Predictive value of the -1031T/C polymorphism in the tumor necrosis factor-α gene for malnutrition prediction in patients with adenocarcinoma of the esophagogastric junction

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Abstract

Introduction: The prevalence of malnutrition in patients with locally advanced adenocarcinoma of the gastroesophageal junction (AEG) is remarkably high, and it significantly influences the prognosis beyond treatment outcomes and postoperative complications. This study aimed to investigate the potential of TNF-α-1031 T/C gene polymorphism as a predictive biomarker for malnutrition in AEG patients, as well as its efficacy in predicting oral nutritional therapy.

Material and methods: The study included 243 patients with locally advanced AEG. DNA genotyping analysis using SNP1 software was conducted on the tailoring DNA. Patients identified as high risk for malnutrition prior to treatment received concurrent oral nutritional therapy alongside neoadjuvant chemotherapy over a period of 7–9 weeks.

Results: Compared to patients carrying the TT genotype, those harboring the C allele exhibited a significantly higher susceptibility to developing malnutrition. Furthermore, there was a substantial increase in the susceptibility to malnutrition. Multivariate regression analysis revealed that carrying the C allele independently serves as a prognostic factor for malnutrition in AEG patients. Furthermore, our findings suggest that the C allele acts as an independent prognostic factor for improved nutritional status following oral nutritional therapy.

Conclusions: The TNF-α SNP (-1031 T/C) has been identified as an independent prognostic factor associated with malnutrition in patients with advanced AEG. Patients carrying the C allele exhibited a significantly poorer nutritional status compared to those with the TT genotype. Moreover, in the context of neoadjuvant chemotherapy combined with oral nutritional therapy, the nutritional status of C allele carriers was significantly poorer compared to that of TT genotype patients.

Key words: adenocarcinoma of esophagogastric junction, malnutrition, TNF-α, gene single nucleotide polymorphisms, nutritional therapy.

Introduction

In recent years, there has been a global surge in the incidence of adenocarcinoma of the esophagogastric junction (AEG), a prevalent malignant tumor of the upper digestive tract that particularly affects individuals residing in the Taihang mountains [1]. Regrettably, most AEG patients

are diagnosed at an advanced stage. Malnutrition is highly prevalent among AEG patients due to chronic tumor depletion, preoperative neoadjuvant chemotherapy, and inadequate nutritional intake resulting from cardiac obstruction. The malnutrition rate in locally advanced AEG patients is estimated to be as high as 50%, which not only impacts treatment outcomes and postoperative complications but also significantly correlates with poor prognosis [2].

Malnutrition refers to an imbalance between energy intake, energy expenditure, and the quality of nutrient intake [3, 4], which is specifically characterized by progressive depletion of adipose tissue reserves and skeletal muscle [5]. The detrimental effects of perioperative malnutrition have emerged as a growing concern among clinicians. Consequently, nutritional assessment has become an integral component of clinical management for cancer patients and serves as the primary determinant for timely initiation of nutritional intervention. However, in many malnourished patients, oral nutritional supplements alone fail to ameliorate malnutrition. This implies a more intricate metabolic mechanism underlying the development of malnutrition.

The precise cytokines responsible for malnutrition in patients with malignant tumors remain incompletely understood; however, the role of tumor necrosis factor-α (TNF-α) and other inflammatory cytokines implicated in carcinogenesis in the development and progression of malnutrition is increasingly recognized [6]. The binding of TNF-α to TNF receptors on the surface of muscle cells triggers activation of the nuclear factor-κB signaling pathway, leading to upregulation of proteins such as microglial response factor-1 and muscle atrophy F-box. This subsequently activates the ubiquitin proteasome pathway for muscle protein degradation [7, 8]. Moreover, TNF-α can stimulate fat breakdown by activating mitogen-activated protein kinases (p44/42) and Jun n-terminal kinase pathways [9]. Elevated levels of TNF-α not only contribute to lipid and muscle atrophy but also induce anorexia, promote skeletal muscle protein degradation, inhibit protein synthesis, induce insulin resistance, mediate systemic inflammation in cancer-related malnutrition, and further exacerbate malnutrition [10].

Concurrently, a growing body of evidence has substantiated that host genes govern the regulation of cytokine levels in the human body, and the polymorphic sequence of cytokine genes may serve as a genetic marker for susceptibility [11]. Given the stable nature of single nucleotide polymorphisms (SNPs) in disease, it has been postulated that genetic predisposition may contribute to the susceptibility to malnutrition [12, 13]. The cytokine TNF-α is widely recognized as a prototypical marker for malnutrition. To date, numerous functional SNPs within the TNF-α gene have been identified and characterized as genetic alterations associated with cancer [6]. The impact of various SNPs within the promoter region (-238, -244, -308, -376, -489, -575, -610, -851, -857, -863 and-1031) of TNF-α on both gene expression and disease susceptibility has been extensively documented [14–18]. The most recent research has demonstrated a potential association between the TNF-α-1031T/C SNP (rs1799964) and malnutrition [6, 19].

The mRNA expression of TNF-α is reported to be increased in individuals with the CC genotype compared to those with the TC and TT genotypes [20]. Furthermore, patients carrying the CC genotype exhibit significantly lower body weight than those with the TT and CT genotypes [5]. Additionally, individuals harboring the C allele have a roughly 2.5-fold higher susceptibility to malnutrition compared to those with the TT genotype [21].

The currently available tools for screening and evaluating malnutrition in clinical practice encompass the Nutritional Risk Screening 2002 (NRS-2002) and the Global Consensus on Malnutrition Diagnostic Criteria (GLIM) [4, 22]. In this study, we employed NRS-2002 and GLIM to ascertain the presence of malnutrition in patients with locally advanced AEG, while also investigating the multiple factors associated with malnutrition in AEG patients. Concurrently, we assessed the TNF-α-1031T/C SNP (rs1799964) as a potential indicator for predicting malnutrition and prognosis in AEG patients.

Material and methods

Trial design

This study is a one-arm practical clinical trial conducted in Anyang Tumor Hospital. The trial protocol (AZLL2020122708) was approved by the Scientific Ethics Review Committee of XX Hospital, and written informed consent was obtained. The study enrolled patients diagnosed with locally advanced Siewert type II AEG who were scheduled to undergo neoadjuvant chemotherapy followed by radical gastrectomy at the Department of Abdominal Oncology, Anyang Tumor Hospital, between January 2021 and June 2023. The study was completed on 30 September 2023. This study adhered to the principles outlined in the Declaration of Helsinki. The clinical staging prior to treatment was conducted in accordance with the 2016 American Joint Committee on Cancer eighth edition of esophageal cancer TNM staging criteria [23], encompassing 126 patients classified as clinical stage III and 117 patients classified as clinical stage IVa.

Inclusion criteria: (1) Participants aged 18 years or older. (2) Patients were diagnosed with advanced Siewert type II AEG, confirmed by gastroscopy and pathological biopsy [24], with a clinical stage before treatment classified as stage cIII or cIVa [25]. (3) There were no absolute contraindications to surgical intervention. (4) None of them had received prior chemotherapy, radiotherapy, targeted therapy, or immunotherapy. (5) No other concurrent malignant tumors were identified.

The exclusion criteria included non-adherence to prescribed chemotherapy or surgery, severe allergic reactions to chemotherapeutic agents, acute uncontrollable conditions during treatment that impeded its continuation, or incomplete clinicopathological data.

General information

The patient's gender, age, height, weight, weight loss, body mass index (BMI), clinical tumor stage, personal medical history, and performance status were extracted from the electronic health record system. The patients' performance status was evaluated using the Eastern Cooperative Oncology Group scale [26].

Measurements

NRS-2002 and GLIM were employed as assessment tools to evaluate the nutritional status of all enrolled patients prior to neoadjuvant chemotherapy. NRS-2002 evaluates the risk of malnutrition based on a patient's nutritional status, disease severity, and age. According to NRS-2002, a score < 3 indicates a low risk of malnutrition while a score ≥ 3 suggests a high risk of malnutrition [21]. GLIM was utilized to further confirm the presence of malnutrition in patients identified as high risk by NRS-2002. GLIM consists of three phenotypic criteria (involuntary weight loss, low body mass index, and muscle loss) and two etiologic criteria (reduced intake or impaired digestion and absorption, inflammation or disease burden) [4, 27]. The diagnosis of malnutrition requires at least one phenotypic criterion and one etiologic criterion. Oral nutritional therapy was administered to all patients identified as being at high risk for malnutrition during neoadjuvant chemotherapy, spanning a duration of 7–9 weeks. Subsequently, their nutritional status was reassessed using the NRS-2002 score and GLIM criteria.

Therapeutic regimen

The SOX regimen (oxaliplatin + S-1) was administered to all patients as neoadjuvant chemotherapy, with a treatment cycle of 3 weeks. This treatment was repeated for a total of 2 cycles.

Nutritional support: The nutrition specialist nurse practitioner assesses and determines the precise amounts and proportions of various nutrients required for each enrolled patient. Patients identified as being at high risk of malnutrition receive targeted nutritional therapy, guidance on improved dietary habits, and blood sugar management when necessary. The nutritional intervention plan comprises daily supplementation with whey protein (1.2 to 1.5 g/kg of ideal body weight, or 20% of total caloric intake) for the patient, along with an extra oral nutritional supplement providing 400 to 900 kcal/day, which is to be consumed in conjunction with the regular diet to optimize nutritional status and stimulate muscle protein synthesis [28]. A logbook was provided to participants, and a professional dietitian supervised their nutritional intake, monitored adherence, and addressed any questions or issues through weekly phone consultations. The NRS-2002 scale was employed once again as an evaluative tool to gauge the amelioration of nutritional status in patients within a span of 2–4 weeks subsequent to the cessation of oral chemotherapy medications (i.e. approximately 7–9 weeks following the initiation of initial chemotherapy).

Genotyping

In accordance with the manufacturer's guidelines, genomic DNA was isolated from peripheral blood leukocytes using the Animal DNA Extraction Kit (TSINGK, China). Subsequently, amplification of the DNA was performed following established protocols [21], followed by electrophoresis and Sanger sequencing. Genotyping of selected polymorphisms was conducted using SNP1 software (TSINGK, China), while strictly adhering to the manufacturer's recommended protocol conditions.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics software (version 26.0 for Windows). The impact of demographic, clinical, and genetic variables on nutritional status was evaluated through univariate logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Multivariable logistic regression models were employed to analyze the susceptibility to malnutrition and factors associated with TNF-α genotypes, incorporating variables that demonstrated statistical significance in the univariate analysis ($p < 0.05$). The chi-square (χ^2) test was used to compare categorical data. A p-value < 0.05 indicated a statistically significant difference.

Results

General characteristics of the study group

The study included a total of 243 patients diagnosed with locally advanced AEG. According to the clinical TNM staging system for esophageal cancer, 51.85% of the patients were classified as stage III, while 48.15% were categorized as stage IVa. The median age of the patient cohort was 64.9 years (range: 38–87 years), with a median weight and BMI of 56.2 kg (range: 38.0–90.0 kg) and 20.8 kg/m^2 (range:14.0–29.3 kg/m^2), respectively. The prevalence of high risk of malnutrition, as defined by the NRS-2002 criteria, was observed in approximately 60.49% of the study population, whereas the prevalence of malnutrition based on the GLIM criteria was found to be around 32.92%.

Table I. Characteristics of the study group

Variable		Study group (n = 243)
Gender	Male	193 (79.42%)
	Female	50 (20.58%)
Age [years]	Median (range)	64.9 (38–87)
	≥ 65	139 (57.20%)
	< 65	104 (42.80%)
T stage	T2	40 (16.46%)
	T3	112 (46.09%)
	T4	91 (37.45%)
N stage	N0	48 (19.75%)
	N1	80 (32.92%)
	N2	82 (33.74%)
	N3	33 (13.58%)
Clinical TNM staging	III	126 (51.85%)
	IVa	117 (48.15%)
Weight [kg]	Median (range)	56.2 (38.0–90.0)
	< 56.2	122 (50.21%)
	≥ 56.2	121 (49.79%)
BMI [kg/m^2]	Median (range)	20.8 (14.0–29.3)
	< 20.8	125 (51.44%)
	≥ 20.8	118 (48.56%)
Initial body weight loss percentage	< 5%	51 (20.99%)
	> 5%	192 (79.01%)
	No	146 (60.08%)
Smoking status	Smoker	89 (36.62%)
	Nonsmoker	154 (63.37%)
NRS-2002	< 3	96 (39.51%)
	≥ 3	147 (60.49%)
GLIM	No	163 (67.08%)
	Yes	80 (32.92%)
Performance status	≤ 1	193 (79.42%)
	> 1	50 (20.58%)

Among the AEG patients, 8 individuals possessed the CC genotype, 67 individuals had the CT genotype, and 168 individuals exhibited the TT genotype. The distribution of TNF-α-1031T/C SNP (rs1799964) genotypes in AEG patients adheres to Hardy-Weinberg equilibrium (Table I).

Univariate logistic regression analysis before oral nutrition therapy

The malnutrition risk status was assessed in all patients using the NRS-2002 scale and GLIM as measurement tools. Single-factor regression analysis was employed to identify potential factors associated with an increased prevalence of malnutrition.

According to the NRS-2002 scale, older patients (≥ 65 years) exhibited a 1.6-fold higher susceptibility to developing severe nutritional susceptibility (≥ grade 3) (p = 0.038; OR = 1.625). Patients with invaded serous membranes had a 4.9-fold increased susceptibility to developing a higher degree of nutritional vulnerability (p < 0.001; OR = 4.937). Patients with clinical N grades 2–3 showed a significant 9.7-fold increase in the susceptibility to developing severe nutritional vulnerability (p < 0.001; OR = 9.785). Furthermore, patients diagnosed with clinical stage IVa demonstrated an even greater susceptibility, with a 10.6-fold elevation compared to those at clinical stage III (p < 0.001; OR = 10.675). For patients with poor performance status, the nutritional susceptibility was nearly 5 times higher (p < 0.001; OR = 5.471). Patients carrying the C allele exhibited a significantly elevated susceptibility to malnutrition, with an odds ratio of 5.4 (p = 0.002; OR = 5.399), compared to those with the TT genotype (Table II).

According to GLIM, patients with serosal surface involvement exhibited a 4.1-fold higher susceptibility to developing severe malnutrition (p < 0.001; OR = 4.153). Patients with clinical N grades 2–3 had a 6.3-fold increased susceptibility to developing advanced malnutrition (p < 0.001; OR = 6.302). In patients with clinical stage IVa, this susceptibility was elevated by 4.3 times (p < 0.001; OR = 4.396). The presence of poor performance status resulted in nearly a 3.6-fold increase in the susceptibility to malnutrition (p < 0.001; OR = 3.627). Individuals carrying the C allele exhibited an approximately 6.7-fold increased susceptibility to developing malnutrition compared to those with the TT genotype (p < 0.001; OR = 6.758) (Table III).

Multivariable logistic regression analysis before oral nutrition therapy

The multiple logistic regression model included each statistically significant univariate predictor

Table II. Impact of demographic, clinical, and genetic variables on NRS-2002 scale assessed through univariate regression analysis

Variable		NRS-2002 Scale		Univariable analysis	
		< 3	≥ 3	OR [95% CI]	*P*-value
Gender	Male	78	115	1.206 [0.633–2.298]	0.570
	Female	18	32		
Age [years]	≥ 65	48	91	1.625 [1.028–2.569]	0.038*
	< 65	48	91		
Clinical T stage	T4	17	74	4.937 [3.009–8.098]	< 0.001*
	T2–3	79	73		
Clinical N stage	N2–3	16	99	9.785 [3.457–27.693]	< 0.001*
	N0–1	80	48		
Clinical TNM stage	IVa	16	101	10.675 [6.427–17.730]	< 0.001*
	III	80	46		
Performance status	> 1	6	44	5.471 [2.714–11.027]	< 0.001*
	≤ 1	90	103		
Excessive alcohol consumption	Yes	40	57	1.128 [0.668–1.905]	0.653
	No	56	90		
Smoking status	Smoker	30	59	1.256 [0.568–2.953]	0.161
	Nonsmoker	66	88		
TNF-α genotype	CC and CT	19	56	5.399 [1.868–17.267]	0.002*
	TT	77	91		

Table III. Impact of demographic, clinical, and genetic variables on GLIM assessed through univariate regression analysis.

Variable		GLIM		Univariable analysis	
		No	Yes	OR [95% CI]	*P*-value
Gender	Female	30	20	1.478 [0.777–2.810]	0.233
	Male	133	60		
Age [years]	≥ 65	93	34	0.982 [0.608–1.587]	0.941
	< 65	70	34		
Clinical T stage	T4	45	46	4.153 [2.645–6.520]	< 0.001*
	T2–3	118	34		
Clinical N stage	N2–3	61	54	6.302 [3.389–11.718]	< 0.001*
	N0–1	102	26		
Clinical TNM stage	IVa	61	56	4.396 [2.748–7.033]	< 0.001*
	III	102	24		
Performance status	> 1	22	28	3.627 [2.172–6.058]	< 0.001*
	≤ 1	141	52		
Excessive alcohol consumption	Yes	70	39	1.477 [0.846–2.580]	0.170
	No	93	41		
Smoking status	Smoker	58	31	0.873 [0.503–1.517]	0.631
	Nonsmoker	105	49		
TNF-α genotype	CC and CT	21	54	6.758 [2.785–16.399]	< 0.001*
	TT	142	26		

for further analysis. According to the NRS-2002 scale, independent predictors associated with an increased prevalence of malnutrition were disease clinical stage according to TNM ($p < 0.001$; OR = 8.777) and presence of the individuals carrying the C allele e ($p = 0.022$; OR = 3.673). Additionally, according to the GLIM model, significant independent predictors associated with malnutrition

included clinical N stage (p = 0.002; OR = 3.959) and carrying the C allele (p = 0.018; OR = 3.882) (Table IV).

Univariate logistic regression analysis after oral nutrition therapy

Before undergoing neoadjuvant chemotherapy, 147 patients with high-risk factors for malnutrition received oral nutritional therapy in conjunction with neoadjuvant chemotherapy, improved dietary habits, and implemented necessary blood glucose management. Following a period of 7–9 weeks of oral nutrition treatment, the nutritional status of all 147 patients was reassessed using the NRS-2002 scale and GLIM as measuring tools. Despite these interventions, there remained a subset of patients whose nutritional status did not exhibit significant improvement. Univariate regression analysis was conducted to identify potential factors influencing the enhancement of nutritional status.

According to the NRS-2002 scale, 26 patients were classified as high risk for malnutrition while the remaining 121 patients were categorized as low risk. Univariate logistic regression analysis revealed that elderly patients (≥ 65 years old) exhibited a 2.1-fold increased susceptibility to developing a high-risk state of malnutrition (p = 0.038; OR = 2.116). The presence of serous membrane invasion was associated with a four-fold increased susceptibility to developing a high-risk state of malnutrition (p < 0.001; OR = 4.090). Patients with clinical N grade 2–3 had a 2.1-fold increased susceptibility to developing a high-risk state of malnutrition (p = 0.041; OR = 2.108). In patients with stage IVa, the susceptibility was elevated by 2.6 times (p = 0.028; OR = 2.631). Poor performance status was associated with an approximately 2.3-fold higher nutritional susceptibility (p = 0.013; OR = 2.351). Compared to patients with the TT genotype, individuals carrying the C allele exhibited significantly elevated susceptibility in developing high-risk states of malnutrition, with an odds ratio of nine (p < 0.001; OR = 9.341) (Table V).

According to the GLIM scale, 15 patients still exhibited malnutrition, while the remaining 132 were non-malnourished. Univariate logistic regression analysis revealed a significant 8.4-fold increased prevalence of malnutrition in individuals with serous membrane invasion (p = 0.001; OR = 8.426). Patients with clinical N grade 2–3 demonstrated a substantial 5.3-fold heightened susceptibility to malnutrition (p < 0.041; OR = 5.342). Moreover, in patients with clinical stage IVa, this susceptibility was further amplified by a remarkable factor of 12 (p = 0.016; OR = 12.063). Patients with poor performance status exhibited an almost fourfold higher incidence of malnutrition (p = 0.001; OR = 3.990). The presence of the C allele was associated with a significantly elevated susceptibility to malnutrition compared to patients with the TT genotype, demonstrating an odds ratio of 9.5 (p < 0.001; OR = 9.537) (Table VI).

Multivariable logistic regression analysis after oral nutrition therapy

Each statistically significant univariate predictor was included in the multiple logistic regression model for further analysis. It was observed that, based on the NRS-2002 scale, individuals carrying

Table IV. Impact of demographic, clinical, and genetic variables on susceptibility to malnutrition evaluated through multivariable regression analysis

Variable		Multivariable analysis			
		NRS-2002		GLIM	
		OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Age [years]	≥ 65	1.263 [0.740–2.155	0.393	–	
	< 65				
Clinical T stage	T4	1.243 [0.565–2.867]	0.711	1.819 [0.816–4.056]	0.143
	T2–3				
Clinical N stage	N2–3	2.542 [0.761–8.491]	0.130	3.959 [1.664–9.422]	0.002*
	N0–1				
Clinical TNM stage	IVa	8.777 [4.271–18.036]	< 0.001*	1.745 [0.789–3.859]	0.169
	III				
Performance status	> 1	1.006 [0.386–2.621]	0.990	1.882 [0.801–4.422]	0.147
	≤ 1				
TNF-α genotype	CC and CT	3.673 [1.205–11.189]	0.022*	3.882 [1.454–11.760]	0.018*
	TT				

Footnote: Variables that achieved statistical significance (p < 0.05) in the univariate analysis were subsequently included in the multivariate logistic regression model for further evaluation.

Table V. Impact of demographic, clinical, and genetic variables on the NRS-2002 scale following oral nutritional therapy evaluated through univariable regression analysis

Variable		NRS-2002		Univariable analysis	
		< 3	≥ 3	OR [95% CI]	*P*-value
Age [years]	≥ 65	67	20	2.116 [1.102–4.939]	0.038*
	< 65	54	6		
Clinical T stage	T4	54	20	4.090 [1.917–8.725]	< 0.001*
	T2–-3	67	6		
Clinical N stage	N2–3	22	9	2.108 [1.030–4.313]	0.041*
	N0–1	99	17		
Clinical TNM stage	IVa	79	22	2.631 [1.113–6.220]	0.028*
	III	42	4		
Performance status	> 1	32	12	2.351 [1.201–4.601]	0.013*
	≤ 1	89	14		
TNF-α genotype	CC and CT	33	22	9.341 [5.124–15.128]	< 0.001*
	TT	88	4		

Table VI. Impact of demographic, clinical, and genetic variables on the GLIM scale following oral nutritional therapy evaluated through univariable regression analysis

Variable		GLIM		Univariable analysis	
		No	Yes	OR [95% CI]	*P*-value
Age [years]	≥ 65	80	11	1.787 [0.589–5.426]	0.305
	< 65	52	4		
Clinical T stage	T4	61	13	8.426 [2.456–28.911]	0.001*
	T2–3	71	2		
Clinical N stage	N2–3	33	8	5.342 [2.290–12.463]	< 0.001*
	N0–1	109	7		
Clinical TNM stage	IVa	86	14	12.063 [1.601–90.873]	0.016*
	III	46	1		
Performance status	> 1	35	9	3.990 [1.727–9.216]	0.001*
	≤ 1	97	6		
TNF-α genotype	CC and CT	41	14	9.537 [5.269–17.262]	< 0.001*
	TT	91	1		

the C allele were identified as the sole independent predictors of a high risk of malnutrition after oral nutritional therapy ($p < 0.001$; OR = 38.065). According to the GLIM scale, significant independent predictors of malnutrition following oral nutritional therapy included clinical N grade 2–3 ($p = 0.009$; OR = 5.306), as well as individuals harboring the C allele ($p < 0.001$; OR = 63.319) (Table VII).

Relationship between TNF-α polymorphism and body weight loss

Our statistical analysis indicated that, during the initial visit, among the 192 patients experiencing a weight loss of ≥ 5% over the past three months, the proportion carrying the C allele was significantly higher compared to the 51 patients with a weight loss of < 5% (34.38% vs. 17.65%). This difference was statistically significant ($\chi^2 = 5.284$, $p = 0.022$). Furthermore, among the 147 patients with an NRS-2002 score of ≥ 3, 129 patients demonstrated varying degrees of weight gain after receiving oral nutritional therapy, while 18 patients showed no significant change in weight. Notably, 15 of these 18 patients carried the C allele, whereas only 3 had the TT genotype. This difference was also statistically significant ($\chi^2 = 18.470$, $p < 0.001$).

Discussion

Malnutrition may occur in patients with early-stage cancer, but it is more prevalent in those with advanced-stage cancer and can progress to cancer cachexia [29, 30]. The presence of malnutrition significantly impacts the overall quality of life for cancer patients, leading to shortened survival time, reduced treatment compliance and

Table VII. Impact of demographic, clinical, and genetic variables on susceptibility to malnutrition following oral nutritional therapy assessed using a multivariable regression analysis

Variable		Multivariable analysis			
		NRS-2002		GLIM	
		OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Age [years]	≥ 65	2.994 [0.991–9.051]	0.052	–	
	< 65				
Clinical T stage	T4	2.450 [0.823–7.294]	0.107*	2.562 [0.532–12.340]	0.241
	T2–3				
Clinical N stage	N2–3	1.289 [0.439–3.784]	0.644	5.306 [1.507–18.683]	0.009*
	N0–1				
Clinical TNM stage	IVa	1.094 [0.449–2.668]	0.619	5.336 [0.432–65.926]	0.192
	III				
Performance status	> 1	2.541 [0.770–8.388]	0.126	1.265 [0.334–4.798]	0.729
	≤ 1				
TNF-α genotype	CC and CT	38.065 [8.597–168.532]	< 0.001*	63.319[18.008–528.132]	< 0.001*
	TT				

Footnote: Variables that achieved statistical significance (p < 0.05) in the univariate analysis were subsequently included in the multivariate logistic regression model for further evaluation.

effectiveness, and increased incidence of complications, ultimately becoming a significant cause of death in this population [31]. Due to the unique location characteristics of AEG tumors, varying degrees of digestive tract obstruction often arise during their development, resulting in decreased food intake. In newly diagnosed AEG cases, the prevalence rate of malnutrition can be as high as 60% [31]. The existence of malnutrition adversely affects functional ability, quality of life, and overall survival outcomes. According to statistics, approximately 85% of AEG patients will eventually develop cancer cachexia [32]. Furthermore, previous studies have demonstrated that malnutrition serves as an independent prognostic factor for AEG [33]. Therefore, it is imperative to investigate the underlying mechanisms that contribute to the occurrence and progression of malnutrition among patients with advanced AEG, while also identifying early susceptibility factors for malnutrition. These crucial steps are essential in order to implement timely and accurate nutritional interventions that can effectively prevent or halt its progression into cancer cachexia. Ultimately, these efforts aim to optimize functional ability, enhance quality-of-life measures, and augment overall patient survival.

The study revealed a significant correlation between serum TNF-α concentration and TNF-α-1031T/C gene polymorphism with the susceptibility to malnutrition in patients diagnosed with gastric cancer [12]. Previous research has also suggested that serum TNF-α concentration can serve as an indicator for malnutrition and decline in quality of life among individuals with gastric cancer [34]. Numerous studies have consistently identified TNF-α-1031T/C as a valuable biomarker for predicting susceptibility to malnutrition [35]. Further investigations showed a significantly higher incidence of malnutrition in gastric cancer patients carrying the C allele compared to those with TT genotype, indicating an elevated susceptibility to malnutrition associated with this genetic variant [21].

In this study, we detected the presence of serum TNF-α-1031 T/C gene polymorphism in patients with locally advanced AEG. Our findings revealed a significant correlation between the occurrence of malnutrition and serum TNF-α-1031 T/C gene polymorphism in AEG patients.

In our study, we employed the NRS-2002 score and GLIM clinical diagnosis to evaluate the influence of demographic, clinical, and genetic variables on malnutrition in patients with AEG. Through univariate analysis, we observed potential associations between patient age, tumor clinical stage (including T stage, N stage, and TNM stage), performance status, TNF-α-1031 T/C gene polymorphism and a high susceptibility to malnutrition. Subsequently, multifactorial logistic regression models were applied, revealing that TNF-α-1031 T/C gene polymorphism independently correlated significantly with malnutrition in patients. Specifically, individuals carrying the C allele exhibited higher susceptibility to malnutrition compared to those with TT genotype.

Currently, the standard treatment for locally advanced AEG involves a sequential approach consisting of neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. The duration of neoadjuvant chemotherapy, which is crucial for

optimizing patients' nutritional status and ensuring surgical safety, typically spans 7 to 9 weeks. In this study, patients identified as being at high risk of malnutrition were provided with concurrent oral nutritional therapy alongside neoadjuvant chemotherapy, guidance on enhancing dietary habits, and blood sugar management when necessary. A certified nutrition nurse practitioner conducted individual assessments to determine the precise nutrient requirements for each patient. Each participant was given a logbook to document their dietary intake. A professional dietitian supervised the nutritional regimen, monitored adherence, and addressed any questions or issues via weekly telephone consultations, ensuring that all patients at high risk of malnutrition received adequate and effective nutritional support. While our comprehensive treatment measures have generally led to improved nutritional status in most patients, there remains a subset who fail to exhibit significant improvement or even experience deterioration. The underlying factors contributing to this discrepancy have not been thoroughly investigated. Therefore, we conducted a study that identified age, tumor clinical stage (including T stage, N stage, and TNM stage), performance status, and TNF-α-1031 T/C gene polymorphisms as potential correlates of enhanced nutritional status following oral nutritional therapy. Subsequently, employing multiple logistic regression models revealed that the TNF-α-1031 T/C gene polymorphism independently influenced whether an individual's nutritional status improved after receiving oral nutrition therapy. Specifically, it indicated that patients carrying the C allele were unable to achieve significant improvements in their nutritional status despite long-term oral nutrition therapy or might even experience further deterioration.

We calculated the weight loss of AEG patients before treatment and found that the proportion of patients with the C allele was significantly higher in patients with ≥ 5% weight loss. This also indicates that AEG patients who carry the C allele have a high susceptibility to significant weight loss. All patients with an NRS-2002 score of ≥ 3 were given oral nutritional therapy along with neoadjuvant chemotherapy. When the patients' weight was measured again after the end of treatment, we found that only 40 of the 55 patients carrying the C allele gained weight (72.73%), which was significantly lower than the 96.74% (89/92) of the TT genotype. It can be seen that patients with advanced AEG carrying the C allele have poor oral nutritional treatment.

However, there are certain limitations to our research. Firstly, the sample size of patients in our study was relatively small and limited to a single center, which may restrict its ability to comprehensively reflect the true impact of factors influencing the nutritional status of all AEG patients. Secondly, we did not fully explore the role of tumor itself in contributing to malnutrition through potential food intake issues. Additionally, we did not evaluate the influence of individual genotype on gene expression (and subsequent protein expression) for the studied gene. Despite these constraints, TNF-α-1031 T/C gene polymorphisms have been identified as promising predictors for AEG malnutrition and can serve as indicators for determining whether oral nutritional therapy effectively improves nutritional status.

In conclusion, according to our findings, the SNP (-1031 T/C) of TNF-α has been identified as an independent prognostic factor associated with malnutrition in patients with locally advanced AEG. Patients with the C allele exhibited poorer nutritional status compared to those with the TT genotype. Moreover, for high-risk malnourished patients receiving neoadjuvant chemotherapy combined with oral nutritional therapy, there was a significant disparity in nutritional improvement between C allele carriers and patients with the TT genotype. Specifically, after oral nutritional therapy, the rate of nutritional improvement among C allele carriers was significantly lower compared to patients with the TT genotype. Consequently, it appears that enhancing the nutritional status of individuals carrying the C allele through oral nutritional therapy alone is challenging. Therefore, early consideration of alternative routes, such as intravenous nutrition support, may be warranted.

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Ethical approval

Approval number: AZLL2020122708.

Conflict of interest

The authors declare no conflict of interest.

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