# Comment on: matrix effects in LC-MS/MS amino acid analysis: an underestimated risk in metabolic screening

FIB-4 index and PET/CT parameters in HCC

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**To the editor:**

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has become the primary method for amino acid analysis used in the diagnosis and monitoring of hereditary metabolic disorders. Its high sensitivity and ability to perform multiparameter analyses simultaneously provide significant analytical advantages over conventional methods. However, despite its widespread clinical use, some analytical limitations of the method, particularly matrix effects and ion suppression, have not been adequately addressed in numerous published studies and reports. Amino acid analyses are extremely critical in the diagnosis and monitoring of metabolic diseases. Amino acid values below the determined reference ranges and at low concentrations may lead to situations that affect clinical decisions and the course of the disease.[1,2] The matrix refers to the content of the sample excluding the substance being analyzed. The matrix often influences the analysis process and can reduce the accuracy of the results. Interference with the matrix during analysis is called the matrix effect. The presence of multiple components simultaneously can lead to competition in the ionization process, resulting in a reduction in MS signals. Thus, the signal of one component in a mixture will be lower than the signal of the pure component at the same concentration. This is called ion suppression, and this phenomenon can reduce the sensitivity of LC-MS analysis. Salts and some phospholipids in plasma, serum, and urine samples can present limitations, particularly in direct injection methods, creating a co-elution-like situation. Buffers and other mobile phase additives used in the method are also sources of suppression. Even the slightest ion suppression can lead to clinically significant underestimation of low-quantity amino acids.[3] The matrix effect can be reduced by improving the extraction and cleaning steps of the method, changing the type of ionization, optimizing liquid chromatography conditions, and using corrective calibration methods, etc. Although stable isotope-labeled internal standards (ISs) are often used to eliminate matrix effects, precise quantification may still not be achieved. Small differences in chromatographic behavior or ionization efficiency between analytes and the internal standards used for them can lead to deviations, especially at low concentration levels. This may be because some methods use group internal standards, the matching is based on structural similarity, and the same internal standards are used for isomers. Furthermore, restricting the limit of quantification and matrix-compatible calibration steps during the validation phase can hide potential errors at clinically significant low concentrations. In inherited metabolic disorders, diagnostic decisions are often based on interpreting amino acid concentrations according to cutoff values.[4] Even slight analytical underestimations due to ion suppression can cause values to fall below the clinical decision limits. This type of misclassification can delay confirmatory testing and genetic evaluation, or the initiation of treatment, especially in newborns and children, where timely diagnosis is critical. In the context of newborn screening and early metabolic assessment, analytical accuracy is essential, as inaccurate assessments can have significant long-term consequences. As the role of LC-MS/MS in metabolic diagnosis expands, systematic evaluation and transparent reporting of matrix effects should be encouraged. Strengthening analytical validation practices will ultimately increase clinical confidence in quantitative amino acid analysis.

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*How to cite this article:*
Özlem Demirelce. Comment on: matrix effects in LC-MS/MS amino acid analysis: an underestimated risk in metabolic screening. Ann Clin Anal Med 2026;17(Suppl 2):S407

DOI: 10.4328/ACAM.50085 Received: 18/02/2026 Accepted: 16/03/2026 Published Online: 17/03/2026 Printed: 20/03/2026 Ann Clin Anal Med 2026;17(Suppl 2):S211
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