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Association Between Nutritional Status and Survival in Patients Requiring Treatment for Spinal Metastases

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BACKGROUND AND OBJECTIVES: The Patient-Generated Subjective Global Assessment (PG-SGA) is a standardized tool for assessing malnutrition in patients with cancer. The primary aim of this study was to assess the impact of preoperative nutritional status as measured by PG-SGA on survival in patients requiring surgical intervention and/or radiotherapy for spinal metastases.

METHODS: Patients with spinal metastases who underwent surgery and/or radiation therapy for symptomatic spinal metastases were enrolled in the AO Spine Metastatic Tumor Research and Outcomes Network, a prospective international multicenter research registry, between September 2017 and August 2022. Using the PG-SGA, nutritional status was classified into 3 categories: A, well nourished; B, moderately malnourished; and C, severely malnourished.

RESULTS: A total of 589 patients met the inclusion criteria; 362 were classified as well nourished (61%), 159 were moderately malnourished (27%), and 68 were severely malnourished (12%). The median survival was 491 days, 328 days, and 117 days for well-nourished, moderately malnourished, and severely malnourished patients, respectively. In the multivariate analyses, severe malnourishment (HR 2.5 95% CI 1.4–4.3, $P < .01$) and an ECOG performance status of 3 or 4 (HR 2.7 95% CI 1.2–6.0) remained associated with significantly worse survival.

CONCLUSION: Malnutrition as measured by the PG-SGA demonstrated to be significantly and independently associated with postoperative survival. The PG-SGA is a simple and useful tool to identify spinal metastases patients at risk of early postoperative mortality, and inclusion in the preoperative evaluation of these patients should be considered.

KEY WORDS: Nutritional status, Spinal metastases, Radiation therapy, Surgery, Survival

Approximately 10% to 20% of all patients with cancer will develop symptomatic spinal metastases.^{1,2} Radiation therapy alone or surgery with adjuvant radiotherapy have

become the mainstay for treatment of symptomatic spinal metastases as many studies have demonstrated significant improvements in health-related quality of life.^{3–6} Despite these benefits,

ABBREVIATIONS: ECOG, Eastern Cooperative Oncology Group; MTRON, Metastatic Tumor Research and Outcomes Network; PG-SGA, Patient-Generated Subjective Global Assessment.

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surgery is associated with a substantial incidence of adverse events, reflecting the considerable vulnerability of this patient population.⁷

Given the palliative intent of treatment, treatment risks must be judiciously weighed against potential benefits. Prognostic factors for survival and adverse events—such as primary tumor histology, age, performance status, neurological status, and metastatic burden—are well established; however, most are non-modifiable.⁷⁻¹⁰ It is therefore important to identify prognostic factors that are modifiable as interventions directed at these factors can potentially lower the risk of adverse events and may even improve survival. Nutritional status might be one of those factors.

Historically, anthropometric and laboratory measurements were used to objectively quantify nutritional status. However, many of these measures are influenced by other non-nutritional conditions such as infection, disease state, and volume depletion.¹¹ In addition, the anthropometric assessment methods are often time consuming and require well-trained staff. To overcome these barriers, the Patient-Generated Subjective Global Assessment (PG-SGA) was developed.¹² The PG-SGA is an easy-to-use measurement that was specifically developed for and validated in the cancer population and has also been correlated to objective measures of nutritional assessment and clinical outcomes such as adverse events and mortality.¹³⁻²⁰

Current literature on nutritional status and clinical outcomes in patients with spinal metastases is limited, with most studies focusing on isolated laboratory markers or assessing malnutrition as a component of the broader frailty syndrome.²¹⁻²³ The primary objective of this study was to investigate whether nutritional status as measured by the PG-SGA is predictive of survival for patients requiring surgical intervention and/or radiotherapy alone for spinal metastases.

METHODS

Design

This study is part of the AO Knowledge Forum Tumor's Metastatic Tumor Research and Outcomes Network (MTRON), an international multicenter prospective observational registry including patients with spinal metastases (Clinical trials identifier: NCT02830451). Patients were eligible if they are 18 years or older and are diagnosed with a metastatic spinal tumor that requires treatment with either surgery and/or radiotherapy. Treatment decisions were determined at the discretion of

the treating physician. The research protocol was approved by the research ethics board at each of the participating centers. All patients provided written informed consent.

For this predefined research question, patients were eligible for inclusion in the analyses if they completed a PG-SGA questionnaire at baseline. Patients were included in the study if they were enrolled between September 2017 and August 2022.

Outcome Measures

Baseline demographics, primary tumor histology, presence of visceral and/or brain metastasis, presence of neurological deficit (American Spinal Injury Association [ASIA]), performance status (Eastern Cooperative Oncology Group [ECOG] Performance Status), treatment (radiation alone or surgery ± radiation), adverse events (including medical adverse events, wound healing problems, and wound infections), length of stay, and nutritional status data were prospectively collected for each patient. Nutritional status was determined based on the PG-SGA^{12,14} (**Supplement 1**, <http://links.lww.com/NEU/F104>).

The PG-SGA consists of 2 components: one reported by the patient and the second by the healthcare professional. The patient component consists of 4 boxes which evaluate weight history, food intake, nutritional impact symptoms, activities, and function. The physician component evaluates catabolic and metabolic demand. The patient component of the PG-SGA, also known as the PG-SGA short form (PG-SGA SF), determines the PG-SGA category. PG-SGA category A represents a well-nourished patient, category B a patient with suspected or moderate malnutrition, and category C a severely malnourished patient.^{12,14} The total numerical score is based approximately 90% on the patient component. A score from 0 to 3 represents a well-nourished patient or a patient with a low risk of malnutrition requiring no intervention or education only, a score between 4 and 8 represents suspected malnutrition requiring an intervention by a dietitian, and a score of 9 or greater represents a high risk of or a severely malnourished patient with a critical need for a nutritional intervention (Table 1).

The primary outcome of this study was the association between nutritional status, as measured by the PG-SGA category score, and survival in patients who underwent radiotherapy alone or surgery with or without adjuvant radiotherapy for spinal metastases. The secondary outcomes included the association between nutritional status, and length of hospital stay and adverse events. The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed. All patient data were collected and stored in a deidentified format in a secure web-based database (REDCap v6.5.2, Vanderbilt University).

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TABLE 1. The PG-SGA Categories and Numerical Score Cutoff Values

	Well nourished	Moderated malnutrition	Severely malnourished
Weight	No weight loss OR recent weight gain	<5% loss in 1 month OR <10% loss in 6 mo OR progressive weight loss	>5% weight loss in 1 month OR >10% loss in 6 mo OR progressive weight loss
Food intake	No deficit OR recent improvement in intake	Decrease in intake	Severe deficit in intake
Nutrition impact symptoms	No symptoms	Presence of nutrition impact symptoms	Presence of nutrition impact symptoms
Activities and function	No deficit OR recent significant improvement	Moderate functional deficit OR recent deterioration	Severe functional deficit OR recent significant deterioration
Physician scored physical exam	No deficit OR chronic deficit but with recent improvement	Mild to moderate loss of muscle mass &/OR loss of subcutaneous fat	Obvious signs of malnutrition (severe loss of muscle, fat)
PG-SGA score	Recommendation		
0-1	No nutritional intervention required		
2-3	Patient and family education by dietitian		
4-8	Intervention by dietitian recommended combined with pharmacological intervention as needed depending on nutritional impact symptoms		
>9	Critical need for improved symptom management and nutritional interventions		

PG-SGA, Patient-Generated Subjective Global Assessment.
Data adapted from Ottery FD.¹²

Statistical Analysis

Descriptive statistics were used to display demographic and patient-reported outcome data at baseline. Differences in baseline parameters were analyzed by using a *t*-test or Wilcoxon rank sum test for continuous variables, whereas the χ^2 test or Fisher exact test were used for categorical variables. The associations between the PG-SGA score, survival, and length of hospital stay was analyzed using Kaplan-Meier estimates with 95% CIs. A multivariate Cox regression model was used to model the impact of nutritional status and other patient and treatment factors on the hazards of survival. The survival models were controlled for age at baseline, Charlson Comorbidity Index, ASIA impairment scale, ECOG performance status, Spinal Instability Neoplastic Score, Bilsby score, surgical indication, chemotherapy before treatment, duration of surgery, presence of visceral metastases, and primary tumor site. A logistic regression model was used to analyze the impact of nutritional status on the occurrence of adverse events. Significance was defined as $P < .05$. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc).

RESULTS

Demographics

A total of 589 patients were identified from the MTRON registry that met the inclusion criteria for the analyses. Of these patients, 469 (80%) underwent surgery $\pm$ adjuvant radiotherapy and 120 (20%) were treated with radiotherapy alone. Baseline

demographics are listed in Table 2. The most common primary tumor type was breast (17%, $N = 101$), followed by lung (17%, $N = 98$), renal cell (14%, $N = 84$), and prostate (13%, $N = 76$).

Treatment Details

Of the surgically treated patients, 443 (95%) underwent a posterior-only surgical approach, 13 (3%) an anterior approach, and 8 (2%) a combined approach. The mean operating time was 3.8 hours with a median number of 5 (IQR 3-6) instrumented levels. In the surgical treatment group, 170 patients underwent adjuvant radiation therapy within 3 months postoperatively.

Nutritional Status

Of those who underwent surgery $\pm$ adjuvant radiotherapy, 302 (64%) were classified as well-nourished (PG-SGA A), 125 (27%) as moderately malnourished or had suspected malnutrition (PG-SGA B), and 42 (9%) as severely malnourished (PG-SGA C). For patients who were treated with radiotherapy only, 60 (50%) were well nourished, 34 (28%) were moderately malnourished or had suspected malnutrition, and 26 (22%) were severely malnourished. Based on the numerical PG-SGA SF score for all patients, 122 patients did not require any nutritional intervention (score 0-1); 127 patients required nutritional education (score 2-3), 181 patients required a nutritional intervention by a dietician (score 4-8), and 159 patients had a critical need for improved nutritional

TABLE 2. Baseline Demographics

	Surgery ± radiotherapy (N = 469)	Radiotherapy alone (N = 120)
Gender		
Female	186 (40%)	58 (48%)
Male	283 (60%)	62 (52%)
Age at baseline		
Mean	61.1 (SD 11.9)	58.8 (SD 12.0)
Site of primary tumor		
Breast	71 (15%)	30 (25%)
Lung	75 (16%)	23 (19%)
Prostate	56 (12%)	20 (17%)
Kidney	76 (16%)	8 (7%)
Other	191 (41%)	39 (32%)
Visceral/brain metastases		
Yes	201 (43%)	58 (48%)
ASIA impairment scale		
A/B/C	28 (6%)	12 (10%)
D/E	427 (94%)	105 (90%)
ECOG performance scale		
0	46 (10%)	8 (7%)
1-2	309 (67%)	79 (66%)
3-4	109 (23%)	33 (27%)
PG-SGA category		
A	302 (64%)	60 (50%)
B	125 (27%)	34 (28%)
C	42 (9%)	26 (22%)
SINS		
Stable (0-6)	70 (15%)	12 (10%)
Indeterminate (7-12)	278 (59%)	92 (77%)
Unstable (8-13)	121 (26%)	16 (13%)
Bilsky		
Low (0-1C)	162 (37%)	47 (40%)
High (2-3)	279 (63%)	71 (60%)
Charlson Comorbidity Index		
Median	6.0 (IQR 6-7)	6.0 (IQR 6-7)

ASIA, American Spinal Injury Association; ECOG, Eastern Cooperative Oncology Group; PG-SGA, Patient-Generated Subjective Global Assessment; SINS, Spinal Instability Neoplastic Score.

symptom management and nutritional intervention (score 9 or above).

In the month before treatment, 75% of patients experienced a weight loss of less than 3% of their body weight, 8% lost 3% to 4.9% of their body weight, and 16% of patients lost 5% or more of their body weight. Most patients (53%) reported one or more nutritional impact symptoms in the 2 weeks before treatment that prevented them from eating enough (Table 3).

Survival and Clinical Outcomes of Patients Who Underwent Surgery

The Kaplan-Meier survival analysis of the patients who underwent surgery $\pm$ adjuvant radiotherapy demonstrated a significantly ($P \leq .001$) impaired survival rate for patients who were severely malnourished (Figure A). The median survival was 117 days (95% CI 52-246 days) for severely malnourished patients (PG-SGA C), 332 days (95% CI 233-441 days) in patients with suspected or moderate malnutrition (PG-SGA B), and 492 days (95% CI 416-735 days) in patients who were well nourished (PG-SGA A). The mortality rate for severely malnourished patients at 30, 60, and 180 days was 14%, 34%, and 62%, respectively. For well-nourished patients, the mortality rate at 30, 60, and 180 days was 2%, 5%, and 23%, respectively (Table 3). In the multivariate analyses, severe malnourishment (PG-SGA C, HR 2.5 95% CI 1.4-4.3), ECOG performance status of 3 or 4 at baseline (HR 2.7 95% CI 1.2-6.0), Charlson Comorbidity Index (HR 1.1 95% CI 1.04-1.3), presence of visceral and/or brain metastases (HR 1.6 95% CI 1.06-2.4), and surgical indication for high-grade metastatic epidural cord compression (HR 1.6 95% CI 1.13-2.44) were significantly associated with impaired survival.

The median length of hospital stay for well-nourished patients who underwent surgery was 7 days (95% CI 7-8) as compared with 9 days (95% CI 8-13) for both moderately malnourished and severely malnourished patients ($P = .20$). A total of 38 (8%) intraoperative adverse events and 96 (21%) postoperative adverse events occurred in 469 patients who underwent surgery $\pm$ adjuvant radiotherapy. No association between adverse events and nutritional status was observed.

Survival and Clinical Outcomes of Patients Who Underwent Radiotherapy Alone

Kaplan-Meier survival analysis of patients who were treated with radiotherapy alone demonstrated no significant difference ($P = .18$) in survival between the PG-SGA categories A, B, and C. However, when looking at the survival of well-nourished and moderately malnourished patients compared with severely malnourished patients, a trend toward a statistically significant difference was observed ($P = .063$) with an impaired survival rate for the severely malnourished patients (Figure B). The median survival in malnourished patients was 111 days, compared with 257 days in moderately malnourished or suspected malnourished patients, and 228 days in well-nourished patients. The mortality

rate for severely malnourished patients at 30, 60, and 180 days was 8%, 28%, and 60%, respectively. For well-nourished patients, the mortality rate at 30, 60, and 180 days was 7%, 23%, and 48%, respectively. Table 4 demonstrates the mortality rates per PG-SGA category.

DISCUSSION

Key Results

Malnutrition is very common in patients with cancer, with approximately 35% of the patients who underwent surgical intervention and 50% of the patients being treated with radiotherapy being moderately to severely malnourished in our study. Patients with cancer are at high risk of malnutrition not only because of the disease itself but also secondary to pain and side effects of various anticancer therapies. Malnutrition has previously been shown to be associated with impaired survival and decreased quality of life in patients^{24,25} with cancer, but data are limited for patients with metastatic spine disease. In this study, the mortality rate for patients who were severely malnourished was significantly higher as compared with patients who were well nourished. More importantly, in the multivariate analyses, malnourishment and decreased performance status demonstrated to be independently associated with impaired postoperative survival.

Interpretation and Generalizability

The postoperative mortality rate for patients who underwent surgery $\pm$ radiotherapy at 30 days was 14% for severely malnourished patients as compared with 3% for well-nourished patients. This difference in mortality rate could potentially be explained by the surgery-induced stress response, which is characterized by hormonal, metabolic, and immunological changes.²⁶⁻²⁸ The human body responds to surgical intervention with changes in the metabolism, with the level of metabolic changes being in proportion to the invasiveness of the intervention.²⁷ Factors that are relevant from a nutritional perspective are hyperglycemia and activation of whole-body protein catabolism that occur in response to surgical stressors.^{26,27} To be able to appropriately respond to this, patients require adequate physiological reserve. Patients with decreased reserve such as malnourished patients, frail and/or sarcopenic have decreased capacity to respond to surgical stress with an increased risk of mortality as demonstrated in our study by the significantly decreased survival rates at 30 days in malnourished and moderately malnourished patients as compared with well-nourished patients.

The theory of the surgical-induced stress response and the required physiological reserves to withstand treatment is further supported by the findings in the cohort of patients treated with radiotherapy alone. As radiotherapy is a less invasive treatment, patients will not experience the same metabolic changes after treatment and therefore require a lower physiological reserve to withstand treatment. This is reflected by a similar 30-day survival

TABLE 3. The Patient-Generated Subjective Global Assessment Scores at Baseline

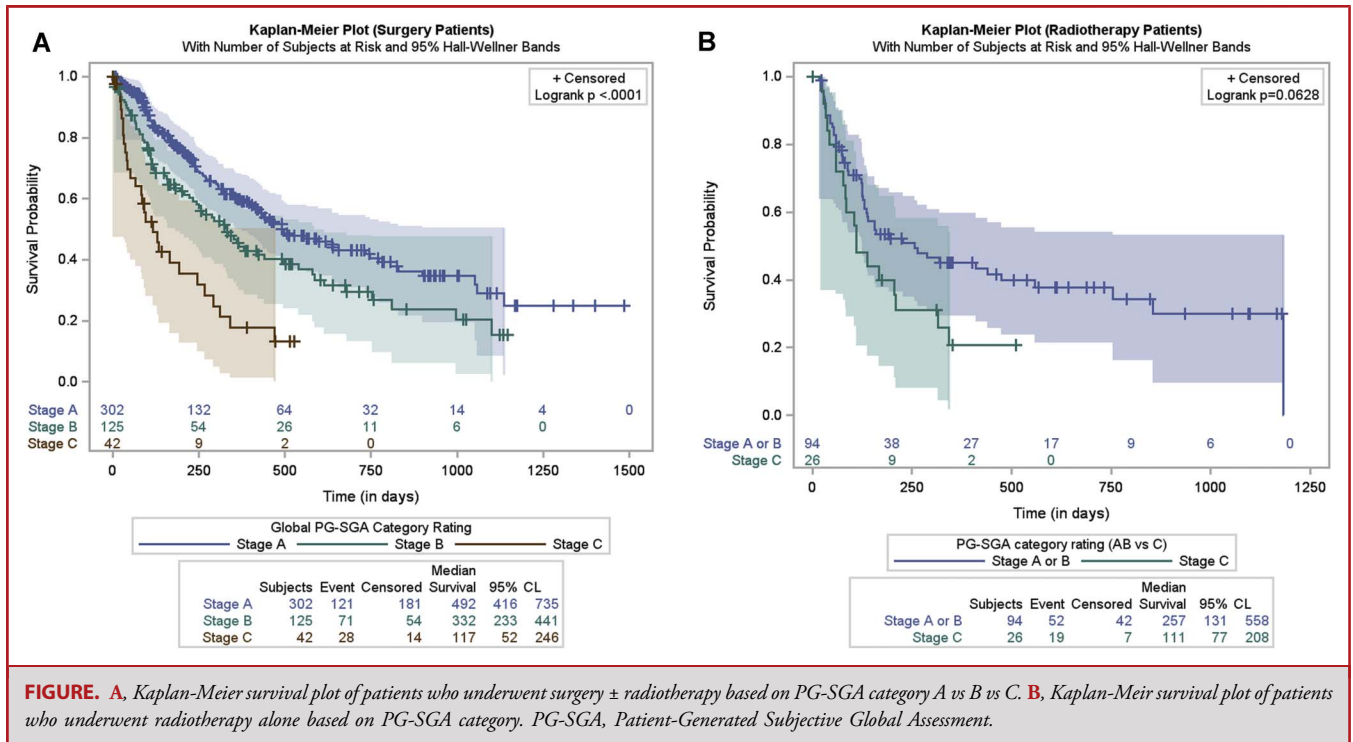
	Surgery ± radiotherapy (N = 469)	Radiotherapy alone (N = 120)
Box 1: Weight loss in 1 month		
10% or greater	34 (7%)	11 (9%)
5%-9.9%	39 (8%)	19 (16%)
3%-4.9%	34 (7%)	12 (10%)
<3%	362 (77%)	78 (65%)
Box 2: Food intake		
Unchanged/more than usual	276 (59%)	66 (55%)
Less than normal amount	169 (36%)	48 (44%)
Little solid food	16 (3%)	34 (3%)
Only liquids/only nutritional supplements	3 (1%)	1 (1%)
Vert little of anything	5 (1%)	1 (1%)
Box 3: Symptoms		
No problems eating	224 (48%)	51 (43%)
1-3 food intake symptoms	98 (21%)	38 (32%)
>4 food intake symptoms	147 (31%)	31 (25%)
Box 4: Activities and function		
Normal with no limitations	33 (7%)	18 (15%)
Not my normal self, but able to be up	169 (36%)	36 (30%)
Not feeling up to most things, but in bed or chair less than half the day	91 (19%)	22 (18%)
Able to do little activity and spend most of the day in bed or chair	146 (31%)	44 (37%)
PG-SGA numerical score		
0-3 (no intervention required)	207 (44%)	42 (34%)
4-8 (requires intervention)	138 (29%)	43 (37%)
>8 (critical need for nutrition intervention)	124 (27%)	35 (29%)
PG-SGA rating		
A (Well nourished)	302 (64%)	60 (50%)
B (Moderately malnourished)	125 (27%)	34 (28%)
C (Severely malnourished)	42 (9%)	26 (22%)

PG-SGA, Patient-Generated Subjective Global Assessment.

rate, yet a trend toward statistically significant impaired survival at 60 days and 180 days for severely malnourished patients as compared with well-nourished and moderately malnourished patients. The sample size of the radiation therapy cohort was significantly smaller than the surgical cohort causing a lack of power to demonstrate a definitive statistically significant difference in survival; however, the demonstrated difference in median

survival and the difference in 60-day and 180-day survival is a clinically meaningful difference.

Frailty and sarcopenia are terms that are often used interchangeably; however, they are distinctly different conditions. Frailty is generally understood as a progressive age-related decline in physiological systems that results in decreased reserves which increases the risk of adverse events.²⁹ Sarcopenia is the loss of



muscle mass and function and is a major component of frailty.³⁰ Malnutrition plays a key role in both frailty and sarcopenia. In an effort to identify modifiable prognostic factors for outcomes in patients with spinal metastases, different studies have looked at the prognostic value of sarcopenia and frailty. In the study of Bourassa-Moreau et al,³¹ sarcopenia was associated with impaired survival and the occurrence of adverse events. Frailty as defined by the Metastatic Spinal Tumor Frailty Index, a composite measure

of frailty, has also been studied and has been shown to be predictive of adverse events and survival.^{21,31} The difficulty with both frailty and sarcopenia as a prognostic factor is that the assessment requires investigations, such as laboratory markers, advanced imaging measurements, and specific physical examination maneuvers, which are costly and time consuming.²⁹ On the contrary, malnutrition assessment using the PG-SGA is a quick, easy-to-use, and noninvasive measurement.¹² It enables health professionals other than nutritionists or medical oncologists to accurately assess a patient's nutritional status. In this study, we demonstrated that malnutrition as defined by the PG-SGA was independently associated with impaired survival postoperatively as compared with patients who were well nourished. This information is of great value to both clinicians and patients when deciding up on treatment.

With nutritional status being a modifiable factor and prognostic for both the occurrence of adverse events as well as survival in several studies,¹³⁻²⁰ the question arises: Can we effectively modify nutritional status? And what is the effect of a nutritional intervention on survival, adverse events, and other clinical outcomes? In an attempt to answer these questions, Ehresmann et al performed a retrospective review of patients who underwent surgical intervention for spinal metastases to investigate whether a preoperative nutritional consult was associated with decreased complication rates and hospital length of stay.³² They stratified patients using the Nutritional Risk Index and separated them into 2 groups: moderate-to-severe malnutrition and minimal or no malnutrition. They also recorded the utilization of a preoperative

TABLE 4. Mortality Rate Per PG-SGA Category

PG-SGA category rating	Time, days		
	30	60	180
Surgery +/- radiotherapy, %			
A (well nourished)	2%	5%	23%
B (moderately malnourished)	8%	13%	36%
C (severely malnourished)	14%	34%	62%
Radiotherapy alone, %			
A (well nourished)	7%	23%	48%
B (moderately malnourished)	7%	16%	45%
C (severely malnourished)	8%	28%	60%

PG-SGA, Patient-Generated Subjective Global Assessment.

nutritional consult. They found that patients who received a nutritional consult had a lower 30-day adverse event rate and a shorter length of hospital stay.³² The results of this study support the hypothesis of the benefit of a nutritional consultation preoperatively and the modifiability of nutritional status. Moreover, a meta-analysis focused on the effect of prehabilitation using nutritional support for patients undergoing colorectal surgery mainly for cancer diagnoses demonstrated improved functional outcomes, shorter length of stay, and protective effect against the occurrence of postoperative complications in patients who received nutritional support.³³

Limitations

Although this study has several strengths including large number of patients, prospective collection of data, and international multicenter nature, it is not without its limitations. A limitation of this study is the uncertainty whether the included patients received any nutritional interventions. Nevertheless, it is most likely that patients who did receive a nutritional intervention were moderately or severely malnourished. This could lead to a potential underestimation, rather than overestimation, of the effect of malnutrition on survival rather than overestimation. In contrast to other studies demonstrating a relationship between malnutrition and adverse events, our study did not demonstrate any significant association.^{15,16,18,20} MTRON collected adverse events data using a validated and reliable process, but under reporting of adverse events is still possible.

CONCLUSION

In summary, this study demonstrated that malnutrition as measured by the PG-SGA is independently and significantly associated with impaired survival after surgery for patients with symptomatic spinal disease. The prognostic information provided by the PG-SGA is of great value to both the clinician and the patient and can help inform clinical decision making. Future studies should focus on the ability to modify nutritional status and the effect on clinical outcomes.

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Supplemental Data 1. The Patient-Generated Subjective Global Assessment (PG-SGA).
