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Metabolic regulation of amino acids provides an important basis for individualized nutritional therapy for patients with gastric cancer during the perioperative period

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Abstract

Background Gastric cancer is a prevalent malignancy worldwide, with early detection and treatment being vital to improving patient outcomes. Amino acids (AAs), as essential regulators in cancer cell metabolism, are implicated in the progression and response to treatment.

Methods This study aimed to investigate the dynamics of plasma AA levels in gastric cancer patients preoperatively, postoperatively, and following nutritional intervention, comparing them to healthy controls. We analyzed 22 AAs in plasma samples from 66 gastric cancer patients and 55 healthy individuals.

Results The results show that significant preoperative elevation of AAs, such as threonine (Thr), serine (Ser), proline (Pro), lysine (Lys), arginine (Arg), citrulline (Cit), glutamine (Gln), glycine(Gly), and alanine (Ala), with reductions in taurine (Tau), phenylalanine (Phe) and hydroxylysine (Hylys). Post-surgery, levels of many AAs decreased markedly, but were partially restored following nutritional intervention, with some exceeding preoperative values. Nevertheless, specific AAs, including methionine (Met) and Gln, remained lower than in healthy controls, suggesting potential benefit from targeted supplementation. Correlations between AA changes and postoperative recovery indicators were observed; notably, increased postoperative Thr, Ser, Tau, tyrosine (Tyr), glutamic acid (Glu), and Hylys levels were associated with quicker gastrointestinal recovery. Additionally, several AAs, such as Pro, Lys, Tyr, Met, Cit, and Glu, were linked to reduced inflammation, as reflected by C-reactive protein (CRP) and white blood cell (WBC) levels, suggesting roles in the postoperative immune response. Pathway enrichment analysis highlighted metabolic pathways involving Gly, Ser, Phe, Tyr, Lys, and Met as critical in the recovery process.

Conclusions These findings underscore the potential of AA profiles as biomarkers for postoperative recovery and suggest nutritional interventions targeting specific AAs may improve outcomes.

Keywords Gastric cancer, Perioperative recovery, Amino acids profiles, Biomarker, Nutritional intervention

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Introduction

Gastric cancer is one of the most common malignant tumors of the digestive system worldwide, and early diagnosis and treatment are critical for improving patient survival rates [1, 2]. Metabolic changes before and after surgery are key to understanding disease progression and assessing treatment efficacy. AAs play a significant role in cancer metabolism, and studying changes in amino acid levels can provide valuable insights into postoperative recovery and prognosis [3].

AAs, as fundamental metabolites and regulatory molecules, have extensive effects on cancer cells. AAs serve as the primary nitrogen source for hexosamine, nucleotides, and other nitrogen-containing compounds in cancer cells [4, 5]. Furthermore, AAs regulate gene expression and protein phosphorylation cascades. For example, sufficient essential AAs stimulate MYC oncogene mRNA translation by inhibiting the GCN2-eIF2A-ATF4 pathway, leading to MYC-dependent transcriptional amplification [6]. Gln, Arg and leucine (Leu) induce cell-specific phosphorylation of mTORC1, thus regulating intracellular protein turnover [7]. Additionally, Gln, Cit and Met can activate the mTORC1 signaling pathway by modulating the concentration of phosphatidic acids within the late endosome/lysosome system and the activity of Ras homologs enriched in the brain [8]. Conversely, AA metabolism is also tightly regulated and closely interconnected with other metabolic networks, such as lipid and glucose metabolism [9].

Although AA concentrations in the circulation remain stable under healthy conditions, numerous studies have shown that various cancers, including gastric, colorectal, lung, and breast cancers, can alter AA levels [10, 11]. In recent years, the AminoIndex has garnered considerable attention. This index was developed by establishing a multivariate profile from the spectrum of free AAs in blood, which aids in assessing the likelihood of certain health conditions and diseases [12]. Using these indices, researchers have differentiated various cancer types, including gastric, lung, colorectal, breast, prostate, gynecological, and pancreatic cancers, from healthy controls [13, 14]. However, the patterns of AA alterations differ across cancer types, and further investigation is needed to determine whether changes in AA profiles correlate with postoperative prognosis and the risk of complications in cancer patients.

This study included 66 early-stage gastric cancer patients and 55 healthy controls who were admitted for physical examinations during the same period. Plasma samples were collected from gastric cancer patients preoperatively, on the first postoperative day, and on the third postoperative day, as well as from healthy controls. AAs were profiled via mass spectrometry, which measured 22 AAs in total, including 8 essential and 14 common nonessential AAs. We analyzed differences in plasma AA expression profiles between gastric cancer patients and healthy controls, as well as changes in amino acid levels in patients before and after surgery. Furthermore, we examined the relationship between these changes and the clinical prognosis of patients, exploring relevant metabolic pathways involving these altered AAs. This study also aimed to investigate whether variations in AA profiles could serve as potential indicators for assessing postoperative complication risks, recovery rates, or long-term prognoses.

Materials and methods

Patient characteristics

This retrospective study assessed 66 gastric cancer patients enrolled in a disease group who underwent cancer surgery at the Department of Gastrointestinal Surgery at the Second Affiliated Hospital of Soochow University from November 2021 to October 2022 and randomly selected 55 healthy individuals in the control group who underwent routine health examinations at the same hospital during the same period, with no history of malignancy.

The inclusion criteria were as follows: (1) aged 18 or older, (2) underwent gastric cancer surgery, (3) had an Nutritional Risk Score-2002(NRS-2002) score of ≥ 3, (4) had a plasma amino acid concentration of 18 or older, (4) received parenteral nutrition treatment (total energy for parenteral nutrition set at 1400 kcal, protein intake at 61 ~ 63 g, fluid volume at 1700 ~ 1840 mL), and (5) had no prior cancer-related treatments such as radiotherapy or chemotherapy.

The exclusion criteria were as follows: (1) patients who underwent prior gastric surgeries for nontumour reasons, (2) had NRS-2002 scores < 3, (3) weighed less than 46 kg, (4) received radiotherapy and chemotherapy before surgery, and (5) had incomplete patient data.

Data collection

In the disease group, relevant clinical information was gathered, including height, weight at admission and discharge, surgical method, postoperative time to first flatus, postoperative time to first bowel movement, postoperative hospital stay, and preoperative and postoperative day 1 and day 3 blood routine and biochemical indicators, such as WBC and CRP levels.

Amino acid profiles were performed for both the disease group and the control group. Amino acid concentrations were determined using liquid chromatography-tandem mass spectrometry (LC–MS/MS) with a Qlife Lab 9000 system (Nanjing Pinsheng Medical Technology Co., Ltd., China). A total of 22 AAs were detected

and analyzed, including 8 essential AAs: Phe (Phe), tryptophan (Trp), isoleucine (Ile), Leu, Met, Lys, valine (Val), and Thr, as well as 14 nonessential AAs: Gly, Ser, sarcosine (Sar), aspartic acid (Asp), cystine (Cys), Glu, Gln, Hylys, Pro, Arg, Tyr, Ala, Tau, and Cit.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University.

Statistical analyses

Continuous variables are expressed as medians and interquartile ranges (IQRs), whereas categorical variables are presented as counts and percentages. The chi-square test was used for between-group comparisons of categorical data, and the t test or Mann–Whitney U test was used for between-group comparisons of continuous data. Metabolic pathway analysis was performed via MetaboAnalyst 5.0 software. All the statistical analyses were conducted via SPSS 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad, San Diego, CA, USA). A two-sided P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The basic characteristics and clinical information of the 66 early-stage gastric cancer patients and 55 healthy controls included in this study are shown in Table 1. Due to the different impacts on amino acid absorption patterns among different surgical approaches, two main surgical approaches were used to classify the patients: 52 patients underwent partial gastrectomy, and 14 patients underwent total gastrectomy. All patients began receiving parenteral nutritional therapy postoperatively. The parenteral nutrition treatment adopts the "all-in-one" approach, in which the total energy for parenteral nutrition is set at 1400 kcal, the protein intake is 61 ~ 63 g, and the fluid volume is 1700–1840 mL.

Differences in amino acid changes

The levels of various AAs in the plasma of healthy controls, preoperative gastric cancer patients, and postoperative gastric cancer patients on the first and third days are shown in Supplementary Table 1S. By comparing the changes in amino acid levels between healthy controls and gastric cancer patients before surgery, on the first postoperative day, and on the third postoperative day (postnutritional intervention), this study revealed that 12 AAs in the serum of gastric cancer patients were significantly different from those in the healthy control group ($P < 0.05$). Among these, the levels of Thr, Ser, Pro, Lys, Arg, Cit, Gln, Gly and Ala were significantly increased in the plasma of gastric cancer patients, whereas the levels of Tau, Phe and Hylys were markedly decreased (Fig. 1).

Comparisons of preoperative and postoperative amino acid levels revealed a significant decrease in the levels of most AAs, including Ile, MEA, Asp, Thr, Ser, Pro, Tau, Tyr, Lys, Arg, Sar, Cit, Gln, Glu, Gly, Ala, and Hylys, after surgery (Fig. 2).

By implementing nutritional intervention in postoperative patients, we further compared the changes in amino acid levels on the third day postsurgery with those before and immediately after surgery. The results indicated the following: First, compared with immediately postoperative levels, the levels of Ile, MEA, Val, Asp,

Table 1 Patient characteristics

		Cases ($n = 66$)	Controls($n = 55$)
Age,years (IQR)		64.70 ± 11.34	67.71 ± 8.66
Gender			
	Males	39	35
	Females	27	20
BMI[a] (kg/m^2)			
	< 18.5	2	8
	18.5 ~ 24.0	47	26
	24.0 ~ 28.0	13	17
	≥ 28.0	4	4
Operation			
	Partial gastrectomy	52	
	Total gastrectomy	14	
Postoperative time to first flatus		3.22 ± 0.80	
Postoperative time to first bowel movement		3.98 ± 1.29	
Postoperative hospital stays		11.8 ± 8.80	

[a] *BMI* Body Mass Index

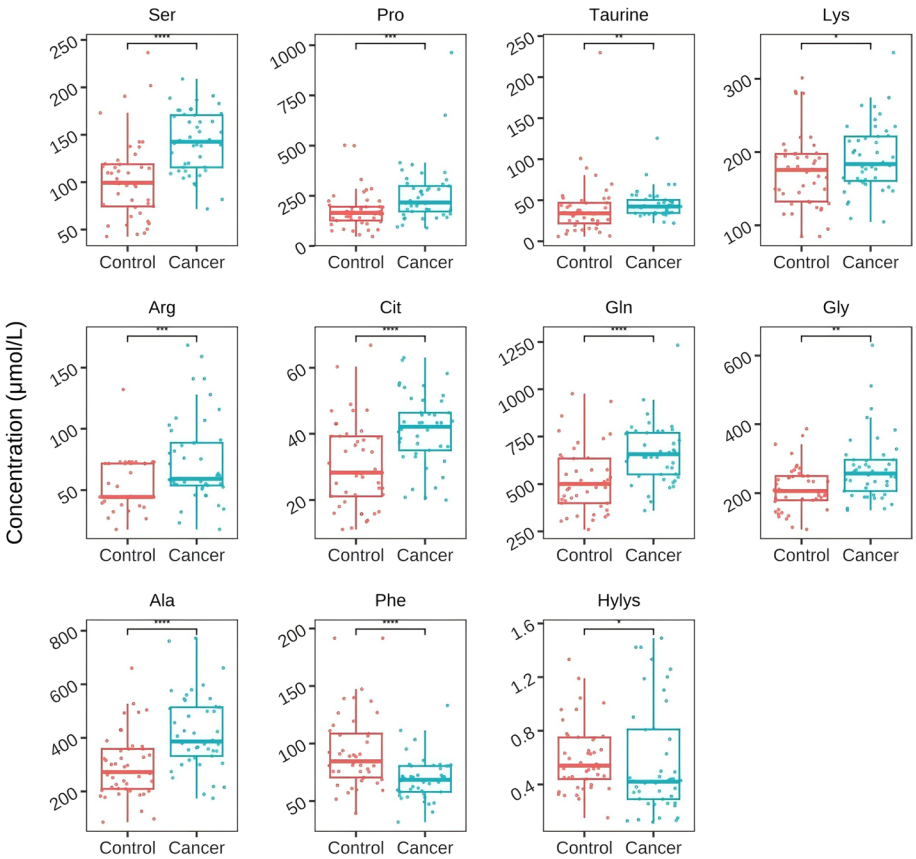

Fig. 1 Differences in plasma amino acid content between preoperative gastric cancer patients and healthy subjects

Thr, Trp, Leu, Arg, Cys, Glu, Phe, AAD, and Hylys significantly increased by the third day postintervention. Among these, the levels of Ile, Asp, Trp, AAD, and Hylys were not different from the preoperative levels. However, MEA, Thr, Arg, and Glu remained lower than the preoperative levels, with MEA and Glu also below those in healthy individuals, suggesting that nutritional supplementation did not fully restore these AAs to optimal levels. Second, the levels of Val, Leu, Cys, and Phe exceeded the preoperative values, with Val and Cys even surpassing the levels observed in healthy controls (Fig. 3). In addition, the level of Gln remained lower than the preoperative level postintervention but did not significantly differ from the level in healthy controls.

Correlations between postoperative amino acid content changes and exhaust time, length of hospital stay, and inflammatory markers

To investigate whether changes in the amino acid profile can serve as potential indicators for assessing postoperative complications, recovery speed, or long-term prognosis, we further analyzed the relationships between changes in amino acid levels in gastric cancer patients before and after surgery and clinical outcome indicators. We first examined the correlation between postoperative amino acid changes and the time to first flatus (Fig. 4). The results revealed a negative correlation between the postoperative changes in the Thr, Ser, Tau, Tyr, Glu, GABA, and Hylys levels and the time to first flatus in gastric cancer patients. These findings indicate that higher postoperative amino acid levels are associated with a shorter time to first flatus.

Additionally, we analyzed the correlation between changes in amino acid levels before and after surgery and postoperative CRP levels in gastric cancer patients. As shown in Fig. 5A and B, higher levels of Ser, Pro, Leu, Tyr, Lys, Met, Cit, and Glu on the third postoperative day were associated with lower CRP levels. Furthermore, changes in Leu, Tyr, and Cys levels before and after surgery were negatively correlated with changes in CRP levels postoperatively. We also analyzed the correlation between changes in amino acid levels before and after surgery and postoperative WBC counts. As shown in Fig. 5C, changes in MEA, Pro, Lys, Tyr, Arg, Met, Gln, and Ala levels before and after surgery were negatively correlated with changes in WBC count postoperatively.

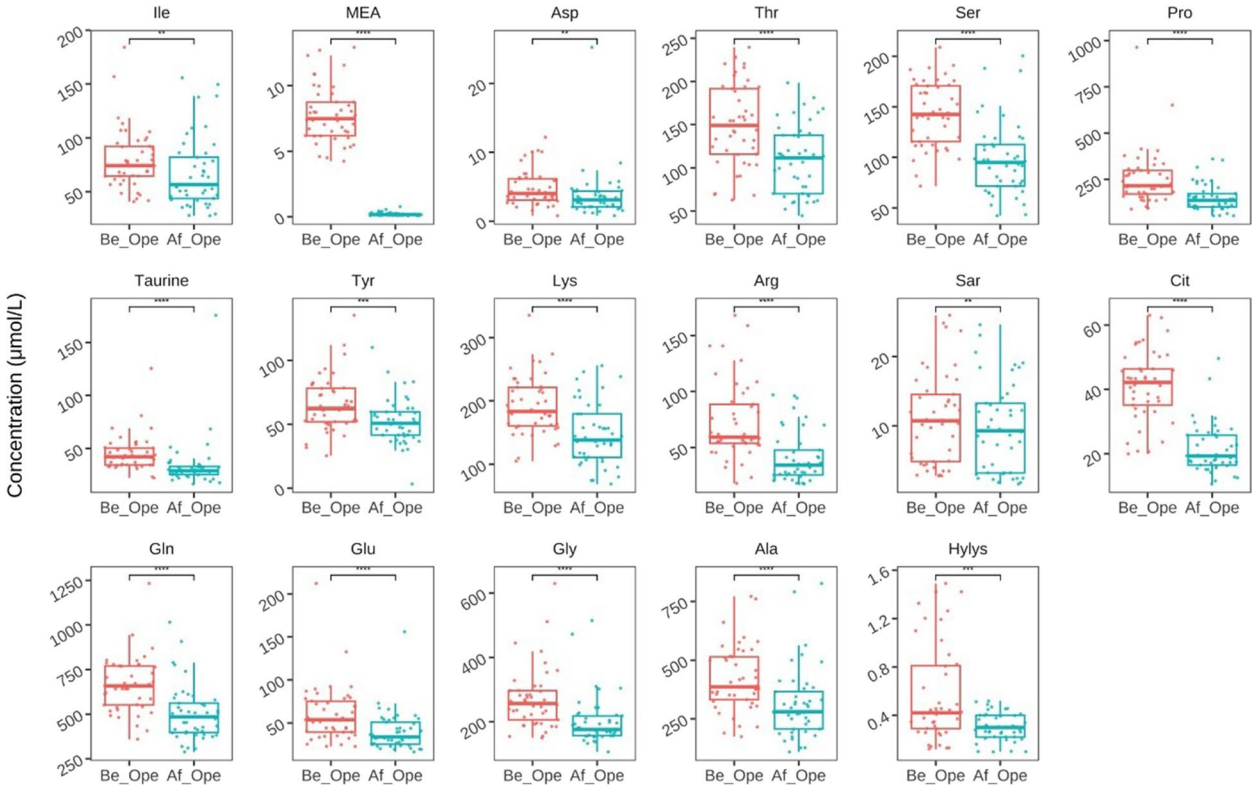

Fig. 2 Difference in plasma amino acid content between preoperative and postoperative gastric cancer patients

This finding suggests that greater increases in these AAs are associated with smaller fluctuations in WBC counts. These findings similarly indicate that significant changes in these AAs may serve as potential predictors of patient recovery after surgery.

Pathway enrichment analysis of differential AAs

We analyzed the AAs associated with time to first flatus and inflammation levels postsurgery and found that Ser, Tyr, Glu, Pro, Leu, Lys, and Met were consistently involved in at least two correlation analyses (Fig. 6A). Further pathway enrichment analysis revealed that these AAs are involved primarily in the following metabolic pathways: Gly and Ser metabolism, Phe and Tyr metabolism, Lys degradation, ammonia recycling, and Met metabolism (Fig. 6B).

Discussion

Numerous studies have demonstrated metabolic dysregulation, including disruptions in amino acid metabolism, in cancer patients. As fundamental components of proteins, AAs play crucial roles in sustaining normal physiological functions and meeting the nutritional and energetic demands of tumor cells [9]. Amino acid preparations rich in branchedchain amino acids are recommended by many experts for cancer patients, and they are helpful for improving muscle loss, maintaining liver function, and balancing aromatic amino acids in cancer patients. Among them, ESPEN recommends supplementation doses ranging from 1 g/(kg·d) to 1.2–2.0 g/(kg·d) for tumor patients [15], and the German guidelines for parenteral nutrition for tumor patients recommend amino acid supplementation of 1.2–1.5 g/(kg·d) [16]. Previous research has shown that AAs undergo significant alterations in cancer, leading to the development of indices derived from these altered AAs, such as the amino index, which has been used for cancer screening and monitoring of cancer therapy [14]. In this study, we investigated changes in the plasma amino acid profile of gastric cancer patients before and after surgery and following nutritional intervention and compared these profiles with those of healthy individuals. The results revealed a distinct pattern of amino acid changes in gastric cancer patients across these stages. This variation is likely the combined result of increased metabolic demands of the tumor, surgical trauma, and postoperative stress responses.

The results of this study indicate that in gastric cancer patients, preoperative plasma levels of Thr, Ser, Pro, Lys, Arg, Cit, Gln, Gly, and Ala are significantly elevated,

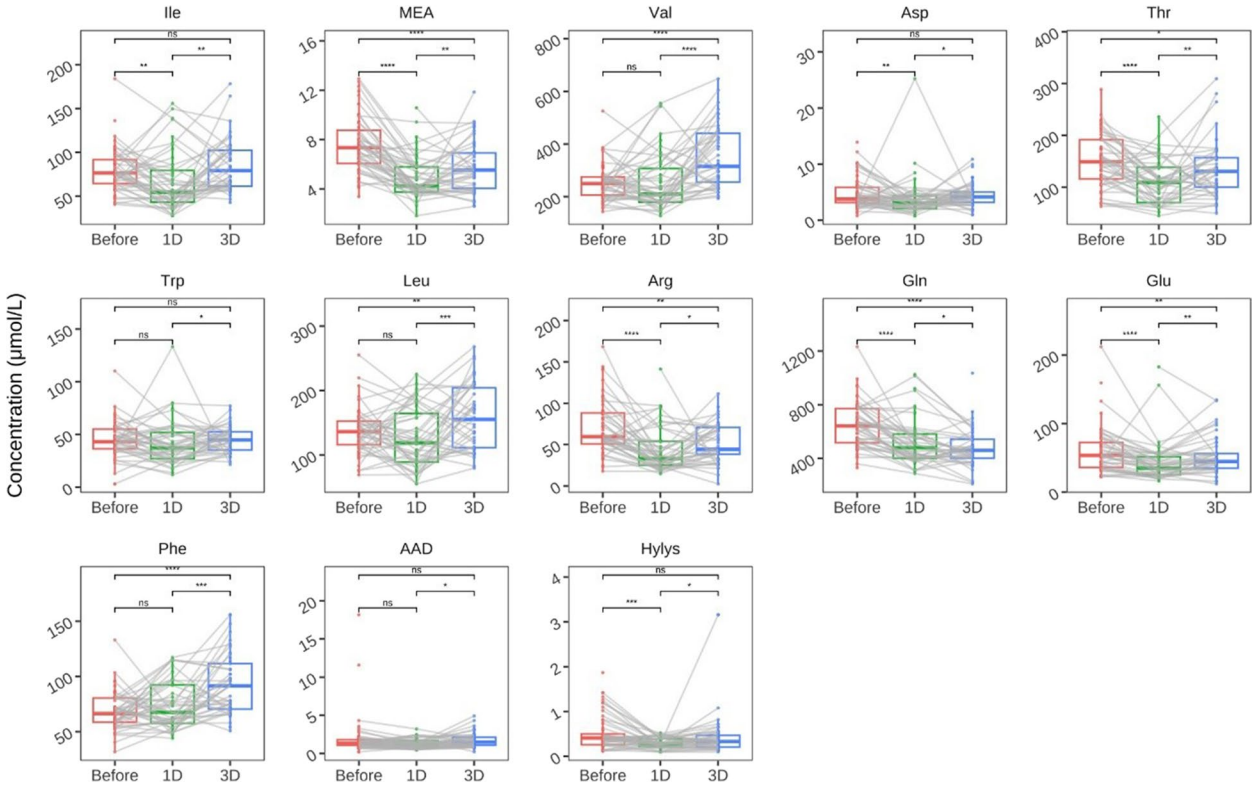

Fig. 3 Changes in amino acid content in gastric cancer patients before and after surgery and after nutritional therapy

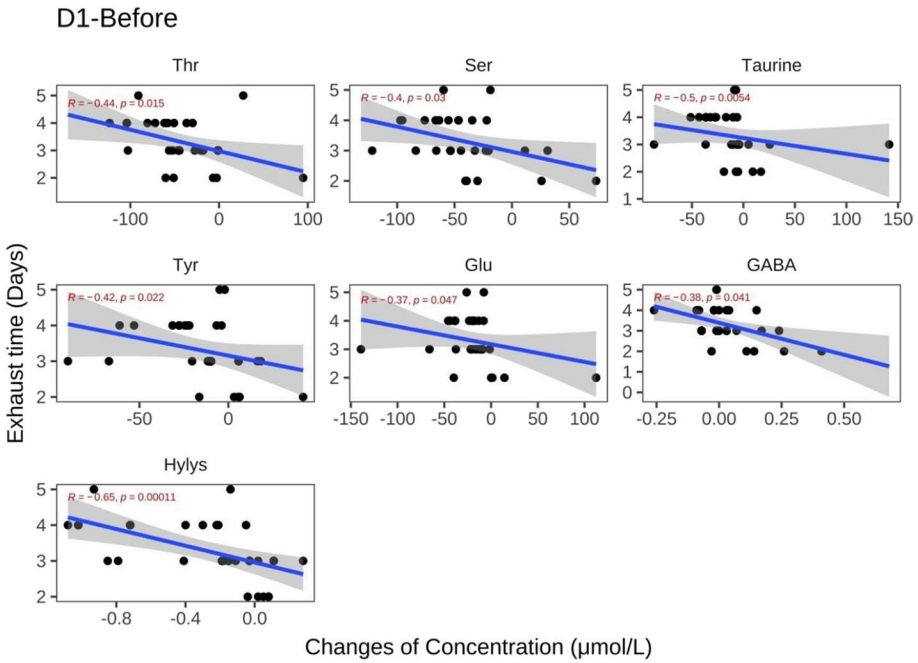

Fig. 4 Correlation between postoperative amino acid changes and exhaust time in patients with gastric cancer

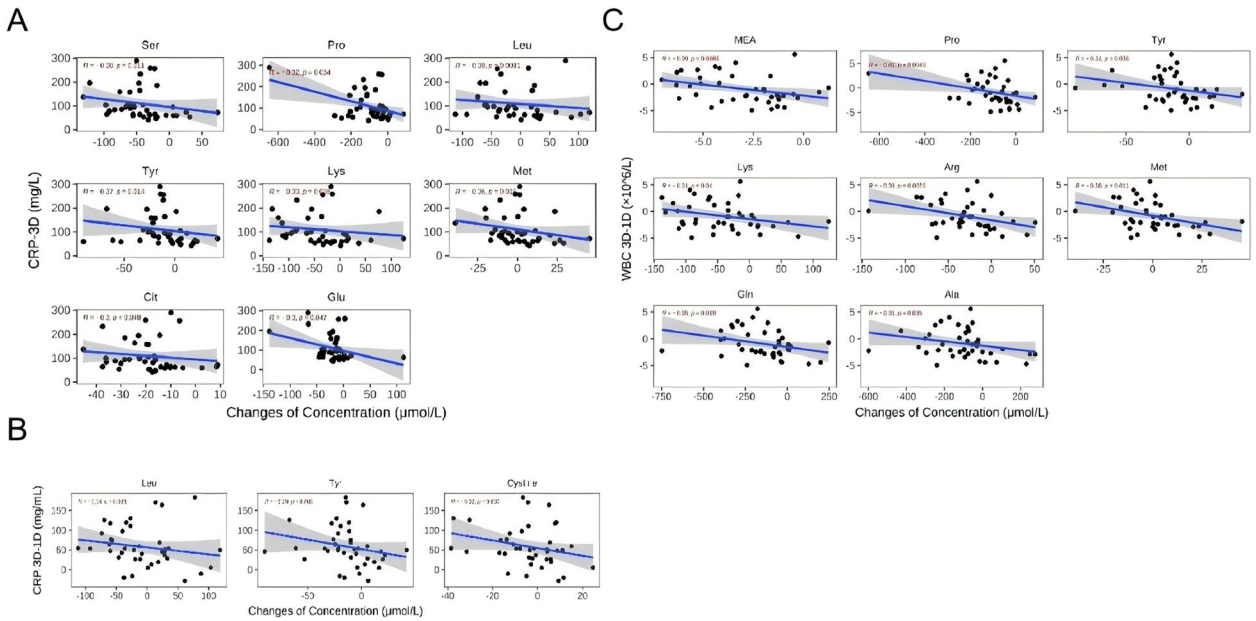

Fig. 5 Correlation between postoperative amino acid changes and postoperative inflammatory markers (CRP and WBC) in patients with gastric cancer. **A** The changes of AAs before and after surgery were correlated with CRP on the third day after surgery. **B** Correlation between preoperative and postoperative amino acid changes and preoperative and postoperative CRP changes in patients. **C** Correlation between preoperative and postoperative amino acid changes and preoperative and postoperative WBC changes in patients

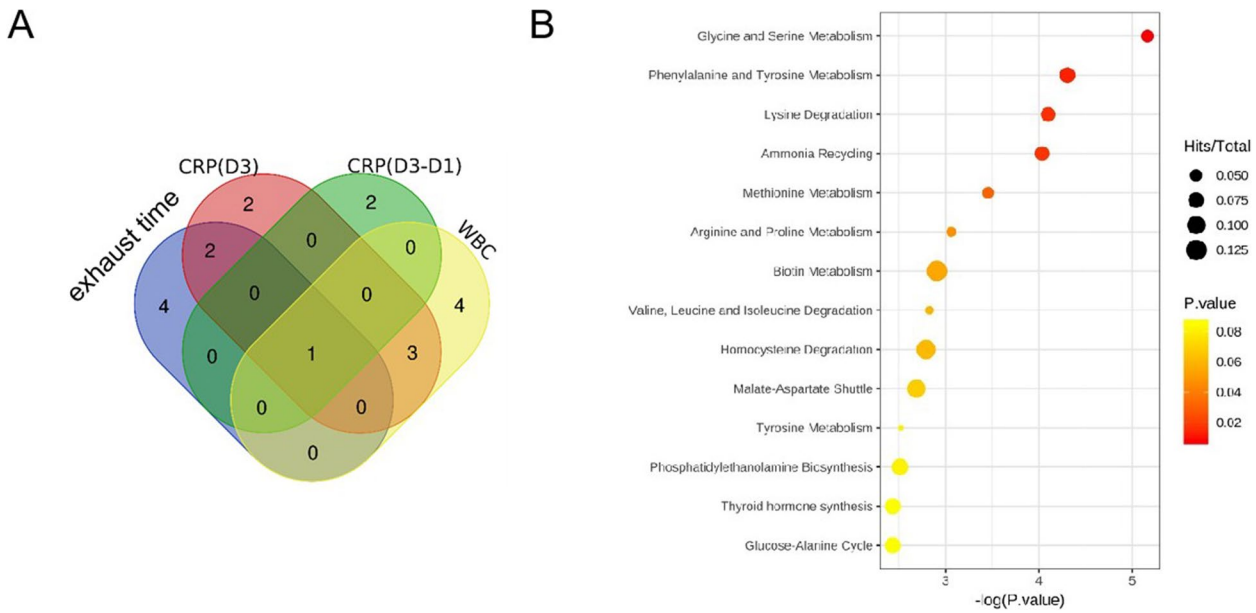

Fig. 6 Enrichment of metabolic Pathways for Differential AAs. **A** Venn diagram of AAs with correlations between changes in content and inflammatory markers. **B** Pathway enrichment of AAs

whereas Tau, Phe, and Hylys are markedly reduced. We believe that these differences are due primarily to a combination of factors, including the increased metabolic demands of the tumor, impaired digestive function, chronic malnutrition, systemic inflammatory response, and abnormal liver function [17].On the first day postsurgery, the levels of numerous AAs, including Ile, MEA, Asp, Thr, Ser, Pro, Tau, Tyr, Lys, Arg, Sar, Cit, Gln, Glu, Gly, Ala, and Hylys, significantly decreased. We hypothesize that the postoperative reduction in amino acid

levels may result from a combination of factors, including the stress response after surgery, changes in the metabolic state, alterations in liver function, inflammatory responses, and increased protein synthesis [4]. These factors collectively lead to an elevated demand for AAs, which is reflected as a decrease in their concentrations in the blood. Following nutritional intervention, certain AAs (such as Ile, MEA, Val, Asp, Thr, Trp, Leu, Arg, Cys, Glu, Phe, AAD, and Hylys) had notably recovered by the third postoperative day, with some even surpassing preoperative levels. Despite the overall effectiveness of nutritional intervention, the levels of certain AAs, such as MEA and Glu, remained below those of healthy individuals, suggesting that increasing the content of these AAs for nutritional support or extending the intervention period may be beneficial, as previously reported [18]. Additionally, the levels of Val and Cys exceeded those in the healthy group, indicating a marked response to nutritional intervention for these AAs. This could also reflect shifts in the patients' postoperative metabolic state. Therefore, it may be advisable to moderately reduce the doses of these AAs in postoperative supplements or shorten the duration of their nutritional intervention.

To investigate the relationship between amino acid profile changes and postoperative recovery, this study further analyzed the correlations between amino acid levels and postoperative time to first flatus, inflammation levels, and WBC count. The results revealed that postoperative increases in Thr, Ser, Tau, Tyr, Glu, GABA, and Hylys were negatively correlated with time to first flatus, suggesting that elevated amino acid levels may reflect faster recovery of gastrointestinal function. This shorter time to first flatus may reflect a combination of factors, including recovery rate, protein synthesis, gastrointestinal function, nutritional support, the inflammatory response, and liver function recovery. These findings suggest that changes in amino acid levels may serve as potential biomarkers for the speed of postoperative recovery. In addition, postoperative levels of Ser, Pro, Leu, Tyr, Lys, Met, Cit and Glu were negatively correlated with CRP levels, and the decrease of CRP levels was correlated with cancer cell activity and postoperative inflammatory response. Therefore, these amino acids negatively correlated with CRP levels may help to evaluate the activity of tumor cells and the severity of postoperative inflammatory reaction. Similarly, changes in MEA, Pro, Lys, Tyr, Arg, Met, Gln, and Ala were negatively correlated with WBC changes, suggesting that these AAs may play a significant role in the postoperative immune response and could serve as potential biomarkers for postoperative recovery.

Pathway enrichment analysis of AAs associated with both the time to first flatus and postoperative inflammation levels revealed that these AAs were mainly involved in the following metabolic pathways: Gly and Ser metabolism, Phe and Tyr metabolism, Lys degradation, ammonia recycling and Met metabolism. These pathways likely play key roles in the recovery process following gastric cancer surgery. For example, Ser and Gly metabolism is closely related to immune regulation and cell proliferation, potentially influencing postoperative recovery by modulating inflammatory responses [19, 20]. Tyr and Phe metabolism is crucial for the production of neurotransmitters such as dopamine and adrenaline, and surgery, as a significant stressor, may alter gastrointestinal neural function [21, 22]. Regulating Phe and Tyr metabolism could help restore neurotransmitter balance and accelerate gastrointestinal recovery, thus impacting the time to first flatus. Additionally, the Lys and Met metabolism pathways are closely related to liver function, amino acid metabolism, and antioxidant responses [23]. After surgery, the body requires efficient clearance of metabolic waste and maintenance of the ammonia balance, and adjustments in these amino acid pathways may support these goals. Finally, branched-chain AAs (Leu, Ile, and Val) are essential for protein synthesis and energy metabolism. Under postoperative stress, shifts in the metabolism of these AAs likely reflect the body's adaptation to surgical trauma and its increased metabolic demands during recovery [24].

Postoperative recovery of intestinal function, such as the time to first flatus, is a crucial clinical indicator of patient recovery. Numerous studies have shown that amino acid metabolism is closely related to the gut microenvironment, immune regulation, and the gut–brain axis. Research indicates that specific AAs, such as Glu and Pro, play key roles in intestinal mucosal repair and gut barrier function and that fluctuations in these AAs may directly affect the speed of postoperative gut recovery [25]. Additionally, the interplay between amino acid metabolism and the gut microbiome may also play a critical role postsurgery. The enrichment or deficiency of certain AAs could influence the metabolic activity of the gut microbiota, thereby indirectly regulating intestinal function recovery. This observation suggests that amino acid metabolism may be a potential regulatory factor in the recovery of postoperative intestinal function [22, 26]. Postoperative inflammation significantly impacts both the speed and quality of patient recovery. AAs, in addition to serving as essential building blocks for protein synthesis, also regulate inflammatory responses through their metabolic byproducts. For example, Met metabolism is closely linked to the synthesis of glutathione, an important antioxidant that can alleviate oxidative stress induced by postoperative inflammation [27]. Moreover, the Arg and Pro metabolic pathways are crucial for regulating immune cell function [28]. The balance

between postoperative inflammation levels and alterations in these amino acid pathways may create a dynamic interplay influencing recovery. These findings offer new insights into adjusting postoperative recovery via amino acid metabolism, suggesting that specific AAs or their metabolites could serve as potential targets to improve recovery outcomes. Moreover, early postoperative monitoring of these AAs may provide valuable biomarkers for predicting patient recovery trajectories, shedding light on the mechanisms underlying intestinal function recovery, especially in the early stages after surgery.

On the basis of the above analysis, amino acid metabolism may not only serve as a biomarker for postoperative recovery but also represent a potential new strategy for improving patient recovery through nutritional intervention. However, this study has certain limitations. First, the sample size is relatively small, and the generalizability of the data requires further validation. Second, this study focused primarily on early postoperative amino acid changes, lacked long-term follow-up data, and thus cannot comprehensively reveal the role of AAs in long-term postoperative recovery. Additionally, the need for individualized nutritional intervention strategies remains unclear, and optimal intervention plans may vary among patients. Future research could further investigate the role of specific amino acid supplementation in promoting postoperative intestinal function recovery and alleviating inflammation. For example, rational supplementation of branched-chain AAs and modulation of Met and Lys metabolism may offer new approaches for personalized nutritional support.

In conclusion, this study provides preliminary evidence of the relationship between amino acid metabolism and postoperative recovery in gastric cancer patients. These findings offer important insights for further exploration of the role of metabolic regulation in postoperative recovery and lay the foundation for the development of personalized postoperative management strategies in the future.

Conclusion

This study systematically analyzed the changes in plasma amino acid profiles before surgery, after surgery, and following nutritional intervention in gastric cancer patients and revealed a close association between amino acid metabolism and postoperative recovery. The results revealed that the amino acid profile of gastric cancer patients deviated significantly from normal levels before surgery, with certain AAs significantly decreasing postoperatively. Nutritional intervention was able to partially restore the levels of specific AAs, although some remained lower than those in healthy individuals. Further analysis revealed that postoperative amino acid changes were significantly negatively correlated with time to first flatus and the levels of the inflammatory markers CRP and WBC, suggesting that these AAs may play important roles in postoperative intestinal function recovery and inflammation regulation. Pathway enrichment analysis revealed that amino acid metabolic pathways, such as Gly and Ser metabolism, Phe and Tyr metabolism, and Lys and Met metabolism, may play critical roles in the postoperative recovery process.

These findings not only provide new insights into metabolic regulation for postoperative recovery but also support the potential application of amino acid metabolism as a biomarker. Although this study has several limitations, such as a small sample size and a lack of long-term follow-up data, it provides a theoretical foundation and practical guidance for further exploration of the role of metabolic regulation in personalized nutritional support and postoperative rehabilitation. Future studies will aim to expand the sample size and extend the follow-up time to further validate the potential of specific AAs as biomarkers for postoperative recovery. This study is purely observational and does not include interventional trials to assess the causal effects of amino acid supplementation on postoperative recovery. Further research is required to explore the potential benefits of targeted amino acid supplementation in this patient population. Additionally, exploring precise nutritional intervention strategies on the basis of individual amino acid needs may optimize the postoperative recovery process and improve patients' long-term prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03729-x.

Supplementary Material 1.

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Authors' contributions
J.P. and Y.Y.W. conceived and designed the study and gave important suggestions on improving the quality of the analysis, B.L. analysed the data, Q.H.Z., W.Z.S. and C.J.S. managed the collection of all data, W.P., W.Z. and R.R made the figures and tables, Z.X. drafted the manuscript, Z.N.G. revised the manuscript. All authors have read and agreed to the published version of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of The Second Affiliated Hospital of Soochow University (Decision No.2021.(XJS9)).

Consent for publication

All the authors approved the manuscript for publication.

Competing interests

The authors declare no competing interests.

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