Global LC-MS Metabolomics and LASSO-regression: Identify Affected Pathways in Sepsis Patients in the Emergency Department

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INTRODUCTION

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction and failure (**Figure 1**). Despite advances in critical care, sepsis remains a major cause of mortality worldwide. A key feature of sepsis is profound metabolic reprogramming, driven by the host's immune response. By identifying specific metabolic signatures associated with sepsis, we can gain insights into underlying mechanisms. In this study, we applied global liquid chromatography–mass spectrometry (LC-MS) metabolomics to plasma samples from patients presenting in the emergency department (ED) with confirmed sepsis. We aim to identify and characterize metabolic pathways affected in patients with sepsis at time of presentation in the ED.

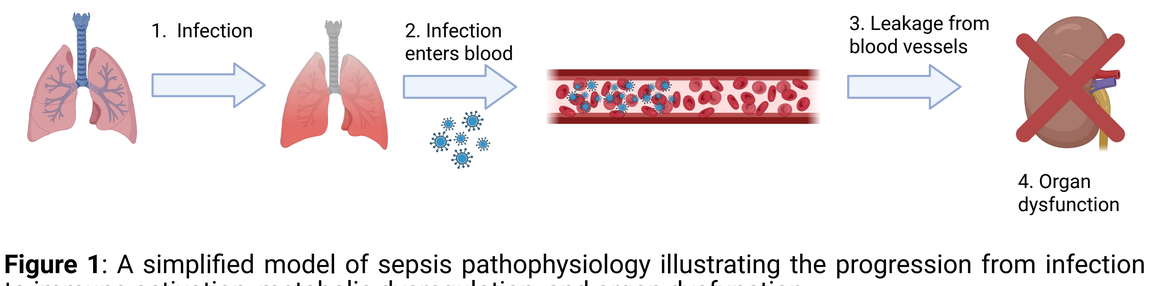

Figure 1: A simplified model of sepsis pathophysiology illustrating the progression from infection to immune activation, metabolic dysregulation, and organ dysfunction.

MATERIALS & METHODS

The study cohort consisted of 70 patients presented to the ED with suspected sepsis: According to post hoc adjudication, 35 had confirmed sepsis (Sepsis-3 criteria) and 35 non-sepsis patients (11 with infection without new-onset organ failure, and 24 with organ failure but no infection), see table below.

GROUP	SEPSIS	INFECTION	ORG. FAILURE
N	35	11	24
GENDER (MALE/FEMALE)	25/11	5/6	18/6
AGE (MEAN±SD)	57±35	64±33	62.5±32.5
POSITIVE BLOOD CULTURE (N)	35	11	0
GRAM NEGATIVE STRAIN (N)	27	7	0
SEPTIC SHOCK (N)	14	0	0
SOFA SCORE (MEAN±SD)	6.17±2.04	2.36±1.75	6.00±2.84
SURVIVAL (%)	100	79	93

EDTA-plasma was extracted using protein precipitation with methanol (1:3 ratio, plasma:methanol) and analyzed by global LC-MS metabolomics following the protocol by Skogvold et al (1).

Differential abundant metabolites and features (DAMs) selected using differential analysis and least absolute shrinkage and selection operator (LASSO) regression, comparing sepsis against infection-only patients, sepsis against organ failure-only patients, and sepsis against non-sepsis patients. Metabolites features were considered differentially abundant if they had an adjusted p-value < 0.1 and a fold change > 1.5.

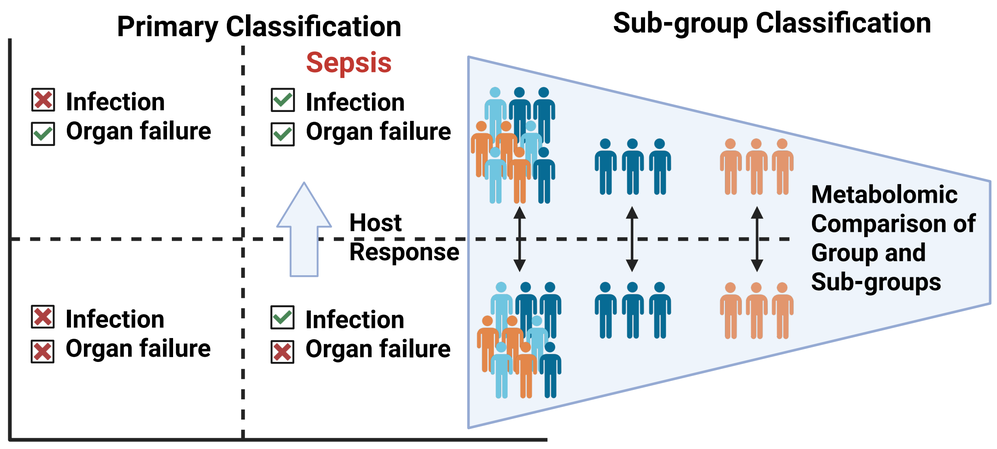

Figure 2: Primary classification of patient according to infection and organ damage, and secondary subgroup classification for comparison of metabolomic profiles

RESULTS

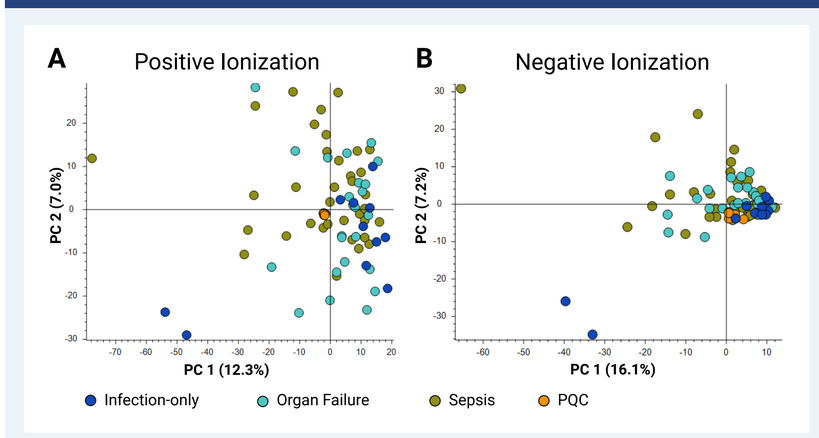

Figure 3: Principal Component Analysis (PCA) in A) positive ionization and B) negative ionization mode.

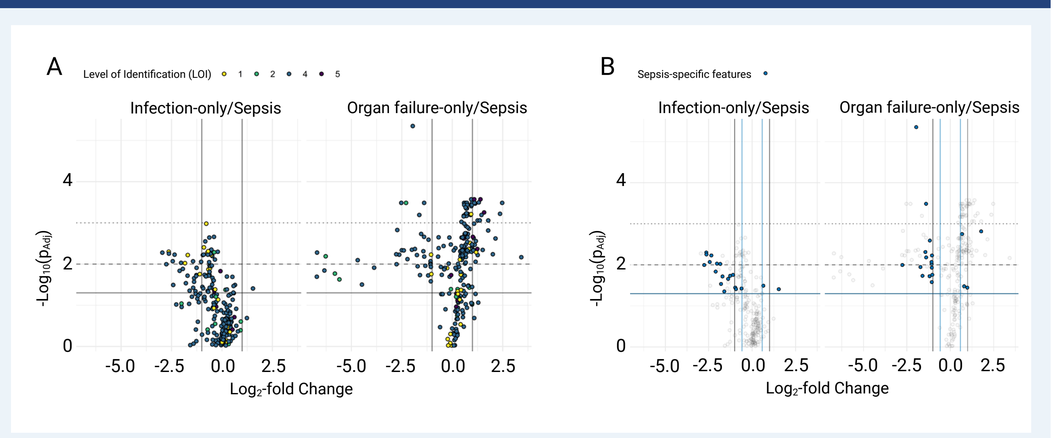

Figure 4: Differential analysis showing A) DAMs found comparing the sepsis group against the infection-only and organ failure-only group and B) sepsis specific DAMs.

Principal component analysis (PCA) (**Figure 3**) was performed to explore global metabolic variation. However, no clear separation was observed between sepsis and non-sepsis groups. From the differential analysis a total of 183 differentially abundant metabolites (DAMs) were identified, 25 were overlapping between the two comparisons (**Figure 4**). Our LASSO-regression results overlapped with several of these features, including N-acetylputrescine, 4-acetamidobutyric acid, LPC(18:1) and diacetylspermidine. With a bootstrapped LASSO-repeatability of 0.829, 0.05, 0.479 and 0.358 respectively (**Figure 6-8**). Pathway analysis identified Arginine and proline metabolism as significantly affected, more specifically the GABA-biosynthesis (**Figure 5**). These metabolites has been shown to be associated with blood stream infections, specifically gram negative strain infections (2). We see a similar trend with elevated levels of N-acetylputrescine in samples with gram negative bacterial strains.

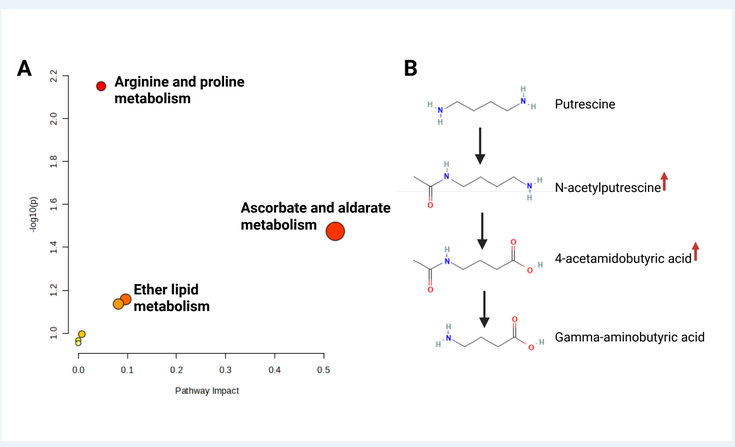

Figure 5: A) pathway analysis using MetaboAnalyst, and B) GABA-biosynthesis for eukaryotic organisms.

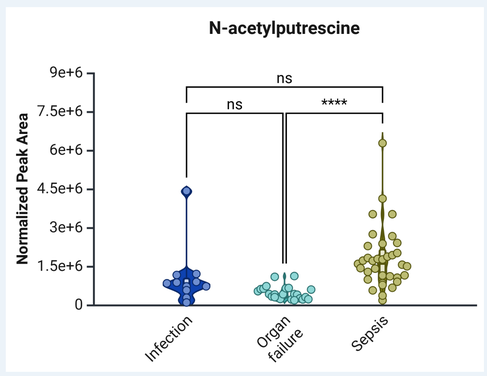

Figure 6: Violin plot of area of N-acetylputrescine.

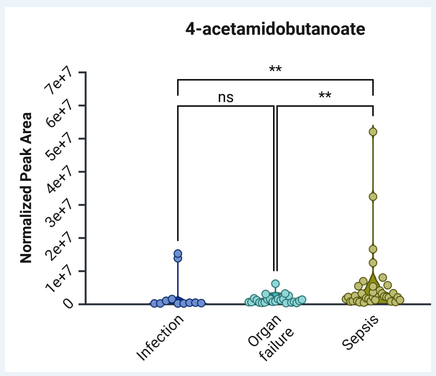

Figure 7: Violin plot of area of 4-acetamidobutanoate.

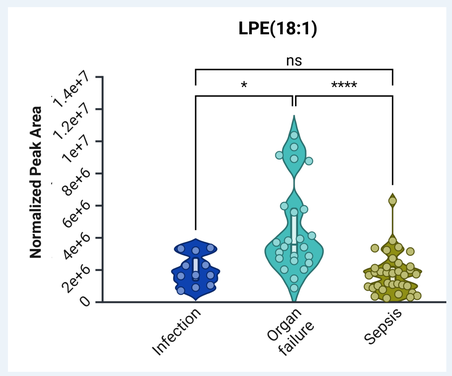

Figure 8: Violin plot of area of LPE(18:1).

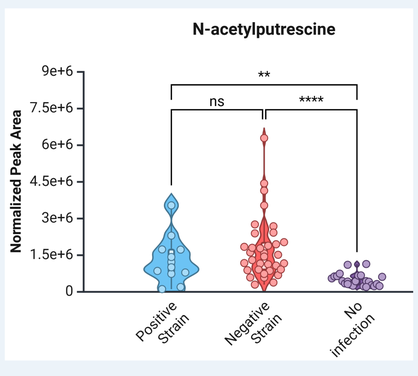

Figure 9: Violin plot of N-acetylputrescine grouped after bacterial classification.

DISCUSSION

By comparing sepsis patients to those with infection or organ dysfunction alone, we aimed to isolate metabolic features specifically associated with the dysregulated host response that defines sepsis. While unsupervised PCA did not reveal clear group separation, differential analysis and LASSO regression identified distinct metabolic signatures. GABA biosynthesis suggest that sepsis response involves alterations in neurotransmitter and polyamine metabolism, a process linked to immune modulation and cellular stress responses. Recent studies have shown that N-acetylputrescine is produced by bacterial enzymes such as SpeG, which acetylates putrescine as part of microbial polyamine metabolism (2). Elevated levels of N-acetylputrescine in patient plasma have been linked to worse clinical outcomes (2).

CONCLUSION

Our findings suggest that the metabolic profile of sepsis reflects a distinct host response, characterized by alterations in pathways such as GABA biosynthesis and polyamine metabolism. These changes may represent early biochemical signatures of the dysregulated immune response that defines sepsis. The identification of N-acetylputrescine as a consistently elevated metabolite highlights its potential as a candidate biomarker for blood stream infection.

1) Skogvold et al. (2025). Global Metabolomics Using LC-MS for Clinical Applications. Clinical Metabolomics. Methods in Molecular Biology, vol 2855.
2) Mayers et al. (2024). A metabolomics pipeline highlights microbial metabolism in bloodstream infections, Cell, Volume 187.

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