaximin-α (I), compared to standard of care or established prophylactic strategies such as norfloxacin (C), may lead to a reduction in spontaneous bacterial peritonitis (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	31.58 (7.02/12.28/12.28)	**68.42** (< 75% threshold) (21.93/38.60/7.89)

PICO	Consensus level	
R2-5.5 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy, including those with ascites (P), treatment with rifaximin-α (I), compared to standard of care (C), may lead to a reduction in recurrent spontaneous-bacterial peritonitis (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	32.35 (2.94/17.65/11.76)	**67.65** (< 75% threshold) (27.94/30.88/8.82)

PICO	Consensus level	
5.6 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy, including those with ascites (P), treatment with rifaximin-α (I), compared to standard of care or established prophylactic strategies such as norfloxacin (C), may lead to an increase in antimicrobial resistance (AMR), as indicated by the emergence of resistant organisms and resistance genes in the gut microbiome (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	31.82 (3.64/10.91/17.27)	**68.18** (< 75% threshold) (27.27/30.00/10.91)

PICO	Consensus level	
R2-5.6 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy, including those with ascites (P), treatment with rifaximin-α (I), compared to standard of care (C), may lead to an increase in AMR, as indicated by the emergence of resistant organisms and resistance genes in the gut microbiome (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	27.94 (4.41/8.82/14.71)	**72.06** (< 75% threshold) (29.41/32.35/10.29)

PICO	Consensus level	
5.7 In patients with decompensated cirrhosis, with or without prior hepatic encephalopathy (P), rifaximin-α (I) compared with placebo or standard of care alone (C) leads to a reduction in biomarkers of gut barrier damage and to improved clinical outcomes (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	25.53 (2.13/19.15/4.26)	74.47 **(< 75% threshold)** (42.55/24.47/7.45)

PICO	Consensus level	
R2-5.7 In patients with decompensated cirrhosis, with prior hepatic encephalopathy (P), rifaximin-α (I), compared to standard of care (C), leads to a reduction in biomarkers of gut barrier damage and to improved outcomes of hepatic encephalopathy (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	8.57 (0.00/5.71/2.86)	**91.43** (25.71/47.14/18.57)

PICO	Consensus level	
5.8 In patients with decompensated cirrhosis, particularly those with prior hepatic encephalopathy (P), rifaximin-α treatment (I) compared with placebo or standard of care alone (C) reduces selected markers of systemic inflammation and gut-derived inflammatory signalling (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	13.46 (0.96/5.77/6.73)	**86.54** (34.62/44.23/7.69)

Section 6 – Terlipressin administration in patients with liver cirrhosis and ACLF

PICO	Consensus level	
6.1 In patients with liver cirrhosis, ascites, and acute kidney injury (P), the use of blood and/or urinary biomarkers, e.g. urinary neutrophil gelatinase-associated lipocalin (uNGAL) (I) compared with standard clinical criteria (C) as defined by the joint consensus group between the International Club of Ascites and the Acute Disease Quality Initiative (ICA/ADQI), may enable earlier and more accurate differentiation of HRS-AKI (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	3.64 (0.00/1.82/1.82)	**96.36** (18.18/53.64/24.55)

PICO	Consensus level	
6.2 In patients with liver cirrhosis, ascites, and acute kidney injury (P), the use of blood and/or urinary biomarkers, e.g. urinary neutrophil gelatinase-associated lipocalin (uNGAL) (I) compared with standard clinical criteria (C) as defined by ICA/ADQI, may facilitate timely and targeted initiation of terlipressin therapy (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	7.27 (0.00/2.73/4.55)	**92.73** (29.09/47.27/16.36)

PICO	Consensus level	
6.3 In patients with liver cirrhosis, ascites, and acute kidney injury (P), the use of blood and/or urinary biomarkers, e.g. urinary neutrophil gelatinase-associated lipocalin (uNGAL) (I) compared with standard clinical criteria (C) as defined by ICA/ADQI, may improve prediction of treatment response and clinically relevant outcomes (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	12.84 (0.00/4.59/8.26)	**87.16** (28.44/40.37/18.35)

PICO	Consensus level	
6.4 In patients with cirrhosis and suspected hepatorenal syndrome–acute kidney injury (P), biomarker-guided early identification of patients likely to benefit from terlipressin therapy - particularly using urinary neutrophil gelatinase–associated lipocalin (uNGAL) and metabolomic profiles (I), compared with the standard diagnostic algorithm including a 24–48-hour albumin challenge prior to treatment initiation (C), may reduce time-to-initiation of terlipressin therapy (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	21.50 (0.00/10.28/11.21)	**78.50** (27.10/37.38/14.02)

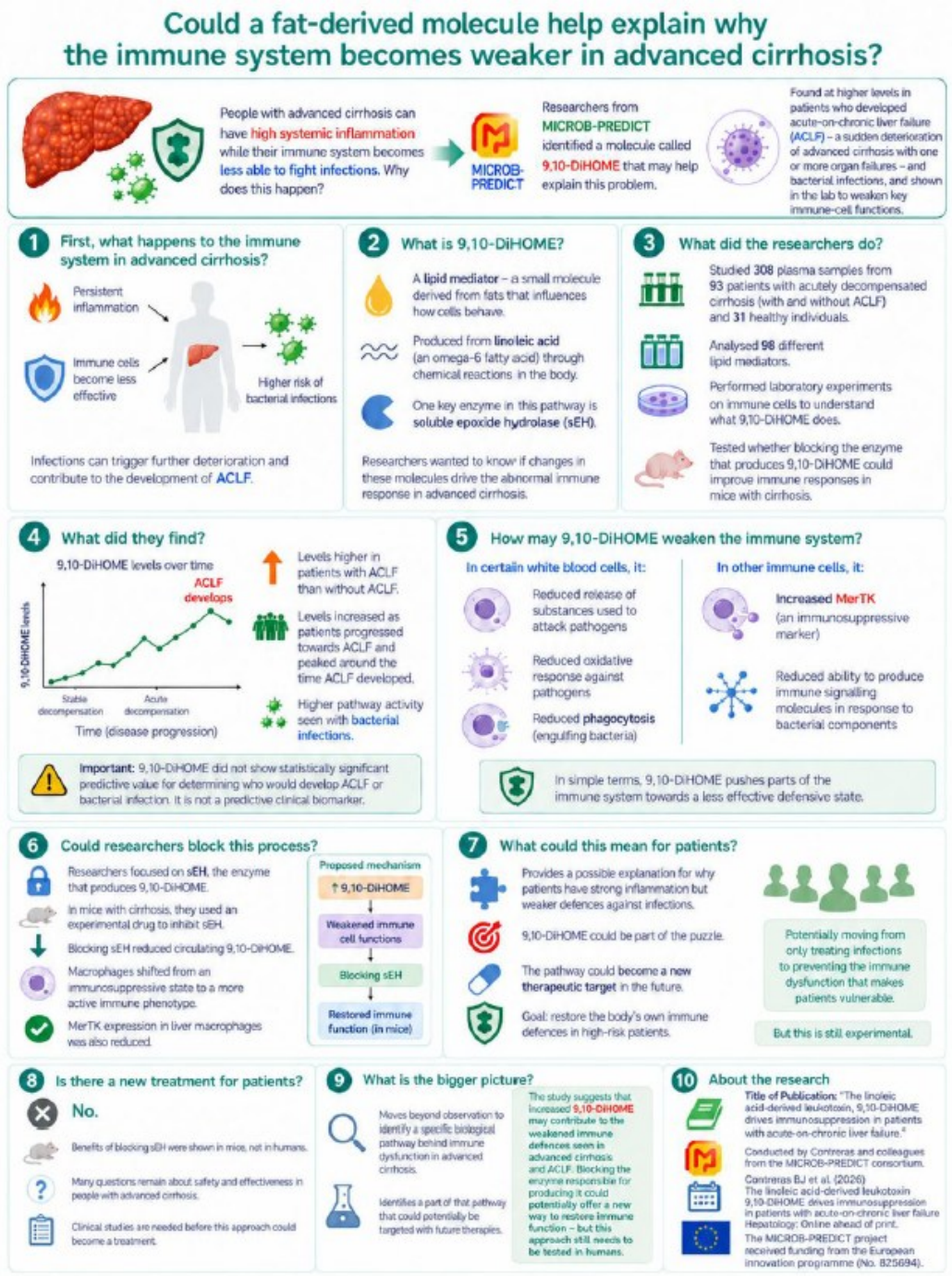
PICO	Consensus level	
6.5 In patients with cirrhosis and suspected hepatorenal syndrome–acute kidney injury (P), biomarker-guided early identification of patients likely to benefit from terlipressin therapy - particularly using urinary neutrophil gelatinase–associated lipocalin (uNGAL) and metabolomic profiles (I), compared with the standard diagnostic algorithm including a 24–48-hour albumin challenge prior to treatment initiation (C), may facilitate timely and targeted initiation of terlipressin therapy (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	12.15 (0.00/5.61/6.54)	**87.85** (28.97/46.73/12.15)

PICO	Consensus level	
6.6 In patients with cirrhosis and suspected hepatorenal syndrome–acute kidney injury (P), biomarker-guided early identification of patients likely to benefit from terlipressin therapy - particularly using urinary neutrophil gelatinase–associated lipocalin (uNGAL) and metabolomic profiles (I), compared with the standard diagnostic algorithm including a 24–48-hour albumin challenge prior to treatment initiation (C), may improve prediction of treatment response and clinically relevant outcomes (O).	Negative Consensus % of replies (1-3)	Positive Consensus % of replies (4-6)
On a scale from 1 to 6, with 1 being "strongly disagree" and 6 being "strongly agree", experts voted:	12.15 (0.00/3.74/8.41)	**87.85** (34.58/41.12/12.15)

6.2. Appendix 2 – Additional Lay Summaries of Key Publications (Visuals & Texts)

Original Publication:

Contreras et al. (2026)
The linoleic acid-derived leukotoxin 9,10-DiHOME drives immunosuppression in patients with acute-on-chronic liver failure
Hepatology: Online ahead of print.



Lay Summary:

Could a fat-derived molecule help explain why the immune system becomes weaker in advanced cirrhosis?

People with advanced cirrhosis can experience a strange combination: Their body may have high levels of systemic inflammation, while their immune system becomes less able to fight infections.

Why does this happen?
Researchers from **MICROB-PREDICT** identified a molecule called **9,10-DiHOME** that may help explain this problem. The molecule was found at higher levels in patients who developed **acute-on-chronic liver failure (ACLF)** - defined by sudden deterioration of advanced cirrhosis with organ failures, bacterial infections, and laboratory experiments showed that it can weaken important immune-cell functions.

First, what happens to the immune system in advanced cirrhosis?
When cirrhosis becomes more advanced and suddenly worsens — known as **acute decompensation** — the immune system can become severely disrupted. On one hand, the body can experience persistent inflammation. On the other, some immune cells become less effective at defending the body against bacteria. This weakened immune response can make people particularly vulnerable to **bacterial infections**, which can themselves trigger further deterioration and contribute to the development of ACLF. Understanding why this immune dysfunction occurs could therefore help researchers find new ways to protect patients with advanced cirrhosis.

What is 9,10-DiHOME?
9,10-DiHOME is a **lipid mediator** — a small molecule derived from fats that can influences cell behaviour. It is produced from **linoleic acid**, an omega-6 fatty acid, through a series of chemical reactions in the body. One of the key enzymes involved in producing 9,10-DiHOME is called **soluble epoxide hydrolase**, or **sEH**. The researchers wanted to understand if changes in these fat-derived signalling molecules could contribute to the abnormal immune response seen in advanced cirrhosis.

What did the researchers do?
The researchers initially studied **308 plasma samples collected over time from 93 patients** with acutely decompensated cirrhosis, with and without ACLF. They also included samples from **31 healthy individuals**. They analysed **98 different lipid mediators** to see whether particular molecules were associated with worsening disease. They then carried out laboratory experiments on immune cells to investigate what 9,10-DiHOME actually does. Finally, they tested whether blocking the enzyme responsible for producing 9,10-DiHOME could improve immune responses in **mice with cirrhosis**.

What did they find?
Among the lipid mediators studied, **9,10-DiHOME stood out**. Its levels were higher in patients with ACLF than in patients with acute decompensation without ACLF. Even more interestingly, when researchers followed patients over time, **levels of 9,10-DiHOME increased as patients progressed towards ACLF and peaked around the time ACLF developed**. Higher activity of the pathway producing 9,10-DiHOME was also seen when some patients developed bacterial infections. However, there is an important distinction: **9,10-DiHOME itself did not show statistically significant predictive value for determining which patients would develop ACLF or bacterial infection.** At this stage, it can therefore not be considered a predictive clinical biomarker.

How may 9,10-DiHOME weaken the immune system?
This was one of the most interesting parts of the study. Researchers exposed healthy immune cells to 9,10-DiHOME and found that it interfered with several of their normal defensive functions. In particular, it reduced the ability of certain white blood cells to:

- release substances used to attack pathogens,
- produce an effective oxidative response against them, and
- engulf bacteria through a process called **phagocytosis**.

In other immune cells, 9,10-DiHOME increased a marker called **MerTK**, which is associated with an immunosuppressive state, and reduced their ability to produce several immune signalling molecules when challenged with bacterial components.
In simple terms, **9,10-DiHOME appeared to push parts of the immune system towards a less effective defensive state.**

Could researchers block this process?
Potentially — and this is where the study becomes particularly interesting for future research.
Instead of targeting 9,10-DiHOME directly, researchers focused on **sEH**, one of the enzymes responsible for producing it. In mice with cirrhosis, researchers used an experimental drug to inhibit this enzyme. Blocking sEH reduced circulating 9,10-DiHOME and shifted macrophages — an important type of immune cell — away from an immunosuppressive state and towards a more active immune phenotype. The treatment also reduced the expression of the immunosuppressive marker MerTK in liver macrophages. The study's visual abstract on **page 1** summarizes this proposed mechanism: increased 9,10-DiHOME weakens several immune-cell responses, while blocking the enzyme that generates it may help reverse some of this immune dysfunction.

What could this mean for patients?
The findings provide a possible new explanation for an important problem in advanced cirrhosis:
Why can patients have strong systemic inflammation while simultaneously becoming less able to fight infections? 9,10-DiHOME could be one part of that puzzle. If future research confirms these findings, the pathway responsible for producing this molecule could potentially become a **new therapeutic target**. Rather than simply treating infections after they occur, researchers might eventually be able to explore approaches that help **restore the body's own immune defences** in patients at particularly high risk. But that possibility is still experimental.

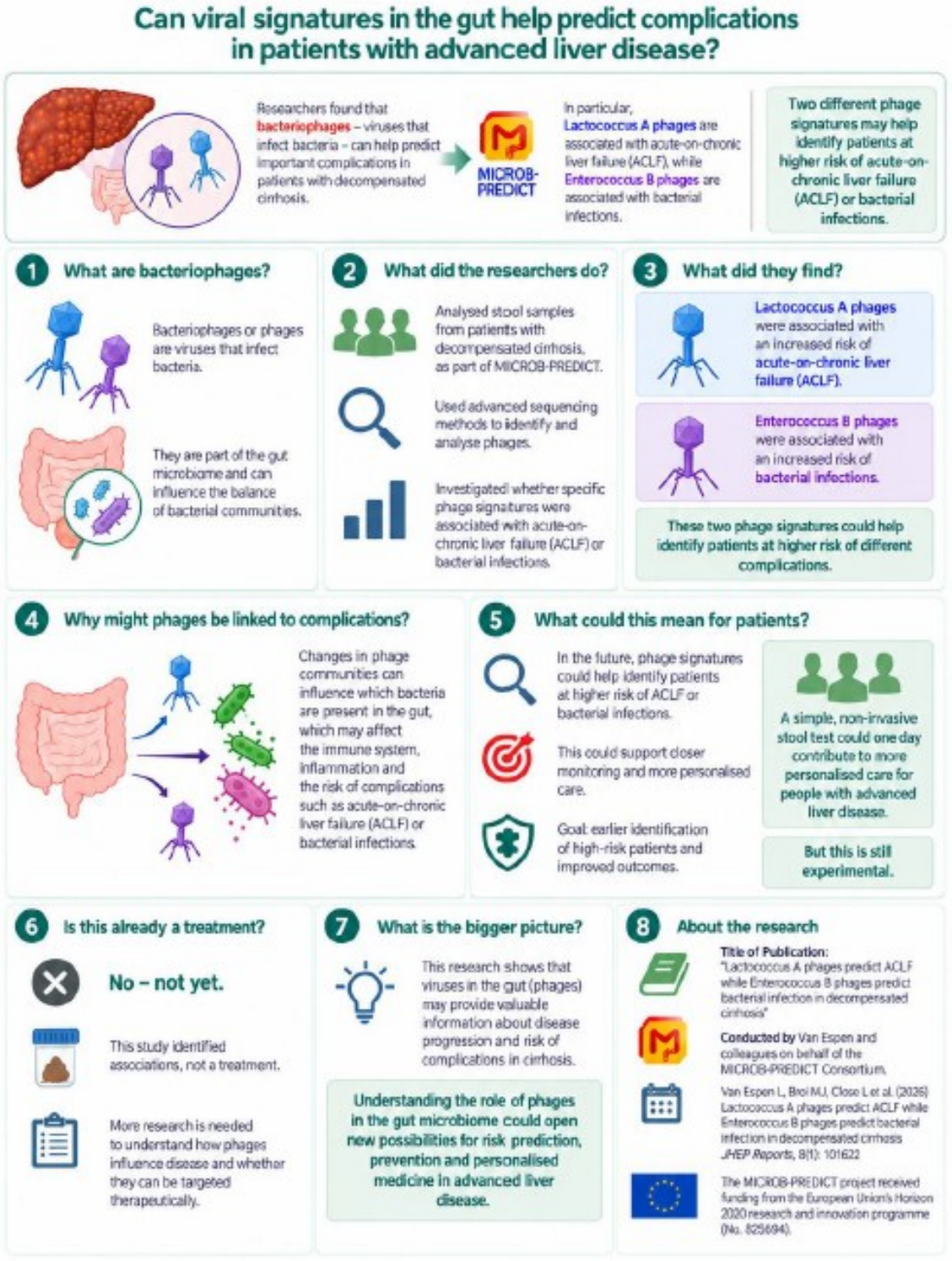
Does this mean there is a new treatment for patients with cirrhosis?
No — not yet. The experiments showing benefits from blocking sEH were performed in **mice**, not in patients with cirrhosis. The researchers themselves highlight several unanswered questions, including whether blocking this pathway in people with advanced cirrhosis would consistently restore healthy immune function or could have unintended effects. Clinical studies would therefore be needed before this approach could be considered a treatment for patients.

What is the bigger picture?
This research moves beyond simply observing that the immune system becomes dysfunctional in advanced cirrhosis. It identifies a **specific biological pathway that may contribute to that dysfunction** and, importantly, a part of that pathway that could potentially be targeted with future treatments. **The study suggests that increased 9,10-DiHOME may contribute to the weakened immune defences seen in advanced cirrhosis and ACLF. Blocking the enzyme responsible for producing it could potentially offer a new way to restore immune function — but this approach still needs to be tested in humans.** For patients, the long-term goal is important: finding ways not only to treat infections and complications once they happen, but potentially to **prevent the immune dysfunction that makes patients so vulnerable to them in the first place.**

About the research
The study, “The linoleic acid–derived leukotoxin 9,10-DiHOME drives immunosuppression in patients with acute-on-chronic liver failure”, was conducted by Contreras and colleagues on behalf of the MICROB-PREDICT consortium and published in the scientific journal *Hepatology* in 2026. The MICROB-PREDICT project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694.

Original Publication:

Van Espen et al. (2026)
Lactococcus A phages predict ACLF while Enterococcus B phages predict bacterial infection in decompensated cirrhosis
JHEP Reports, 8(1): 101622



Lay Summary:

Could bacteriophages (specialised viruses) living in our gut help predict complications of advanced liver disease?

Our gut contains trillions of microorganisms — including not only bacteria, but also bacteriophages. Could some of these bacteriophages help doctors identify people with cirrhosis who are at risk of becoming seriously ill?
Researchers from **MICROB-PREDICT** investigated **bacteriophages**, or simply **phages**, in people with decompensated cirrhosis. They found that certain groups of these phages were associated with the development of **acute-on-chronic liver failure (ACLF)** - defined by sudden deterioration of advanced cirrhosis with organ failures, bacterial infections, and a higher risk of death within 90 days.

First, what are bacteriophages?
When we talk about the gut microbiome, we usually think about bacteria. But our gut also contains a huge number of viruses. Many of these viruses are **bacteriophages**, which means that instead of infecting human cells, they infect bacteria. Taken together, all types of viruses living in the gut are known as the **gut virome**. Phages and bacteria constantly interact with each other. By influencing which bacteria survive and how they behave, phages may indirectly affect inflammation, the immune system, and human health.

Why could this matter in cirrhosis?
In people with advanced cirrhosis, the protective barrier of the gut (also called intestinal barrier can become weaker. This may allow bacteria or bacterial products from the gut to cross the intestinal barrier and contribute to increased inflammation and bacterial infections. These processes can play an important role when the condition of a patient with cirrhosis suddenly worsens. One of the most serious complications in cirrhosis is **acute-on-chronic liver failure (ACLF)** — a severe condition in which someone with chronic liver disease rapidly becomes very ill and may suffer from failure of one or more organs. However, predicting which patients will develop ACLF remains difficult. The researchers therefore asked whether changes in the **gut virome** might provide useful clues.

What did the researchers do?
Researchers analysed stool samples from people with decompensated cirrhosis and ACLF. The main study included **93 patients**, from whom **292 stool samples** were analysed over time. Patients were followed to see whether their condition remained stable, became unstable or progressed to ACLF. The researchers then used another group of **94 patients with decompensated cirrhosis** to test one of their important findings. Using advanced genetic sequencing, they studied the viruses present in the stool and examined how different phages were related to disease progression, bacterial infections, and survival.

What did they find?
The **gut virome changed** as liver disease became more severe. Patients with ACLF tended to have a **greater variety of phages** in their gut. Importantly, researchers could also see this diversity increase within individual patients as they progressed from decompensated cirrhosis to ACLF. The study also found a **change in the types of phages** present as patients became more seriously ill. This suggests that the gut's viral community is **not simply a passive passenger** in advanced liver disease. It changes alongside the patient's clinical condition.
Two groups of viruses stood out
Researchers identified two particularly interesting groups of phages:

1. ***Lactococcus A* phages**
   These phages were more commonly found in patients who **subsequently developed ACLF**. Their presence was also associated with **poorer survival during the following 90 days**. This raises the possibility that Lactococcus A phages could one day help identify patients whose cirrhosis is **at particularly high risk** of worsening. However, this specific finding still needs to be replicated in another independent group of patients.

2. ***Enterococcus B* phages**
   A different group, called ***Enterococcus B* phages**, was associated with **bacterial infections**. Patients carrying these phages also had **poorer 90-day survival**. Importantly, the association between Enterococcus B phages and bacterial infection was also tested in a second, independent group of patients, where the researchers again found higher levels of these phages among patients with bacterial infections.

What could this mean for patients with cirrhosis?
Today, doctors use clinical information, blood tests, and scoring systems to assess how seriously ill a person with cirrhosis is. But predicting **who will go on to develop ACLF** remains challenging. This research suggests that information hidden within the gut virome could potentially provide an **additional warning signal**. In the future, analysing phages in stool samples might help doctors identify patients who are at greater risk of:

- developing ACLF,
- having one or more bacterial infections, or
- experiencing a poor short-term outcome.

This could potentially allow high-risk patients to be **identified and monitored more closely**. However, these possibilities still need further research before they could become part of routine patient care.

Does this mean these viruses cause ACLF or infections?
Not necessarily. The researchers found **associations between particular phages and serious clinical outcomes**, but this does not mean that the phages themselves cause ACLF, infection, or death. However, changes in the gut virome can be **part of the disease process**, **a consequence of worsening disease, or both.** The study therefore opens an important new area for research into the complex relationship between **gut bacteria, gut viruses, inflammation, and liver disease**.

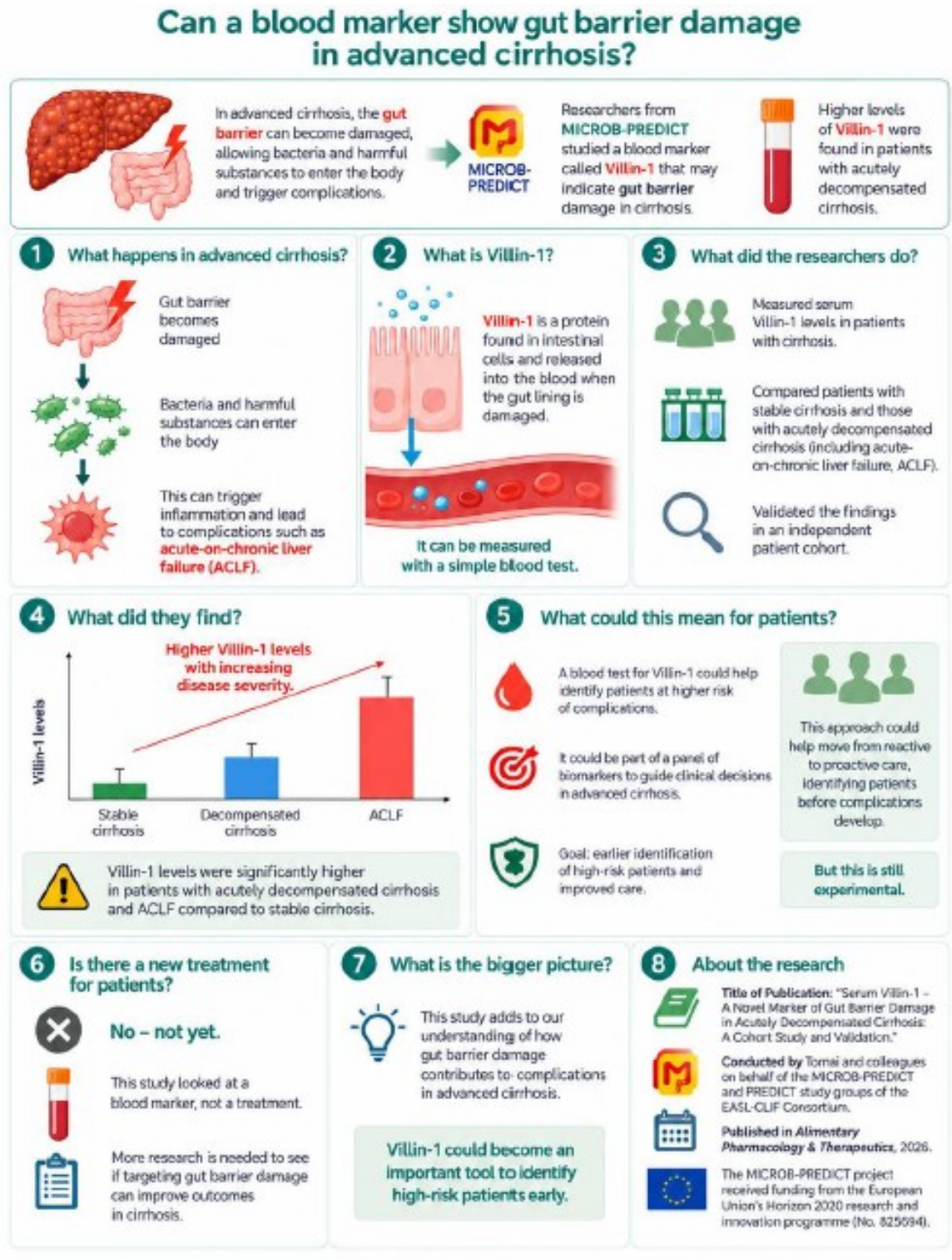
Can doctors test for these viruses today?
Not yet. Gut virome analysis is currently a research tool rather than a routine clinical test. The study involved relatively small and diverse groups of patients, and some findings — particularly the possible ability of *Lactococcus A* phages to predict ACLF — still needs to be validated in additional patient populations. More research is also needed to understand whether these phages are simply **markers of disease** or whether they actively contribute to disease progression.

What is the bigger picture?
This research adds another piece to our understanding of the **gut–liver connection**. The gut microbiome is much more than bacteria. Viruses that interact with those bacteria may also contain valuable information about what is happening during advanced liver disease. **In the future, analysing the viruses living in the gut could potentially help doctors identify people with cirrhosis who are at greater risk of ACLF or bacterial infection — allowing closer monitoring and, potentially, earlier intervention.** For now, this remains a promising research direction rather than a test available in routine clinical care.

About the research
The study, "*Lactococcus A* phages predict ACLF while *Enterococcus B* phages predict bacterial infection in decompensated cirrhosis", was conducted by Van Espen and colleagues on behalf of MICROB-PREDICT and published in *JHEP Reports* in 2026. The MICROB-PREDICT project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694. The study also received funding from other research programmes.

Original Publication:

Tornai et al. (2026)
Serum Villin-1 - A Novel Marker of Gut Barrier Damage in Acutely Decompensated Cirrhosis: A Cohort Study and Validation
Alimentary Pharmacology & Therapeutics, 63(7): pp. 1018-1032



Lay Summary:

Could a blood test help doctors detect damage to the gut barrier in people with advanced liver disease?

The gut and liver are closely connected. But could damage to the gut also help us understand which patients with advanced liver disease are at greatest risk? Researchers from **MICROB-PREDICT and the PREDICT Study Group** investigated a protein called **villin-1 (VIL1)** and whether measuring it in the blood could provide new information about gut damage and the risk of poor outcomes in people whose cirrhosis has suddenly worsened.

Why is the gut barrier important in cirrhosis?
The gut has a protective barrier that helps keep bacteria and other potentially harmful substances inside the intestine and away from the bloodstream. In people with cirrhosis, this barrier can become damaged. When that happens, bacterial products may pass more easily from the gut into the bloodstream, contributing to inflammation and potentially worsening the patient's condition. Despite the importance of this **gut–liver connection**, damage to the gut barrier is not currently included in the main scoring systems doctors use to assess the severity of acutely decompensated cirrhosis. One reason is that there has been no simple and reliable way to measure this damage.

What is villin-1?
Villin-1 is a protein found in cells lining the intestine. It helps maintain tiny structures on the surface of intestinal cells that are important for normal gut function. The researchers investigated whether injury to these cells could cause villin-1 to enter the bloodstream — and whether measuring it in a blood sample could therefore provide information about damage to the gut barrier.

What did the researchers do?
The study included **338 people with acutely decompensated cirrhosis**, including patients with **acute-on-chronic liver failure (ACLF)** - defined by sudden deterioration of advanced cirrhosis with organ failures, as well as **50 healthy individuals**. Researchers measured villin-1 in blood samples. In a smaller group, they also examined intestinal tissue samples. Importantly, the researchers first investigated their findings in a group of patients from University of Debrecen and then tested them again in a separate group of patients recruited from **25 European hospitals**.

What did they find?
The results showed an interesting pattern. In patients with relatively stable decompensated cirrhosis, villin-1 levels in both intestinal tissue and blood were lower than in healthy individuals. However, as acute illness became more severe, **villin-1 levels in the blood increased**, reaching their highest levels in patients with ACLF. Higher levels were also found in some patients **before they developed ACLF**, suggesting that villin-1 may potentially provide an early signal of worsening disease. The study shows this increase as patients move towards more severe stages of illness.

Could villin-1 also tell us something about a patient's risk?
Potentially, yes. Patients who died within 90 days had higher villin-1 levels than those who survived. Higher villin-1 was also associated with increased inflammation. Importantly, villin-1 continued to provide information about the risk of death even when researchers took the severity of the patient's liver disease into account. The researchers also found that combining villin-1 with existing measures of disease severity could improve the identification of patients at particularly high risk. These findings were confirmed in the second patient group.

What could this mean for patients?
If these findings are confirmed in further studies, villin-1 could potentially become a **simple blood-based marker of gut barrier damage**. For doctors, this could provide another piece of information when assessing a patient whose cirrhosis has suddenly worsened. For patients, better risk assessment could eventually mean that those at greatest risk are **identified earlier, monitored more closely and considered for appropriate treatment sooner**. The researchers even propose that severe damage to

the gut barrier might eventually be considered another form of **organ failure** in ACLF, alongside the organ failures already assessed today.

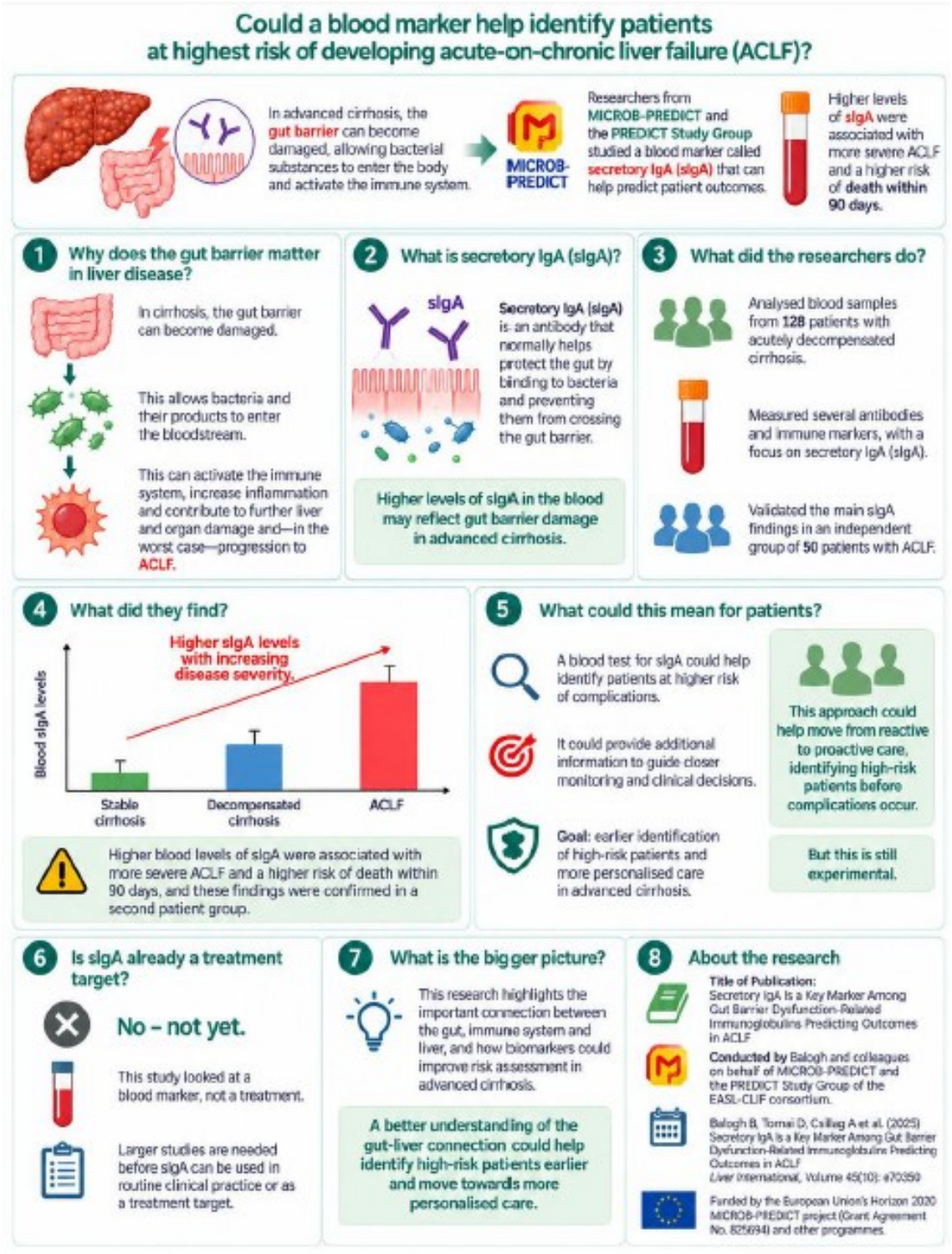
Is villin-1 already used as a biomarker in hospitals?
No. This is an important point. Villin-1 is currently a **promising research biomarker**, not a routine clinical test for people with cirrhosis. The researchers found different optimal villin-1 thresholds in their two patient groups. Before the marker could enter routine clinical practice, it would need further prospective validation, a standardized laboratory method and a clearly established threshold. More research is also needed to confirm exactly where circulating villin-1 comes from and how its levels change as a patient's condition worsens or improves.

What is the bigger picture?
This study highlights something that can sometimes be overlooked in advanced liver disease:
The liver does not become sick in isolation. Damage to the gut barrier, inflammation and liver disease can influence one another. Finding a reliable way to measure gut barrier damage could therefore help researchers and clinicians understand this relationship better. **In the future, a simple blood marker such as villin-1 could potentially help doctors see another important part of the picture — the health of the gut barrier — and identify high-risk patients more accurately.**

About the research
The study, “Serum Villin-1—A Novel Marker of Gut Barrier Damage in Acutely Decompensated Cirrhosis: A Cohort Study and Validation”, was conducted by Tornai and colleagues on behalf of MICROB-PREDICT and the PREDICT Study Group of the EASL-CLIF Consortium and published in *Alimentary Pharmacology & Therapeutics* in 2026. The research included patients from the MICROB-PREDICT cohorts and received funding from the European Union's Horizon 2020 MICROB-PREDICT project (Grant Agreement No. 825694) and other research programmes.

Original Publication:

Balogh B, Tornai D, Csillag A et al. (2025)
Secretory IgA Is a Key Marker Among Gut Barrier Dysfunction-Related Immunoglobulins Predicting Outcomes in ACLF
Liver International, Volume 45(10): e70350



Lay Summary:

Could a blood marker help identify patients at highest risk during acute-on-chronic liver failure?

What if a blood test could give doctors more information about which patients with severe liver disease are at greatest short-term risk? Researchers from **MICROB-PREDICT and the PREDICT Study Group** investigated whether changes in the immune system and the gut barrier could provide important clues. Their study focused on **secretory Immunoglobulin AA (sIgA)**, an antibody closely connected to the gut's protective barrier, and its potential to help predict outcomes in people with **acute-on-chronic liver failure (ACLF)** - defined by sudden deterioration of advanced cirrhosis with organ failures.

Why does the gut barrier matter in liver disease?
The **gut and liver are closely connected**. Normally, the gut barrier helps prevent bacteria and their products from entering the bloodstream. In cirrhosis, this protective barrier can become damaged, allowing more bacterial material to pass from the gut into the circulation. This can activate the immune system, increase inflammation and contribute to further liver and organ damage.

What did researchers want to discover?
Researchers asked: **Could antibodies linked to the gut barrier tell us something about how severe a patient's condition is — and their risk of poor outcomes?** They studied blood samples from **128 patients with acutely decompensated cirrhosis**, measuring several different antibodies and immune markers. They paid particular attention to **secretory IgA**, an antibody that normally plays an important role in protecting the gut against bacteria. An additional group of 50 patients with ACLF was used to validate the main sIgA findings.

What did they find?
The researchers found that changes in several antibodies were associated with the severity of liver disease. But one marker stood out in patients with ACLF: **secretory IgA**. Higher blood levels of sIgA were associated with more severe ACLF and a **higher risk of death within 90 days**. Importantly, the researchers confirmed this association in a second group of patients. The study suggests that high levels of sIgA in the blood may reflect **severe damage to the gut barrier**, allowing substances that would normally remain in the gut to leak into the bloodstream.

What could this mean for patients?
ACLF is a serious condition in which a person with chronic liver disease suddenly becomes much sicker and may develop failure of one or more organs. Identifying patients at greatest risk as early as possible is therefore extremely important. If further research confirms these findings, measuring sIgA could potentially provide doctors with **additional information to help identify high-risk patients and guide closer monitoring and care**.

Does this mean sIgA can already predict what will happen to an individual patient?
No. Although the results are promising, sIgA is **not yet an established clinical test for predicting outcomes in ACLF**. The ACLF groups studied were relatively small, and the authors stress that the findings need to be validated in larger, independent patient populations. sIgA would also need to be interpreted together with existing measures of disease severity rather than on its own.

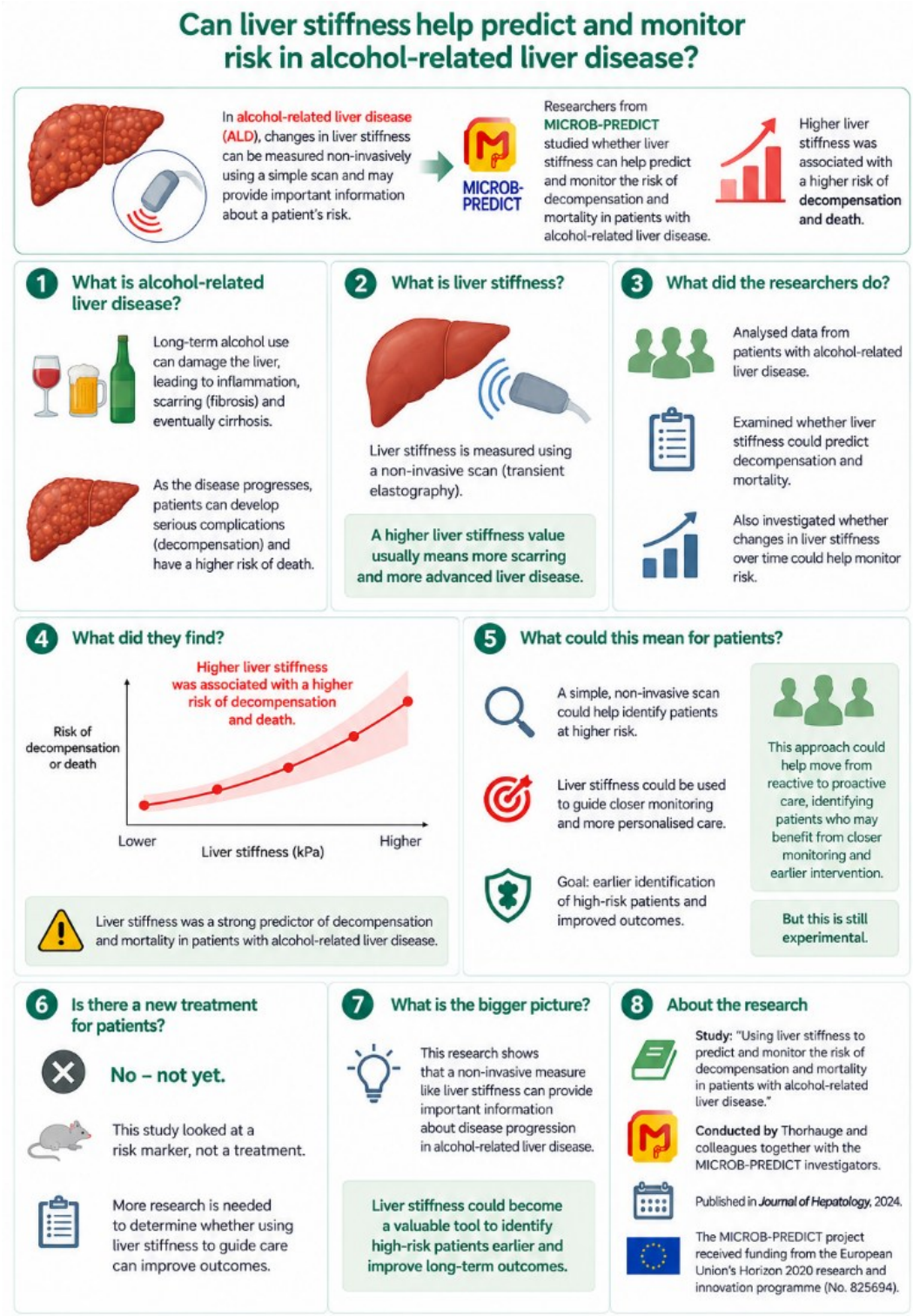
What is the bigger picture?
This research helps us better understand the important relationship between the **gut, immune system and liver**. It also shows how biomarkers could potentially improve the way we identify patients at greatest risk. **A better understanding of the gut–liver connection could help doctors recognise high-risk patients earlier and move towards more personalised care.**
For patients with severe liver disease, better risk assessment could ultimately support **closer monitoring, more informed clinical decisions and earlier intervention when needed**.

About the research

The study, “Secretory IgA Is a Key Marker Among Gut Barrier Dysfunction-Related Immunoglobulins Predicting Outcomes in ACLF”, was published in *Liver International* in 2025 by Balogh and colleagues on behalf of MICROB-PREDICT and the PREDICT Study Group of the EASL-CLIF Consortium. The research received support from the European Union's Horizon 2020 MICROB-PREDICT project (Grant Agreement No. 825694) and other funding programmes.

Original Publication:

Thorhauge et al. (2024)
Using liver stiffness to predict and monitor the risk of decompensation and mortality in patients with alcohol-related liver disease
Journal of Hepatology, 81(1): pp. 23-32



Lay Summary:

Can changes in liver stiffness tell us how alcohol-related liver disease is progressing?

What if a simple, non-invasive test could help doctors see whether liver disease is becoming more or less serious over time?
This is what researchers from the **MICROB-PREDICT, GALAXY and MicrobLiver projects** investigated in people at risk of **alcohol-related liver disease (ALD)**. They studied whether **liver stiffness measurements** could help predict the risk of serious complications — and whether repeating the measurement over time could provide even more useful information.

Why does monitoring liver stiffness matter?
Alcohol-related liver disease can progress gradually, sometimes before a person develops obvious symptoms. A test called **transient elastography** — often known through devices such as FibroScan — can measure how stiff the liver is without a biopsy. Greater liver stiffness can indicate more advanced liver disease. But researchers wanted to go beyond a single measurement: **Could changes in liver stiffness over time tell us whether a patient's risk is increasing or decreasing?**

What did researchers investigate?
The researchers studied **536 people from Denmark and Austria** who were at risk of alcohol-related liver disease but had not yet experienced liver decompensation. They examined whether liver stiffness could predict **decompensation** — when the liver can no longer compensate for the damage and serious complications develop — as well as the risk of death. For **371 participants**, liver stiffness was measured again after a median of approximately two years, allowing researchers to see whether changes over time were linked to future outcomes.

What did they find?
The results showed that **both the initial liver stiffness measurement and changes over time provided important information about a person's future risk**. People who already had compensated advanced chronic liver disease at the beginning of the study had a much higher risk of future decompensation than those without advanced disease. Among people with advanced disease who had repeat measurements, an **increase in liver stiffness of 20% or more** was associated with a higher risk of decompensation and death compared with patients whose liver stiffness decreased. The graphical summary on page 1 captures the main finding clearly: **Liver stiffness can help both predict and monitor risk in alcohol-related liver disease.**

What could this mean for patients?
A liver stiffness measurement may provide more than a snapshot of liver health. **Repeating the test over time could help show whether a person's liver disease and future risk are changing.** This could potentially help healthcare professionals identify people who need closer monitoring and support more informed conversations between patients and their healthcare teams. Importantly, however, **a decrease in liver stiffness does not mean that all risk has disappeared**. People with advanced liver disease still require appropriate follow-up and surveillance.

Does this mean everyone needs regular liver stiffness tests?
Not necessarily. Current recommendations support regular liver stiffness monitoring for people with compensated advanced chronic liver disease, while monitoring for people without advanced disease should be based on their individual risk. The researchers also point out that more studies are needed to determine **how often measurements should be repeated** and how changes should best be interpreted in different patients.

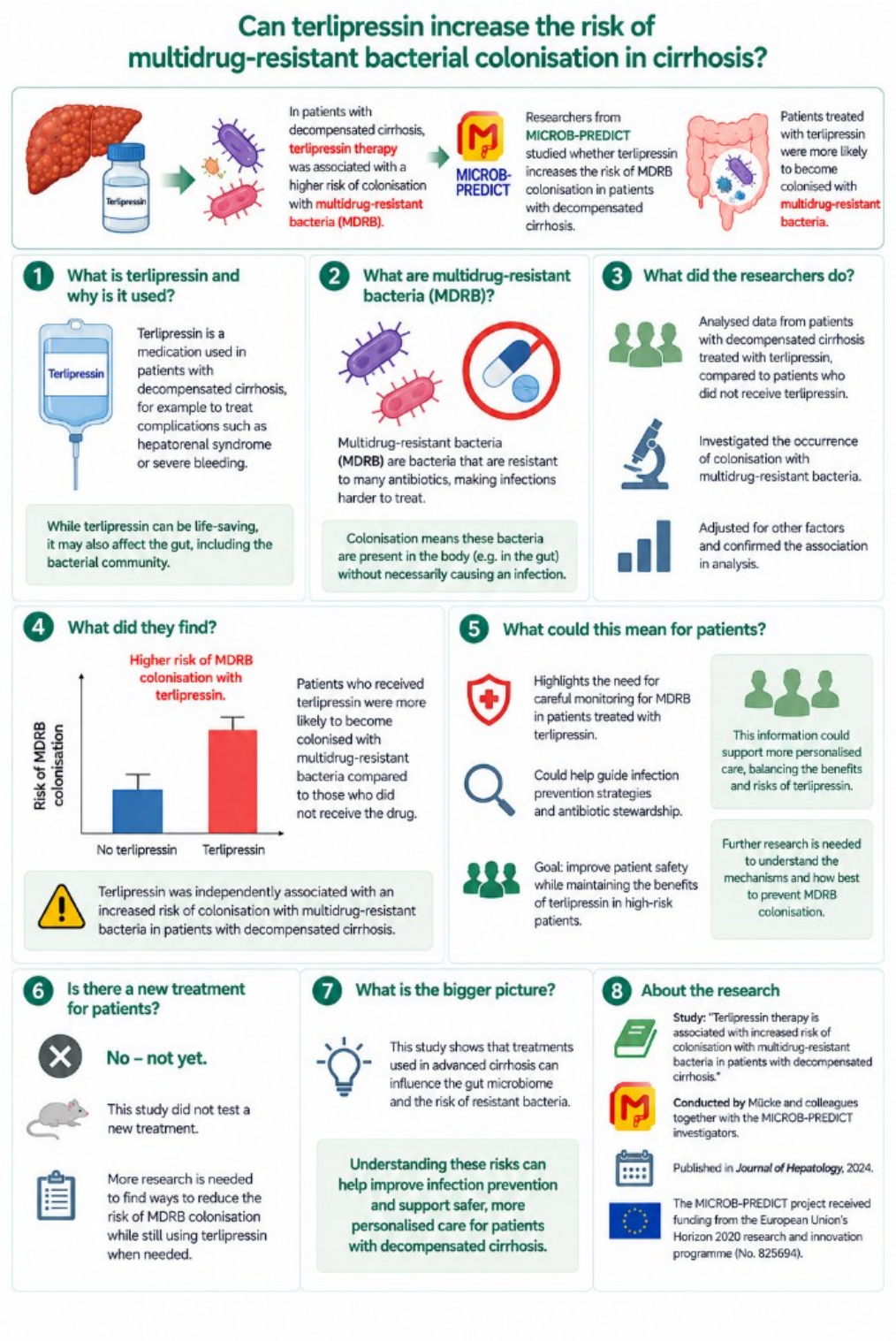
What is the bigger picture?
This research supports an important shift in liver care: **Don't only measure where the patient is today — monitor where their liver health is heading.** Non-invasive tests such as liver stiffness measurement could help healthcare professionals follow disease progression without relying on liver biopsy and identify changes in risk earlier. For patients, this could ultimately mean **better monitoring, earlier recognition of worsening disease and more personalised follow-up**.

About the research

The study, “Using liver stiffness to predict and monitor the risk of decompensation and mortality in patients with alcohol-related liver disease”, was published in the *Journal of Hepatology* in 2024. It included researchers from the MICROB-PREDICT, GALAXY, and MicrobLiver consortia. MICROB-PREDICT has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 825694.

Original Publication:

Mücke et al. (2024)
Terlipressin therapy is associated with increased risk of colonisation with multidrug-resistant bacteria in patients with decompensated cirrhosis
Aliment Pharmacol Ther, 59(7): pp. 877-888



Lay Summary:

Could a treatment for complications of cirrhosis affect the risk of multidrug-resistant bacteria?

Bacterial infections can be particularly dangerous for people with advanced liver disease. But could some treatments also influence the bacteria living in our bodies?
Researchers from the **MICROB-PREDICT project and PREDICT Study Group** investigated this question in people with **decompensated cirrhosis** — a stage of liver disease in which serious complications have developed. Their findings point to an unexpected association between the medicine **terlipressin** and colonisation with multidrug-resistant bacteria.

Why are resistant bacteria a concern for people with cirrhosis?
People with advanced cirrhosis have an increased risk of serious bacterial infections. Some bacteria have become resistant to several antibiotics. These are known as **multidrug-resistant organisms (MDROs)**, and infections caused by them can be much more difficult to treat. Importantly, a person can first become **colonised** with resistant bacteria — meaning the bacteria are present in or on the body without necessarily causing an infection. This colonisation can increase the risk of developing an MDRO infection later. In this study, patients who were colonised were indeed more likely to subsequently develop an MDRO infection.

What did the researchers want to discover?
Researchers wanted to know: Could medicines other than antibiotics also influence the **risk of becoming colonised with resistant bacteria**? Antibiotic use is a well-known risk factor for the development of antibiotic resistance. They therefore examined medications often received by people with acute decompensation or acute-on-chronic liver failure, including **terlipressin**. Terlipressin is used in people with cirrhosis to manage serious complications, particularly **hepatorenal syndrome**, a form of kidney dysfunction associated with advanced liver disease.

What did the study find?
The main analysis included **324 patients** admitted to intensive care in Frankfurt. The researchers also examined additional patient groups from Barcelona and a European multicentre cohort. Around **30% of the 324 patients were colonised with multidrug-resistant bacteria**, and 11% developed an MDRO infection during their hospital stay. As expected, previous antibiotic treatment was associated with a higher risk of MDRO colonisation. However, researchers also found something unexpected: **Among the other medications studied, recent terlipressin treatment was associated with an increased risk of MDRO colonisation.** Additional analyses in other patient groups and analysis of antibiotic-resistance genes in the gut microbiome provided further evidence supporting this observation.

Does this mean terlipressin causes antibiotic resistance?
No. This is a very important distinction. The study found an **association**, but it cannot establish that terlipressin itself causes patients to become colonised with resistant bacteria. The main study was retrospective, and relatively few patients had received terlipressin. The authors also acknowledge that patients receiving terlipressin may have been sicker and therefore already more vulnerable to colonisation and infection. The researchers therefore stress that **future prospective studies are needed to confirm the finding**.

Why could this research matter to patients?
Terlipressin is an important medicine used to manage serious complications of advanced cirrhosis. These findings do **not** mean that patients should stop or avoid treatment. Instead, the research raises a new question about whether patients receiving terlipressin may benefit from **closer monitoring for multidrug-resistant bacteria**. If future studies confirm the association, this knowledge could help healthcare professionals identify patients at greater risk and potentially adapt infection monitoring and treatment strategies accordingly.

What is the bigger picture?
This study highlights how complex the relationship between **medicines, the gut microbiome, and antibiotic resistance** can be. Understanding these connections is particularly important for people with

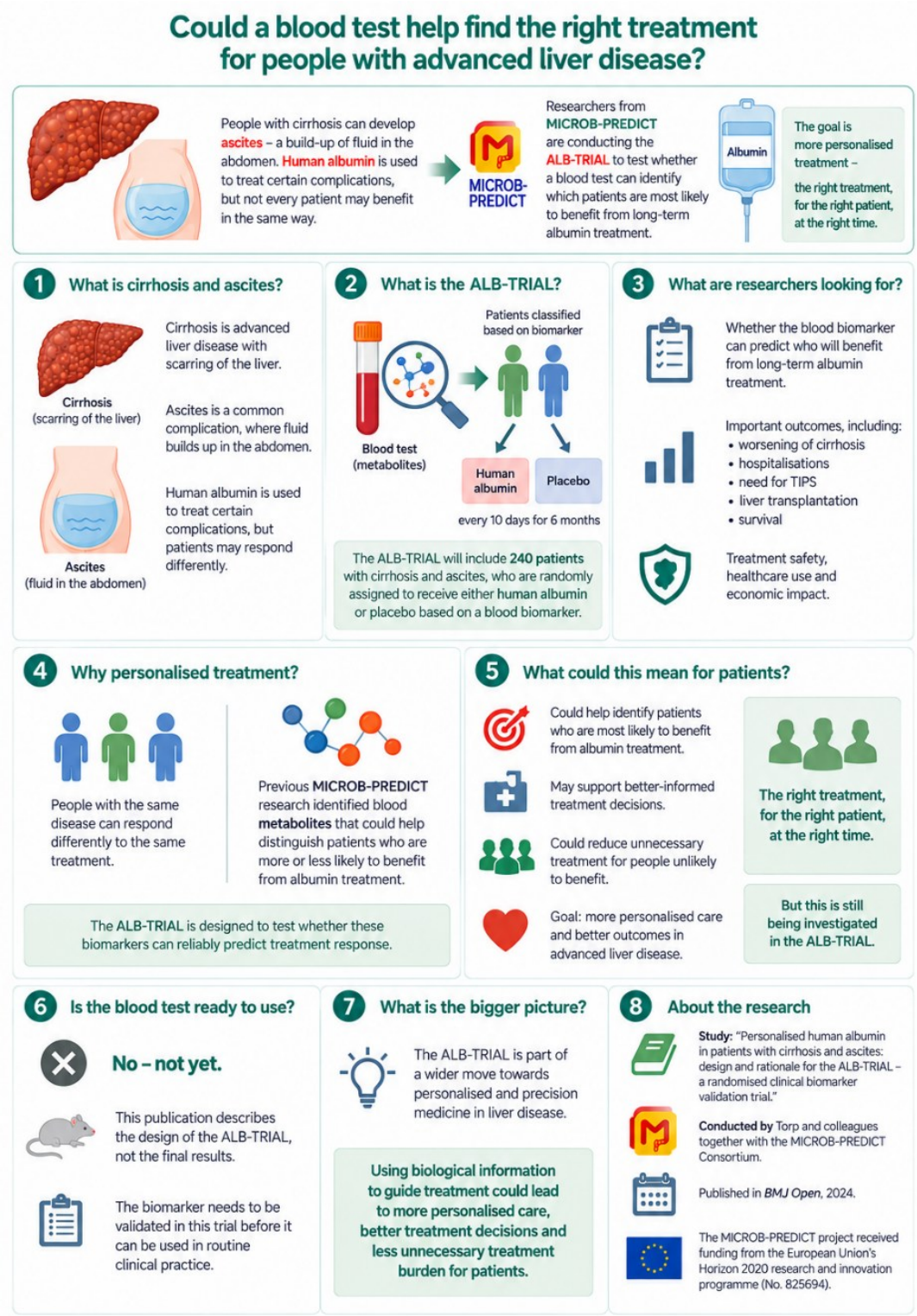
advanced liver disease, where bacterial infections can have severe consequences. The message is therefore not **"terlipressin is unsafe."** Instead, the research tells us: **We may need to understand and monitor infection risk more carefully in patients receiving certain treatments.** More research is needed to determine whether terlipressin directly influences MDRO colonisation, why this association may occur, and how this knowledge could eventually be used to improve patient care.

About the research

The study "Terlipressin therapy is associated with increased risk of colonisation with multidrug-resistant bacteria in patients with decompensated cirrhosis" was published in *Alimentary Pharmacology & Therapeutics* in 2024 by Mücke and colleagues on behalf of MICROB-PREDICT and the PREDICT Study Group of the EASL-CLIF Consortium. The research received support from several programmes, including the EU-funded MICROB-PREDICT project (Grant Agreement No. 825694).

Original Publication:

Torp et al. (2024)
Personalised human albumin in patients with cirrhosis and ascites: design and rationale for the ALB-TRIAL – a randomised clinical biomarker validation trial
BMJ Open, 14(2): e079309



Lay Summary:

Could a blood test help find the right treatment for people with advanced liver disease?

What if doctors could predict which patients are most likely to benefit from a treatment before starting months of therapy?
This is the idea behind the **ALB-TRIAL**, a European clinical study developed within the EU-funded MICROB-PREDICT project. The study focuses on people living with **cirrhosis and ascites** — a build-up of fluid in the abdomen that can occur in advanced liver disease. Human albumin is already used to treat certain complications of cirrhosis, but not every patient may equally benefit from long-term albumin treatment. Researchers therefore want to understand whether treatment could become more personalised.

Why isn't the same treatment right for everyone?
People with the same disease can respond differently to the same treatment. Previous MICROB-PREDICT research identified substances in the blood, called **metabolites**, that could potentially help distinguish patients who are more or less likely to benefit from albumin treatment. The ALB-TRIAL was designed to test whether these **biomarkers can reliably predict response to long-term albumin treatment**.

What is the ALB-TRIAL trying to discover?
The central question is simple: **Can a blood test help identify which patients with cirrhosis and ascites are most likely to benefit from long-term albumin treatment?** The study plans to include **240 patients**. Based on the biomarker, patients are classified as having a higher or lower expected benefit and are then randomly assigned to receive either **human albumin or placebo every 10 days for six months**.

What are researchers looking for?
Researchers want to know whether the biomarker can predict meaningful benefits for patients.
They are looking at important outcomes such as **worsening of cirrhosis, hospitalisations, the need for a transjugular intrahepatic shunt (TIPS), liver transplantation and survival**, as well as treatment safety, healthcare use and economic impact. In other words: **Does the treatment work — and can we predict for whom it will work?**

Why could this matter to patients?
Long-term treatment means repeated infusions and healthcare visits. If researchers could identify in advance who is most likely to benefit, treatment could potentially become more personalised. The longer-term ambition is: **The right treatment, for the right patient, at the right time.** This could support better-informed treatment decisions while potentially reducing unnecessary treatment for people unlikely to benefit.

Does this mean the blood test is ready to use?
No. This publication describes the **design of the ALB-TRIAL**, not its final results. Earlier research provided a promising signal, but the trial is designed to establish whether the biomarker actually works as a reliable tool for predicting treatment response.

Where does the patient voice fit in?
Patients are not only potential beneficiaries of this research — the **patient perspective also contributed to the study**. ELPA President **Marko Korenjak is among the co-authors of the publication**, bringing patient representation into research developed within the MICROB-PREDICT Consortium. Ultimately, personalised medicine should help answer questions that matter to patients: **Will this treatment help me? Is the treatment burden justified? And can my doctors make a better decision based on my individual situation?**

What is the bigger picture?
The ALB-TRIAL is part of a wider move towards **personalised and precision medicine in liver disease**. Instead of treating everyone with the same diagnosis in exactly the same way, researchers

are exploring whether biological information can help guide more individual treatment decisions. If successfully validated, this approach could contribute to **more personalised care, better treatment decisions and less unnecessary treatment burden** for people living with advanced liver disease.

About the research

The MICROB-PREDICT project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694. The study also received funding from other research programmes.