



Letter to the Editor

From the Gut–Liver Axis to the Gut–Liver–Immune–Transplant Continuum in MASLD



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Received: September 02, 2026 | Revised: September 24, 2026 | Accepted: October 08, 2026 | Published online: October 15, 2026

Dear Editors,

We read with interest the review by Joon *et al.*¹ describing the gut–liver axis, intestinal dysbiosis, microbial metabolites, and emerging microbiome-directed therapies in metabolic dysfunction-associated steatotic liver disease (MASLD). We suggest that its translational relevance can be strengthened by extending the gut–liver axis into a gut–liver–immune–transplant continuum.

First, future discussions should apply the updated nomenclature with diagnostic precision. MASLD is defined by hepatic steatosis and at least one cardiometabolic risk factor, whereas metabolic dysfunction and alcohol-associated steatotic liver disease and other forms of steatotic liver disease represent distinct categories.^{2,3} Historical studies of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis remain relevant, but their populations should not be assumed to be interchangeable with contemporary MASLD and metabolic dysfunction-associated steatohepatitis (MASH) cohorts. This distinction matters for microbiome studies because alcohol exposure, diabetes, obesity, diet, ethnicity, medications, and disease stage can each alter microbial composition and host immunity.

Second, the field should move from taxonomic description toward functional and mechanistic interpretation. Barrier disruption, microbial products, bile acids, and short-chain fatty acids may contribute to hepatic inflammation and fibrosis.^{4,5} Nevertheless, microbial signatures are cohort-specific; reported differences in diversity and taxonomic composition do not establish that a particular genus is pathogenic or protective.^{6,7} Standardized sampling, medication and diet metadata, strain- or pathway-level analysis, and independent validation are more important than expanding lists of “good” and “bad” bacteria.

The immune dimension deserves particular emphasis. Microbial components and metabolites may influence epithelial integrity, Kupffer-cell activation, innate immune sensing, inflammatory activity, and proinflammatory versus regulatory T-cell

responses. A systematic review and meta-analysis found that gut microbiota-modulating therapies in chronic liver disease were associated with reductions in tumor necrosis factor- α and C-reactive protein, whereas interleukin-6 results were inconsistent.⁸ These findings suggest an immune role but caution against treating inflammatory markers as validated surrogates for MASH resolution or fibrosis regression. The useful concept may therefore be an “immune–metabolite phenotype,” rather than dysbiosis alone. This framework positions microbiome-derived products and microbial functions as potential modulators of host immunity.

Third, artificial intelligence (AI) should be assigned a specific clinical task: extracting reproducible, nonlinear interactions from high-dimensional microbiome, metabolome, immune, imaging, laboratory, diet, and medication data that are difficult to represent in a conventional regression model. The immediate objective is not to replace clinical scores, but to improve identification of patients with clinically important MASH or fibrosis who might otherwise be misclassified by sequential noninvasive testing, and to identify patterns associated with treatment response or transplant complications. A multistep machine-learning strategy based on clinical variables and serum metabolites predicted MASH and liver-related mortality in geographically distinct cohorts and outperformed the fibrosis-4 index and the nonalcoholic fatty liver disease fibrosis score for MASLD-related mortality prediction.⁹ A separate study developed and externally evaluated a lightweight machine-learning model for biopsy-defined MASH with F2–F3 fibrosis using a limited clinical and metabolomic feature set.¹⁰ These examples clarify what AI adds: multimodal feature selection, interaction discovery, and individualized risk estimation. Any proposed model should still be compared with fibrosis-4, vibration-controlled transient elastography, and magnetic resonance measures, with calibration, clinical utility, dataset shift, potential bias, and clinician oversight reported.

The transplant setting supplies a clinically meaningful endpoint. Patients with advanced MASLD have simultaneous metabolic, cardiovascular, infectious, and immunological vulnerabilities, and current guidance emphasizes multidisciplinary assessment across the pre-, peri-, and post-transplant phases.³ Fecal metabolite profiling in 107 liver-transplant recipients associated reduced microbial diversity, depletion of short-chain fatty acids and secondary bile acids, and pathobiont expansion with postoper-

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How to cite this article: Gadour E. From the Gut–Liver Axis to the Gut–Liver–Immune–Transplant Continuum in MASLD. *J Transl Gastroenterol*. Published online: Oct 15, 2026. DOI: 10.14218/JTG.2026.00035.

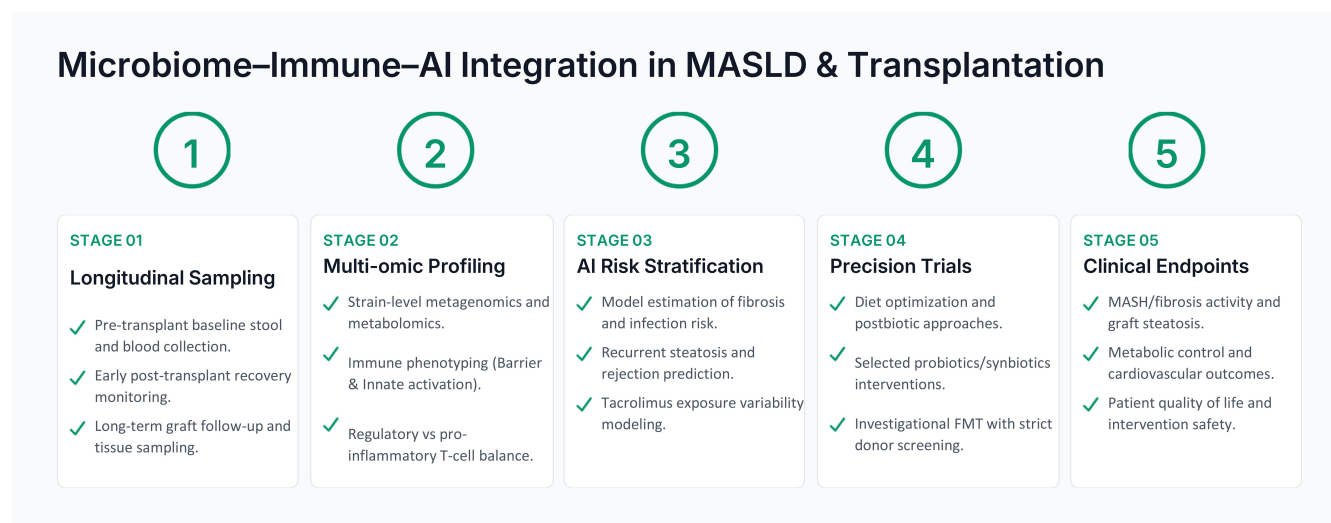


Fig. 1. Proposed translational pipeline for microbiome–immune–AI integration in MASLD and liver transplantation. AI, artificial intelligence; FMT, fecal microbiota transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; T-cell, T lymphocyte.

active infection risk.¹¹ Dysbiosis measures have also been associated with mortality in solid organ transplant recipients, although observational data do not establish causality.¹² Gut microbial composition has been associated with tacrolimus pharmacokinetic variability, raising the possibility of microbiome-informed immunosuppressant monitoring.¹³ Gadour's review highlights the broader movement toward precision transplantation.¹⁴

We propose a prospective, longitudinal strategy (Fig. 1) beginning before transplantation and continuing through recovery and long-term graft follow-up. Standardized stool and blood sampling should be paired with detailed diet, medication, immune, graft, infection, rejection, and recurrent steatosis data. Metagenomics and metabolomics should be integrated with immune phenotyping, and AI models should be tested in geographically distinct validation cohorts. Candidate interventions require randomized or carefully controlled trials, with infection, rejection, tacrolimus exposure, metabolic control, fibrosis, and patient-reported outcomes as safety and effectiveness domains.

Microbiome-directed interventions require a risk-stratified approach in immunosuppressed recipients. Evidence from reviews of fecal microbiota transplantation (FMT) in immunocompromised patients suggests that FMT can be feasible in selected clinical settings, but the evidence is largely observational and lacks adequately powered randomized trials.^{15,16} Probiotic and synbiotic studies in immunocompromised adults have not identified a major safety signal for the evaluated products and populations, but this evidence cannot be generalized to every transplant recipient or to every strain.¹⁷ Transmission of an extended-spectrum β -lactamase-producing *Escherichia coli* through FMT, including a fatal infection, demonstrates why donor screening and ongoing vigilance are essential.¹⁸ Quarantine-based donor-stool screening has subsequently been evaluated as a strategy to reduce multidrug-resistant-organism transmission.¹⁹ Accordingly, FMT, probiotics, synbiotics, and defined postbiotics should be studied in transplant-specific protocols with explicit pathogen and antimicrobial-resistance

surveillance, drug-interaction monitoring, and predefined stopping rules.

In summary, the review by Joon *et al.*¹ provides a useful mechanistic foundation. The next translational step is to replace descriptive dysbiosis with validated microbiome–metabolite–immune signatures that can be interpreted by AI, tested prospectively, and linked to outcomes that matter to patients with advanced MASLD and liver-transplant recipients.

Acknowledgements

None.

Funding

No external funding was received for this Letter to the Editor.

Conflict of interest

None declared.

Author contributions

EG is the sole author of the manuscript.

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