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ORIGINAL ARTICLE

Impact of nutritional risk screening on outcomes of first-line treatment in metastatic esophagogastric adenocarcinoma: a secondary analysis of the AIO-MATEO trial

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Background: Malnutrition is common in patients with metastatic esophagogastric adenocarcinoma (EGA). However, the prognostic impact of nutritional risk screening (NRS) in advanced EGA remains underexplored. This preplanned analysis of the phase II AIO-MATEO trial evaluated the impact of NRS on clinical outcomes for patients with advanced EGA.

Patients and methods: Patients enrolled in the MATEO trial (exploring S-1 maintenance therapy) with an available baseline NRS before induction chemotherapy were included. Patients were stratified by their baseline NRS score (<3 versus ≥ 3). Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan–Meier and Cox regression methods.

Results: Of the 136 patients, 86 had an NRS score <3 and 50 had an NRS score ≥ 3 at baseline. Baseline median European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30) global health score was lower for the NRS ≥ 3 group (37.5 versus 58.3). Nutritional interventions were more frequent in the NRS ≥ 3 group (45.8% versus 10.6%; $P < 0.001$). Patients with NRS ≥ 3 had inferior median PFS (4.9 months versus 6.9 months; $P = 0.025$) and OS (8.2 months versus 13.2 months; $P = 0.003$). Patients whose NRS score improved during induction chemotherapy showed superior median PFS (7.4 months versus 4.1 months; $P = 0.085$) and OS (20.1 months versus 8.0 months; $P = 0.054$) compared with those without improvement. No significant differences in overall toxicity were observed.

Conclusions: Baseline NRS is a significant predictor of outcome in patients with metastatic EGA. Our findings underscore the importance of routinely assessing the nutritional status of patients with metastatic EGA and intervening early.

Key words: chemotherapy, malnutrition, metastatic esophagogastric adenocarcinoma, nutritional intervention, nutritional risk screening

INTRODUCTION

Esophagogastric adenocarcinoma (EGA) is a highly prevalent malignancy, with a global incidence of ∼9.2/100 000.[1] While the incidence of gastric cancer has been declining in recent decades, there has been a marked increase in adenocarcinomas at the esophagogastric junction, particularly in high-income countries.[2] Compared with other gastrointestinal tumors, malnutrition is common and often present at the time of diagnosis in EGA.[3-7] Malnutrition, caused by the tumor disease itself or treatment-related toxicity, negatively impacts treatment tolerance, recovery, and overall survival (OS). This underscores the importance of an early nutritional assessment and intervention as a critical component of EGA management.[8-14]

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The nutritional risk screening (NRS), developed by the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2002, is a widely utilized tool for identifying patients at risk of malnutrition, particularly in hospitalized settings.[15,16] The NRS score evaluates two key components: nutritional status and disease severity. Patients are assigned scores for each component, with an additional point for those over 70 years of age, due to the increased malnutrition risk in elderly patients (Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2025.100297). A score of $\geq$3 indicates an increased nutritional risk and thus recommends a nutritional support intervention.[16] This may include dietary counseling and monitoring, oral nutritional supplements, and enteral or parenteral nutrition.

Studies have shown that tailored nutritional support based on NRS scores improves clinical outcomes, including fewer post-operative complications and better quality of life (QoL) for patients with EGA.[17-19] However, data on the impact of the NRS score on the outcomes of patients with metastatic EGA undergoing systemic treatment are limited. To the best of our knowledge, there are no randomized oncological trials that have included a preplanned analysis of the NRS during the treatment phase.

The international, randomized phase II AIO-MATEO study explored the efficacy and safety of S-1 maintenance therapy—an orally administered chemotherapy drug composed of tegafur, gimeracil, and oteracil—compared with continued platinum-based chemotherapy in Caucasian patients with human epidermal growth factor receptor 2 (HER2)-negative advanced EGA who had no disease progression after 3 months of induction chemotherapy.[20] The MATEO study showed that S-1 maintenance therapy resulted in survival outcomes that were non-inferior compared with ongoing platinum-based combination chemotherapy, while offering better tolerability.[21]

This preplanned analysis of the MATEO trial investigates the impact of baseline nutritional risk, as assessed by NRS score, on progression-free survival (PFS), OS, treatment-related toxicity, and QoL in patients undergoing platinum-based combination chemotherapy as first-line treatment for metastatic EGA.

PATIENTS AND METHODS

Study design and treatment regimens

MATEO is an international, investigator-initiated, randomized phase II trial conducted within the Arbeitsgemeinschaft Internistische Onkologie (AIO) and registered at ClinicalTrials.gov (NCT02128243). The design and protocol of the MATEO study have been previously published.[20] Briefly, patients with histologically confirmed HER2-negative metastatic or locally advanced irresectable EGA who have finished 12 weeks of platinum-based induction chemotherapy without disease progression were randomly assigned in a 2 : 1 ratio to either S-1 monotherapy (arm A) or continuation of platinum—fluoropyrimidine-based combination chemotherapy (arm B). Investigators selected polychemotherapy regimens from a predefined list of recommended doublet or triplet regimens. The trial design is illustrated in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmogo.2025.100297.

This study was conducted in compliance with the Declaration of Helsinki. The trial protocol and all its amendments received approval from the responsible ethics committee. Written informed consent was obtained from all patients before any study-related procedures.

Quality of life, nutritional assessment, and nutritional interventions

QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30). Clinically significant deterioration was defined as a decrease of $\geq$10 points in the global health status. QoL assessments were carried out at baseline (before start of induction therapy) and at randomization (week 12).

The local investigator assessed nutritional status using the NRS at the same time points (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2025.100297). The NRS is a two-step screening tool Supplementary Table S1https://doi.org/10.1016/j.esmogo.2025.100297. In the first step, initial screening evaluates factors such as recent weight loss, body mass index (BMI), reduced dietary intake, and the severity of the underlying disease. If any of these factors are concerning, the second step (final screening) is carried out, assessing the score based on the presence of any nutritional deficiencies and the patient's functional status influenced by disease severity. An additional point is added for patients aged $\geq$70 years. The NRS score ranges from 0 to 7, with higher scores indicating greater nutritional risk. For patients with a negative initial screening, an NRS score of 0 is assigned.

Nutritional interventions were categorized as follows: no nutritional intervention referred to standard oncologic care without any specific nutritional support. Nutritional counseling consisted of individualized dietary advice provided by trained staff. Additional oral high-calorie intake included the prescription of oral nutritional supplements to increase daily caloric and protein intake. Additional parenteral nutrition referred to supplemental intravenous nutrition administered in addition to oral intake. Total parenteral nutrition was defined as the exclusive intravenous nutrition without relevant oral intake. No specific protocol guidance was provided for nutritional interventions.

Statistical analysis

For the preplanned analysis presented in this article, patients were stratified into the NRS $<$3 group and NRS $\geq$3 group based on their NRS score at baseline. PFS and OS were estimated using the Kaplan—Meier method and *P* values between groups were assessed using the log-rank test. Since the primary objective of the MATEO trial was to demonstrate non-inferiority in OS for the S-1 maintenance group compared with the continuation of platinum-

based chemotherapy, outcome results were reported with two-sided 80% confidence intervals (CIs), and two-sided *P* values < 0.2 were considered statistically significant. The Cox proportional hazards model was used for both univariate and multivariate analysis of risk factors. Only variables with a significant association to outcome in the univariate analysis were included in the final multivariate analysis. Comparisons of nutritional interventions and the incidence of adverse events (AEs) between NRS groups were carried out using the chi-square test for categorical variables. For these analyses, *P* values < 0.05 were considered statistically significant.

Patient population for subgroup analysis

Between November 2014 and April 2019, 221 patients were recruited across six European countries, with 162 patients registered before induction therapy. This analysis focuses on 136 eligible patients who completed induction therapy during the study and had an assessed NRS score at baseline before start of systemic treatment. A corresponding CONSORT diagram is shown in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmogo.2025.100297.

RESULTS

Patient characteristics and NRS score distribution

A total of 136 patients were included in this analysis. At screening, 86 patients had an NRS score of <3, while 50 patients had an NRS score of ≥ 3. The distribution of NRS scores at screening is detailed in Table 1. Baseline patient characteristics stratified by NRS groups (<3 versus ≥ 3) are presented in Table 2. Patients in the NRS ≥ 3 group were older (mean age 67.6 years) compared with those in the NRS <3 group (mean age 61.1 years) and had a lower mean body weight (71.5 kg versus 76.9 kg). Additionally, a higher proportion of patients in the NRS ≥ 3 group had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 (74.0% versus 44.2%). FLOT (docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil) as a triplet chemotherapy was used more frequently as induction regimen in the NRS <3 group (59.3% versus 34.0%). A higher proportion of patients in the NRS ≥ 3 group did not undergo randomization due to limiting toxicity or early disease progression (44.0% versus 32.6% in the NRS <3 group). Other characteristics including gender, ethnicity, BMI, histological subtype, M stage at initial diagnosis, prior chemotherapy, or radiotherapy for localized disease were balanced between the two groups.

Nutritional interventions

The frequency of nutritional interventions was significantly different between patients with NRS scores <3 and ≥ 3. At baseline, data were available for 85 patients in the NRS <3 group and 48 patients in the NRS ≥ 3 group. 45.8% of patients in the NRS ≥ 3 group compared with 10.6% in the NRS <3 group ($P < 0.001$) received nutritional interventions. The types of interventions varied. The NRS ≥ 3 group received nutritional counseling more frequently (8.3% versus 3.5%), as well as additional oral high-calorie intake (31.3% versus 4.7%) and parenteral nutrition (6.3% versus 1.2%). By the end of induction chemotherapy, nutritional intervention data were available for 57 patients in the NRS <3 group and 24 patients in the NRS ≥ 3 group. Nutritional interventions remained

Table 1. Nutritional risk score at screening

Nutritional risk score	*n* = 136, % (*n*)
0	13.2 (18)
1	19.1 (26)
2	30.9 (42)
3	21.3 (29)
4	12.5 (17)
5	1.5 (2)
6	1.5 (2)

Table 2. Patient characteristics

Characteristic	NRS < 3 *n* = 86	NRS ≥ 3 *n* = 50
Age, years		
Mean (range)	61.1 (35-83)	67.6 (35-80)
Sex, % (*n*)		
Male	74.4 (64)	64.0 (32)
Female	25.6 (22)	36.0 (18)
Ethnic group, % (*n*)		
Caucasian	100 (86)	98.0 (49)
African	0	2.0 (1)
ECOG PS, % (*n*)		
0	55.8 (48)	26.0 (13)
1	44.2 (38)	74.0 (37)
Body weight, kg		
Mean (range)	76.9 (48-119)	71.5 (38-106)
BMI, kg/m^2		
Mean (range)	25.8 (18-41)	24.5 (15-37)
Tumor localization (primary tumor), % (*n*)		
Distal esophagus (AEG I)	19.8 (17)	16.0 (8)
Cardia carcinoma (AEG II)	36.0 (31)	20.0 (10)
Subcardial carcinoma (AEG III)	7.0 (6)	20.0 (10)
Distal stomach	37.2 (32)	44.0 (22)
Histological subtype, % (*n*)		
Intestinal type	50.0 (43)	40.0 (20)
Diffuse type	24.4 (21)	30.0 (15)
Mixed type	5.8 (5)	10.0 (5)
Unknown	19.8 (17)	20.0 (10)
M stage at initial diagnosis, % (*n*)		
M0	23.3 (20)	22.0 (11)
M1	75.6 (65)	78.0 (39)
Prior chemotherapy, % (*n*)	15.1 (13)	16.0 (8)
Prior radiotherapy, % (*n*)	4.7 (4)	4.0 (2)
Induction regimen, % (*n*)		
FLOT	59.3 (51)	34.0 (17)
FLO	19.8 (17)	48.0 (24)
Modified FOLFOX6	11.6 (10)	12.0 (6)
Cisplatin/S1	7.0 (6)	4.0 (2)
EOX/EOF	0	2.0 (1)
Cisplatin/5-FU	2.3 (2)	0
Study arm, % (*n*)		
A	47.7 (41)	32.0 (16)
B	19.8 (17)	24.0 (12)
Not randomized	32.6 (28)	44.0 (22)

5-FU, 5-fluorouracil; AEG, adenocarcinoma of esophagogastric junction; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EOF, epirubicin, oxaliplatin, 5-FU; EOX, epirubicin, oxaliplatin, capecitabine; FLO, oxaliplatin, folinic acid, 5-FU; FLOT, docetaxel, oxaliplatin, folinic acid, 5-FU; modified FOLFOX-6, oxaliplatin, folinic acid, 5-FU; NRS, nutritional risk screening.

Table 3. Nutritional intervention

	NRS < 3 n = 85	NRS ≥ 3 n = 48	P value
Nutritional intervention at baseline, % (n)	10.6 (9)	45.8 (22)	**<0.001**
Type of nutritional intervention at baseline, % (n)			**<0.001**
No nutritional intervention	89.4 (76)	54.2 (26)	
Nutritional counseling	3.5 (3)	8.3 (4)	
Additional oral high-calorie intake	4.7 (4)	31.3 (15)	
Additional parenteral nutrition	1.2 (1)	6.3 (3)	
Total parenteral nutrition	1.2 (1)	0	
	NRS <3 n = 57	**NRS ≥3 n = 24**	**P value**
Nutritional intervention at end of induction phase, % (n)	15.8 (9)	45.8 (11)	**0.004**
Type of nutritional intervention at end of induction phase, % (n)			**0.040**
No nutritional intervention	84.2 (48)	54.2 (13)	
Nutritional counseling	5.3 (3)	12.5 (3)	
Additional oral high-calorie intake	7.0 (4)	20.8 (5)	
Additional parenteral nutrition	3.5 (2)	12.5 (3)	
Total parenteral nutrition	0	0	

P values indicating statistical significance are printed in bold (standard practice).
NRS, nutritional risk screening.

significantly more common in the NRS ≥3 group (45.8% versus 15.8%; $P = 0.004$), with continued higher use of additional oral high-calorie intake (20.8% versus 7.0%) and additional parenteral nutrition (12.5% versus 3.5%). Detailed data on nutritional intervention by NRS group are provided in Table 3.

Adverse events

No significant differences were observed between the groups regarding the overall incidence of any AE, serious AE (SAE), treatment-related AE or SAE, or the most frequent and clinically relevant AEs. Any AE occurred in 100% of patients in the NRS <3 group and 96.2% of patients in the NRS ≥3 group ($P = 0.151$). SAEs were reported in 26.4% of patients in the NRS <3 and 19.2% of patients in the NRS ≥3 group ($P = 0.483$). Treatment-related AEs were observed in 98.1% and 96.2% ($P = 0.602$), while treatment-related SAEs occurred in 15.1% and 11.5% of patients ($P = 0.668$), respectively.

Survival outcomes and post-study treatment

When analyzing all patients, regardless of the treatment arm assigned, PFS and OS were significantly longer in the NRS <3 group than in the NRS ≥3 group. Specifically, median PFS was 6.9 months (80% CI 6.6-7.5 months) in the NRS <3 group, compared with 4.9 months (80% CI 4.6-5.9 months) in the NRS ≥3 group ($P = 0.025$). Median OS was 13.2 months (80% CI 10.5-14.6 months) in the NRS <3 group, compared with 8.2 months (80% CI 6.8-8.8 months) in the NRS ≥3 group ($P = 0.003$) (Figure 1A and B). Among patients whose NRS score improved from ≥3 to <3 at the end of induction therapy, median PFS was 7.4 months (80% CI 5.9-10.8 months) compared with 4.1 months (80% CI 2.9-8.4 months) for those without improvement ($P = 0.085$), and median OS was 20.1 months (80% CI 8.4-24.3 months) versus 8.0 months (80% CI 4.0-9.8 months) ($P = 0.054$) (Figure 1C and D).

Consistent with the results of the main analysis of the MATEO trial,[21] univariate Cox regression analysis comparing survival outcomes between study arms by NRS groups revealed no significant differences in PFS and OS between study arm B versus study arm A, whereas patients in both NRS groups who were not randomized due to limiting toxicity or early disease progression exhibited significantly worse outcomes. Data from univariate Cox regression are demonstrated in Supplementary Table S2, available at https://doi.org/10.1016/j.esmogo.2025.100297. Kaplan–Meier estimates for PFS and OS by study arm within each NRS group are depicted in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmogo.2025.100297.

Regarding post-study treatments, no significant differences were observed between the NRS groups. Post-study treatment was initiated in 86.9% ($n = 53/61$) of patients in the NRS <3 group and 80.0% ($n = 24/30$) in the NRS ≥3 group ($P = 0.392$).

Quality of life outcomes

The median global health score at screening was significantly worse for the NRS ≥3 group with 37.5 compared with 58.3 for the NRS <3 group. The median time to further deterioration was shorter in the NRS <3 group with 5.9 months (80% CI 5.1-9.2 months), compared with the NRS ≥3 group, where it was not calculable (80% CI 7.4 months- not calculable) ($P = 0.038$) (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmogo.2025.100297) according to the QLQ-C30 questionnaire.

Multivariate analysis

In the multivariate Cox regression analysis including gender, age, and baseline nutritional status as covariates, all three parameters were identified as independent predictors for OS. Patients with NRS ≥3 had a higher risk of death compared with those with NRS <3 [hazard ratio (HR) 1.61, 80% CI 1.15-2.27, $P = 0.071$]. Similarly, patients aged ≥70

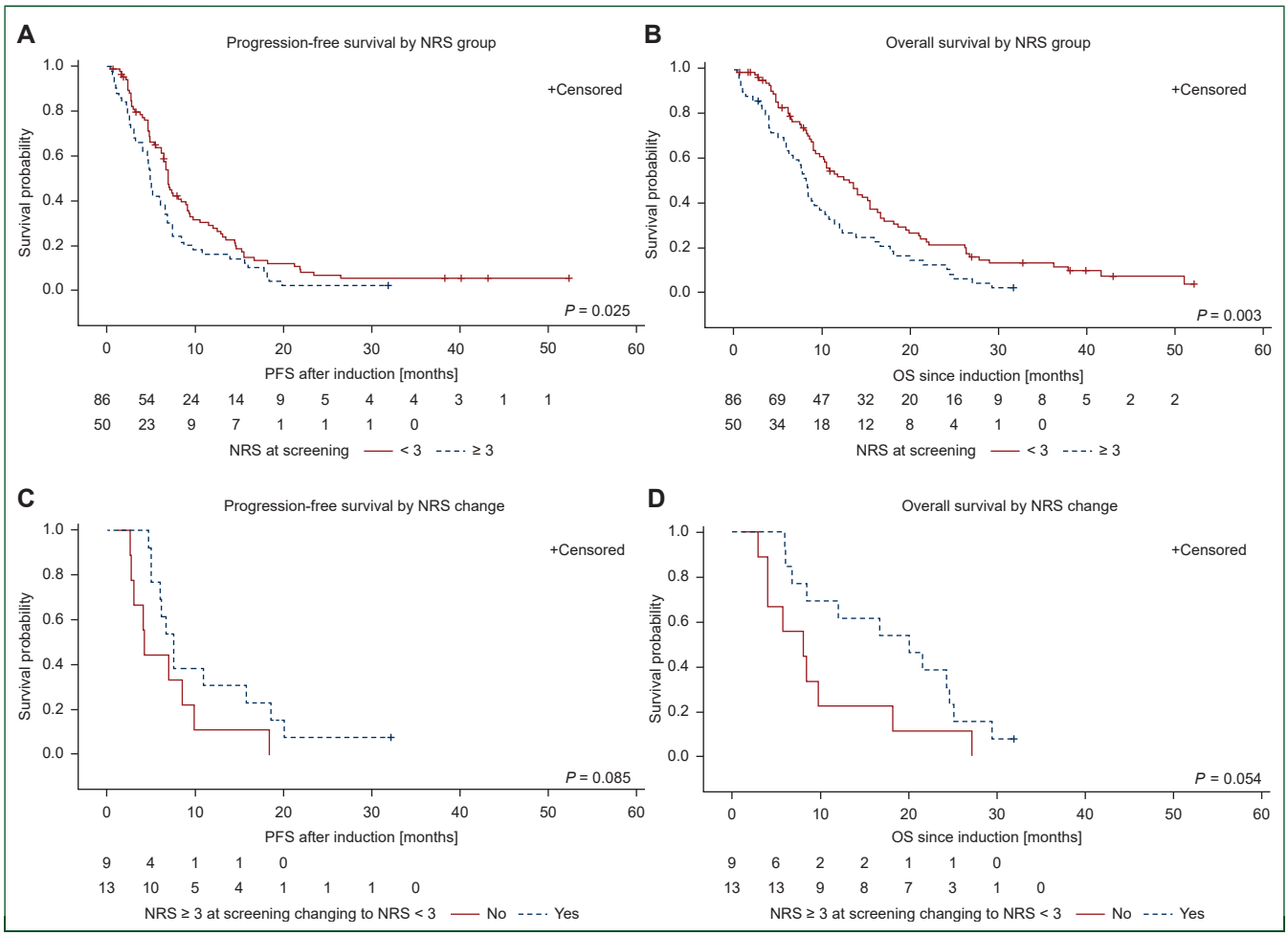

Figure 1. Progression-free survival (PFS) and overall survival (OS) by Nutritional Risk Screening (NRS) group and by NRS change. (A) Kaplan–Meier estimates for PFS by NRS group since start of induction. (B) Kaplan–Meier estimates for OS by NRS group since start of induction. (C) Kaplan–Meier estimates for PFS by NRS change since start of induction. (D) Kaplan–Meier estimates for OS by NRS change since start of induction.

years showed an increased mortality risk compared with those <70 years (HR 1.51, 80% CI 1.08-2.12, $P = 0.120$). Additionally, gender showed significance ($P = 0.048$), with female patients demonstrating a lower risk of mortality than males (HR 0.58, 80% CI 0.40-0.82).

DISCUSSION

To the best of our knowledge, this is the first preplanned analysis of a randomized oncological trial evaluating the impact of nutritional risk on outcome in patients with metastatic EGA undergoing systemic treatment. This analysis of the phase II MATEO trial highlights the significant influence of baseline nutritional risk, assessed by the NRS 2002, on clinical outcomes in patients with HER2-negative metastatic EGA. Our findings underscore the critical role of nutritional status in determining survival, emphasizing the importance of early nutritional assessment and intervention in this patient population.

The groups were categorized into NRS <3 and ≥3, as the ESPEN guidelines recommend nutritional intervention for patients with NRS scores of ≥3.[15,16]

The NRS score ≥3 group tended to be older and had a lower mean body weight compared with the patients in the NRS <3 group, suggesting that older patients and patients with a lower body weight are at higher nutritional risk. Our results demonstrate that patients with a baseline NRS score ≥3 had significantly shorter PFS and OS compared with those with an NRS score <3. These findings are consistent with previous studies indicating that malnutrition adversely affects survival in cancer patients, likely due to reduced treatment tolerance, increased susceptibility to infections, and impaired recovery from therapy.[8-14] However, most prior studies have focused on the impact of NRS in non-metastatic EGA, particularly on post-operative outcomes. To our knowledge, only one cohort study by Li et al. has evaluated the prognostic value of NRS in metastatic gastric cancer. In this study, patients were stratified into groups with NRS ≤3 and >3. Consistent with our findings, patients with an NRS >3 had a significantly shorter PFS and OS compared with those with an NRS ≤3.[19]

Notably, our analysis revealed that patients whose NRS score improved from ≥3 to <3 during the induction chemotherapy exhibited significantly better PFS and OS compared with those whose scores did not improve. One

could speculate that improvement in the NRS score represents a surrogate marker for treatment response, but it may also demonstrate that timely nutritional interventions may reduce the negative impact of malnutrition on survival or treatment tolerance, highlighting the importance of early and effective nutritional support.

Nutritional interventions were significantly more frequent in the NRS $\geq$3 group, with nearly half of these patients requiring high-calorie oral or parenteral nutrition. However, despite the clear international guidelines recommending nutritional screening and support in patients with advanced EGA[15,22], our analysis revealed that only 45.8% of this group of patients received such support. This discrepancy suggests that nutritional risk is often underestimated in daily clinical practice and that there may be substantial differences in how nutritional support is managed between institutions. Further data on the timing and intensity of the nutritional interventions were not assessed in this study. Consequently, the effects of the interventions themselves could not be reliably analyzed but only prognostic associations could be identified.

In general, no significant differences in treatment-related toxicity were observed between the NRS groups.

QoL assessments revealed that patients in the NRS $<$3 group surprisingly experienced a significantly shorter median time to deterioration in global health status compared with the NRS $\geq$3 group. However, the median global health score at screening was already significantly lower for the NRS $\geq$3 group, indicating poorer baseline QoL. This suggests that patients in the NRS $<$3 group started with a higher QoL, offering less potential for improvement, whereas those in the NRS $\geq$3 group may have already experienced substantial impairments. This difference in baseline QoL, along with potential ceiling as well as floor effects, may influence the observed time to deterioration and limit interpretation. Despite this, the shorter time to deterioration observed in the NRS $<$3 group highlights the importance of early QoL monitoring and supportive interventions, even among patients classified as having lower nutritional risk.

Multivariate analysis identified the NRS score at screening as an independent prognostic factor for OS, with patients in the NRS $\geq$3 group exhibiting a 1.61-fold higher risk of death compared with those in the NRS $<$3 group. This fact underscores that nutritional risk, as detected by NRS, is a critical determinant of survival in metastatic EGA, independent of other clinical and treatment-related factors. Additional significant prognostic factors included age and gender, with patients aged $<$70 years and females demonstrating more favorable survival outcomes.

This study has several limitations. The premature closure of the MATEO trial due to slow recruitment and changes in treatment approaches, such as the use of checkpoint inhibitors, may limit the generalizability of our findings. The NRS score was initially developed and validated for inpatients and not for patients in the outpatient setting. Furthermore, the NRS score incorporates factors that may be independent of nutrition such as age and comorbidities, which could act as potential confounders and may independently influence survival outcomes, irrespective of the nutritional status. We also acknowledge that a significantly higher proportion of patients in the NRS $<$3 group received triplet therapy compared with those in the NRS $\geq$3 group which likely impacted the observed survival outcomes. Additionally, the heterogeneity in the center-specific approach to provide nutritional support resulting in different types of nutritional interventions applied might have impacted the results we observed. Thus, the study design of the MATEO trial does not allow an estimation of the benefit of a nutritional intervention. During the study treatment, both improvements and deteriorations of the NRS score have been observed irrespective of the nutritional intervention applied, most likely reflecting the course of the disease.

In conclusion, this analysis of the MATEO trial demonstrates that the NRS is a powerful and independent predictor of survival in patients with metastatic EGA, highlighting the need for early and consistent nutritional interventions in high-risk patients. Despite recommendations of international guidelines, the limited implementation of nutritional support in patients in the NRS $\geq$3 group suggests variability in clinical practice across treatment centers. Future randomized studies focusing on standardizing nutritional interventions and evaluating their impact on survival and toxicity in this vulnerable patient population are warranted. Additionally, the influence of baseline NRS scores on the tolerability of targeted therapies or checkpoint inhibitors warrants further investigation. Integrating nutritional risk assessment and management into routine oncological care could offer a meaningful opportunity to improve outcomes in patients with metastatic EGA.

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DISCLOSURE

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DATA SHARING

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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