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Letter to the Editor

Plasma lipidomic and fungal signatures predict early mortality in acute liver failure

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Dear Editor,

The recent article by Sharma et al. provides important insights into the interplay between plasma lipidomics and fungal peptide-based community analysis in the context of acute liver failure (ALF). Using untargeted lipidomic profiling and machine learning in both discovery (n=40) and validation (n=230) cohorts, the authors identified five key lipid species, including phosphatidylcholines [e.g., PC(15:0/17:0), PC(20:1/14:1)], that robustly distinguish non-survivors from survivors.[1] This lipidomic signature was tightly linked with altered fungal community profiles, notably increased Ascomycota and Basidiomycota peptides in non-survivors, emphasizing the underappreciated role of the plasma mycobiome in ALF pathogenesis.

The study's integrated multi-omics network analyses elegantly connect the dysregulated Kennedy pathway—involving phosphatidylcholine accumulation and phosphatidic acid production, as well as TG-mediated lipotoxicity—with hyperinflammatory states, mitochondrial dysfunction, and multi-organ failure. Machine learning models validated these findings with over 95% predictive accuracy, underscoring their translational potential. Importantly, the authors propose the Kennedy pathway not only as a biomarker axis but also as a putative therapeutic target to mitigate hyperinflammation and improve ALF outcomes.[1]

A unique strength of Sharma et al.'s work lies in its integration of plasma mycobiome (fungal peptide) profiling. Using mass spectrometry-based fungal peptide analysis, the authors identified increased diversity and abundance of *Ascomycota* and *Basidiomycota* in non-survivors, with specific contributions from genera such as *Cryptococcus* and *Penicillium*. Network analysis revealed these fungal peptides to be tightly correlated with lipid modules and clinical severity scores, including model for end-stage liver disease score, hepatic encephalopathy grade, and indicators of multi-organ failure.[1]

Mechanistically, the study highlights the downregulation of fungal surveillance receptors such as C-type lectin domain containing 7A (CLEC7A) in non-survivors, suggesting impaired antifungal immunity that enables fungal overgrowth and systemic translocation.[1] This, coupled with

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Kennedy pathway hyperactivation, creates a "double hit" of immune-metabolic dysfunction leading to hyperinflammation and worse outcomes.

These findings expand the current landscape of ALF research, which has predominantly focused on bacterial dysbiosis[2] and inflammatory mediators,[3] by positioning the mycobiome as an active player in disease progression. Importantly, Sharma et al. propose not only diagnostic utility but also therapeutic potential in targeting these two interconnected metabolic and immune axes.

Although this was a well-conducted study, it also has certain limitations. This investigation was conducted at a single tertiary referral center, involving a relatively small discovery cohort (n=40) and a moderate-sized validation cohort (n=230). Prior studies have shown that lipidomic biomarkers, while promising, may exhibit reduced generalizability when derived from limited and non-diverse patient populations.[4] Furthermore, the use of cross-sectional baseline sampling limits the ability to capture dynamic changes in lipidomic and mycobiome profiles during the disease course, an issue that longitudinal multi-omics designs have been better able to address.[4,5]

In addition, these findings demonstrate strong correlations between dysregulated phosphatidylcholine metabolism, altered fungal peptide diversity, and adverse outcomes in ALF. While network analysis supports the plausibility of a mechanistic link via Kennedy pathway hyperactivation coupled with impaired antifungal immunity, these associations remain correlative. CLEC7A is known to mediate β-glucan recognition and orchestrate antifungal immune responses,[6] but its reduced expression in ALF patients has yet to be linked to functional impairment *in vivo*. Therefore, therapeutic suggestions such as modulating phosphatidic acid metabolism or augmenting antifungal immunity should be considered hypothesis-generating until validated by functional immune assays and well-controlled pre-clinical intervention studies.

Despite these limitations, the present study provides meaningful insights into the underexplored role of fungal components in ALF pathogenesis. In this context, it is informative to consider complementary evidence from other disease models, particularly the work of Zeng et al., who demonstrated in alcohol-associated liver disease that intestinal *Candida albicans* overgrowth leads to Th17 cell expansion, hepatic migration, and IL-17-mediated inflammation through Kupffer cells.[7] Their findings reinforce the potential importance of fungal components in liver disease progression across different etiologies and suggest potential avenues for antifungal or immune-modulating therapies.

In conclusion, Sharma et al.'s study marks a pivotal advance in the multi-omics characterization of ALF, providing a mechanistic framework that integrates lipid metabolism, fungal-host interactions, and immune dysregulation. These insights pave the way for future translational studies aimed at refining biomarker panels and developing targeted interventions to improve ALF outcomes.

Authors' contributions

Kim YJ drafted the original manuscript, and Kim JW contributed to writing – review & editing and supervision. All authors reviewed the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:
ALF, acute liver failure; CLEC7A, C-type lectin domain containing 7A

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