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ORIGINAL ARTICLE

# The association between weight stability and parenteral nutrition characteristics and survival in patients with colorectal cancer

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## Abstract

**Objective:** Knowledge about the impact of metabolic disturbances and parenteral nutrition (PN) characteristics on the survival of cancer patients receiving PN is limited. We aimed to assess the association between clinical and PN characteristics and survival in colorectal-cancer patients receiving PN support.

**Methods:** Our study included 572 consecutive colorectal-cancer patients who had received PN support between 2008 and 2013. Patient characteristics, body mass index, weight, medical/surgical history, indication for PN, PN data and survival were recorded. Associations between clinical and PN characteristics and survival were analysed with important confounding factors.

**Results:** The final cohort included 437 evaluable patients, with a mean age of 57 years. Eighty-one percent of the study population had advanced stage of colorectal cancer. Unstable weight (weight change $\geq$2.5%) prior to PN initiation [hazard ratio (HR) = 1.41, $P = 0.023$] was adversely associated with survival after adjusting for multiple factors including cancer stage. Bowel obstruction (HR = 1.75, $P = 0.017$) as a PN indication was associated with worse survival when compared with without bowel obstruction. Higher PN amino acid by ideal body weight ($g \bullet kg^{-1}$) (HR = 0.59, $P = 0.029$) was associated with longer survival, whereas a higher percentage of non-PN intravenous calories (HR = 1.04, $P = 0.011$) was associated with shorter survival independently of confounding factors.

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**Conclusions:** Body mass index and weight stability can be useful nutritional indices for survival prediction in cancer patients receiving PN. PN planning should take into account of non-PN calories to achieve optimal energy support and balance. Future research is needed to define optimal PN amino-acid requirement and energy balance.

**Key words:** BMI; weight loss; non-parenteral calorie; energy balance; parenteral nutrition

## Introduction

Malnutrition occurs frequently among cancer patients and may even lead to death rather than cancer itself [1]. Cachexia and unintentional weight loss are consistently found to be adverse prognostic factors in studies of cancer-patient outcomes [2, 3]. Parenteral nutrition (PN) has been an important strategy for severe nutritional disorders in cancer patients [1, 4, 5]. Factors that can impact the survival of cancer patients on PN support include cancer type and stage, chemotherapy, cachexia, performance status and infection [6, 7]. Medical comorbid conditions and PN-related nutritional parameters, though they may have prognostic value, have not been extensively reported for cancer patients receiving PN.

Though cancer metabolism affects energy requirements, the nutritional guidelines for the total energy, energy balance and amino-acid (AA) profiles of PN support for cancer patients do not differ from those for patients without a cancer diagnosis in clinical nutrition practice [1]. Non-PN calories (i.e. glucose in drug dilution) are often not counted in the total calorie determination. How these PN-related factors affect survival in patients with cancer is largely unknown. This highlights a critical gap in the clinical evidence in the area of nutritional support for cancer patients.

Our study aimed to assess patients' clinical and PN characteristics in relation to survival to provide useful evidence for clinical practice guidelines and research strategies in improving outcomes of cancer patients receiving PN support.

## Methods

### Study cohort and design

This retrospective study was approved by the University of Texas MD Anderson Cancer Center's Institutional Review Board in accordance with an assurance filed with and approved by the Department of Health and Human Services. Using the pharmacy database, we identified 572 consecutive patients with colorectal cancer who received PN support at MD Anderson Cancer Center between 1 August 2008 and 1 August 2013. The following exclusion criteria were applied to these patients: (i) age less than 18 years, (ii) non-gastrointestinal malignancy and (iii) incomplete medical records.

The patients' age, sex, race, cancer diagnosis, vital status and last contact date were obtained from the MD Anderson Tumor Registry. Data about height, weight, pharmacy information including chemotherapy were obtained from the institutional data warehouse. Trained research personnel reviewed the electronic records to collect information about indications for PN and presence of surgery within 2 weeks prior to PN initiation.

Cancer stage was categorized into advanced if stage IV, otherwise local. Body mass index (BMI) was calculated using the formula: weight•height$^{-2}$ (unit: kg•m$^{-2}$). Weight at the first PN was the mean value of all weight records within 1 week prior to PN initiation and baseline weight was that of weight records (excluding records 1 week before first PN) within 3 months of first PN. Weight-change percentage (%WC) was calculated as: (weight at the first PN infusion − baseline weight) × 100/baseline weight. Stable weight was defined as an absolute weight change of <2.5% of the baseline weight [8]. Recent chemotherapy was defined as receiving chemotherapy within 30 days before the first PN administration. Recent history of surgery was defined as surgery within 2 weeks prior to the first PN infusion (not including minor procedures such as central-line placement). The ICD-9 (International Classification of Diseases, Ninth Revision) codes of each patient were used to calculate the Charlson Comorbidity Index (CCI) [9].

The duration of PN was calculated as the sum of days of PN infusion. PN calories were calculated per PN provider information (dextrose: 3.4 kcal•g$^{-1}$; AA: 4 kcal•g$^{-1}$; and fat emulsion: 10 kcal•g$^{-1}$). The 'non-nutritional' energy delivery (i.e. glucose for drug dilution and maintenance fluid) was expressed as non-PN calories. PN parameters included PN daily calories per weight (kcal•kg$^{-1}$•day$^{-1}$), PN daily calories per ideal body weight (IBW) (kcal•kg$^{-1}$•day$^{-1}$), AA per weight (g•kg$^{-1}$•day$^{-1}$), AA per IBW (g•kg$^{-1}$•day$^{-1}$), calorie-to-AA ratio (kcal:g) and percentage of non-PN calories [non-PN calories × 100/(non-PN calories + PN calories)].

### Statistical analysis

The primary outcome was survival, defined as the number of days a patient survived between the date of PN initiation and the date of death. If a patient was not known to be dead, survival time was censored at their last confirmed contact with the health-care system. Descriptive statistics were reported for patients' demographics, clinical characteristics, cancer stage and PN parameters. The Kaplan–Meier method and the log-rank test were used to calculate and compare the survival distributions between specific groups. Univariate analysis of the association between individual factors and survival was performed using a Cox proportional hazard regression model. Factors with P-value <0.05 from the univariate analysis were further considered for multivariate analysis. In multivariate analysis, we applied variable selection using the Akaike information criterion. The hazard ratio (HR) was calculated with 95% confidential intervals (CIs). Results were considered significant when the P-value was below 0.05.

All statistical analyses were performed using R software (version 3.5.0, The R Foundation, http://www.r-project.org).

## Results

### Patient characteristics

A total of 572 consecutive patients with colorectal cancer who received PN support were identified. The final study cohort consisted of 437 (76.4%) evaluable patients, excluding patients younger than 18 years ($n = 2$), with colorectal malignancies other than adenocarcinoma ($n = 130$) and with incomplete medical record ($n = 3$). The mean age of patients in the study cohort at the

time of first PN infusion was 57 years (Table 1); 67.7% were white. Most of the patients were overweight or obese. Fifty-six percent had unstable weight (weight change >2.5%) before PN initiation with a median weight change of −0.17%. Among the 437 patients, 226 (51.7%) had surgery and 92 (21.1%) had chemotherapy before PN was started. Median PN duration, calories and AA were 10 days, 21 kcal•kg$^{-1}$•day$^{-1}$ and 1.24 g•kg$^{-1}$•day$^{-1}$, respectively.

### Clinical and nutritional characteristics and survival

Table 2 illustrates the univariate analysis of clinical and nutritional characteristics and survival. During the study period, 230 patients died. Cancer stage, BMI, weight stability, CCI, chemotherapy with 30 days prior to PN initiation, surgery within 2 weeks prior to PN initiation, PN indications, PN AA per IBW (g•kg$^{-1}$) and non-PN calorie (%) were all significantly associated with survival.

**Table 1.** Demographics and clinical and nutritional characteristics

| Variable | No. of patients (%) |
|---|---|
| Total | 437 |
| Age, mean [SD], years | 57 [13] |
| Sex | |
| Female | 184 (42.1) |
| Male | 253 (57.9) |
| Race | |
| Non-White | 141 (32.3) |
| White | 296 (67.7) |
| BMI, median [range], kg•m$^{-2}$ | 26 [13, 51] |
| CCI, median [range] | 7 [2, 16] |
| Cancer stage | |
| Local | 84 (19.2) |
| Advanced | 353 (80.8) |
| Weight stability[a] | |
| Stable | 167 (43.7) |
| Unstable | 215 (56.3) |
| Weight change, %, median [range] | −0.17 [−17.83, 76.68] |
| Surgery[b] | |
| No | 211 (48.3) |
| Yes | 226 (51.7) |
| Chemotherapy[c] | |
| No | 345 (78.9) |
| Yes | 92 (21.1) |
| PN indication | |
| Bowel obstruction | 156 (35.7) |
| Post-operative ileus | 98 (22.4) |
| Prolonged poor oral intake | 76 (17.4) |
| Unstable weight/severe malnutrition | 25 (5.7) |
| Others | 82 (18.8) |
| PN calorie, median [IQR], kcal•kg$^{-1}$•day$^{-1}$ | 21 [16, 24] |
| PN calorie per IBW, median [IQR], kcal•kg$^{-1}$•day$^{-1}$ | 24 [20, 26] |
| PN amino acid, median [IQR], g•kg$^{-1}$•day$^{-1}$ | 1.24 [1.08, 1.41] |
| PN amino acid per IBW, median [IQR], g•kg$^{-1}$•day$^{-1}$ | 1.43 [1.23, 1.67] |
| Treatment duration, median [IQR], days | 10 [5, 18] |

SD, standard deviation; BMI, body mass index; CCI, Charlson Comorbidity Index; PN, parenteral nutrition; IQR, interquartile range; IBW, ideal body weight.
[a]Stable, <2.5% weight change; unstable, ≥2.5% weight change. Fifty-five patients with missing weight data are excluded in this group.
[b]Surgery within 2 weeks before parenteral nutrition initiation.
[c]Receiving chemotherapy within 1 month prior to parenteral nutrition initiation.

We further applied model selection in multivariate analysis using the Akaike information criterion. Factors with a *P*-value <0.05 in univariate analysis were included for initial consideration. Cancer stage, weight stability, surgery, PN indication, PN AA per IBW (g•kg$^{-1}$) and non-PN calorie continued to be significant factors associated with survival (Table 3). Surgery prior to PN initiation had the best HR (0.48), with those undergoing surgery having favorable outcomes. Figure 1 illustrates Kaplan–Meier curves for PN AA per IBW (g•kg$^{-1}$), PN calorie-to-AA (kcal:g), PN calorie per IBW (kcal•kg$^{-1}$) and weight stability; among them, PN AA per IBW >1.2 g•kg$^{-1}$ and calorie-to-AA ratio <16:1 were significantly associated with longer survival.

### Weight stability and clinical characteristics

Chi-square analysis revealed significant association between weight stability and clinical characteristics of surgery before PN initiation as well as chemotherapy before PN initiation (Table 4). Among 167 patients with weight stability, 66.5% had surgery ($P < 0.001$) and 14.4% had chemotherapy ($P < 0.001$). No significant relationship was found between weight stability and cancer stage ($P = 0.428$) or PN indication ($P = 0.746$).

## Discussion

Our study illustrates a substantial need for PN intervention as we present the review of 437 patients with colorectal cancer alone who received PN support over a span of 5 years in a single large cancer institution. Weight stability (energy preservation) prior to the start of PN was associated with favorable survival, regardless of cancer stage, complexity of medical comorbidities and indication for PN. Higher BMI (energy reserve) was associated with longer survival in the univariate analysis. PN characteristics including AA quantity and energy balance were both significantly predictive of overall survival, with higher AA support and lower calorie-to-AA ratio both beneficial predictors for longer survival.

Our findings of the impact of energy reserve as well as preservation on survival were consistent with those of previous studies [8, 10–12], with the addition that weight gain may also be a factor adversely related to survival. In our study, the survival advantage of a higher BMI (i.e. larger energy reserves) was not significant in the multivariate analysis, but weight stability was significantly predictive of survival independently of multiple confounding factors. It is physiologically plausible that a larger energy reserve renders a higher tolerance of metabolic instability, whereas the threshold for metabolic bankruptcy is lower with a low energy reserve. However, this advantage is not unlimited. BMI does not accurately represent body composition or an individual's specific type of energy reserve. Sarcopenia, with or without obesity, is associated with a higher death rate in cancer patients than no or less severe sarcopenia [13]. In our study, weight instability including both weight gain and loss was associated with worse survival. However, unlike the weight gain reported in other studies [14], it may not reflect a true gain in the energy reserve among our study subjects. Aggressive hydration or third-spacing of fluid before PN initiation, not an actual increase in the energy reserve, may be the likely cause of weight gain in most of our patients. The limited advantage of higher BMI suggests that combining markers for energy reserve and metabolic stability is likely to be superior in survival prediction than using either alone. Our study also pointed out the value of documenting the common clinical markers of BMI (body energy reserve) and weight stability (energy preservation

**Table 2.** Univariate analysis of clinical characteristics and survival

| Variable | No. of patients | No. of deaths | Survival time (median [95% CI], months) | Univariate analysis | |
|---|---|---|---|---|---|
| | | | | HR [95% CI] | P-value |
| Age | | | | | |
| <60 years | 256 | 141 | 22 [16–34] | | |
| ≥60 years | 181 | 89 | 44 [27–67] | 0.82 [0.63–1.07] | 0.144 |
| Sex | | | | | |
| Female | 184 | 98 | 29 [17–56] | Reference | |
| Male | 253 | 132 | 28 [20–49] | 0.95 [0.73–1.23] | 0.702 |
| Race | | | | | |
| Non-White | 141 | 75 | 22 [12–61] | Reference | |
| White | 296 | 155 | 29 [20–49] | 0.93 [0.7–1.22] | 0.591 |
| CCI | | | | | |
| ≤6 | 180 | 89 | 28 [15 to NA] | | |
| >6 | 257 | 141 | 27 [19–45] | 1.09 [0.83–1.42] | 0.537 |
| Stage | | | | | |
| Local | 84 | 29 | NA [63 to NA] | Reference | |
| Advanced | 353 | 201 | 20 [15–29] | 2.18 [1.47–3.22] | <0.001 |
| Surgery[a] | | | | | |
| No | 211 | 138 | 10 [6–16] | Reference | |
| Yes | 226 | 92 | 63 [49 to NA] | 0.41 [0.32–0.54] | <0.001 |
| Chemotherapy[b] | | | | | |
| No | 345 | 169 | 44 [24–63] | Reference | |
| Yes | 92 | 61 | 11 [6–27] | 1.72 [1.29–2.31] | <0.001 |
| BMI, kg•m$^2$ | 437 | 230 | 28 [20–48] | 0.98 [0.96–1.00] | 0.045 |
| Weight stability[c] | | | | | |
| Stable | 167 | 73 | 56 [32 to NA] | Reference | |
| Unstable | 215 | 122 | 23 [16–44] | 1.50 [1.12–2.01] | 0.006 |
| Calories per IBW, kcal•kg$^{-1}$•day$^{-1}$ | 437 | 230 | 28 [20–48] | 0.99 [0.96–1.01] | 0.338 |
| AA per IBW, g•kg$^{-1}$•day$^{-1}$ | 437 | 230 | 28 [20–48] | 0.47 [0.31–0.71] | <0.001 |
| Non-PN calories (%) | 437 | 230 | 28 [20–48] | 1.03 [1.01–1.06] | 0.006 |
| Calorie-to-AA ratio, kcal:g | 437 | 230 | 28 [20–48] | 1.11 [1.06–1.16] | <0.001 |
| PN indication | | | | | |
| Non-obstruction | 156 | 98 | 49 [34–67] | Reference | |
| Obstruction | 281 | 132 | 10 [6–20] | 1.73 [1.33–2.25] | <0.001 |

AA, amino acid; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IBW, ideal body weight; PN, parenteral nutrition; NA, median survival cannot be defined (survival was greater than 50% at the last time point).

[a]Surgery within 2 weeks prior to PN initiation.

[b]Receiving chemotherapy within 1 month prior to parenteral nutrition initiation.

[c]Stable, <2.5% weight change; unstable, ≥2.5% weight change. Fifty-five patients with missing weight data are excluded in this group.

ability) in predicting survival in cancer patients. We agree that future prospective studies are needed to develop a comprehensive system combining clinical and biochemical indices to accurately predict survival and help justify long-term PN support in patients with incurable cancers [7, 15].

Medical comorbidities, such as diabetes and uncontrolled hyperglycemia, can adversely affect the outcomes of many cancers [16, 17]. Our analysis showed that CCI reflecting a high complexity of medical comorbidities was adversely associated with survival in the univariate analysis. Bowel obstruction as a PN indication was an independent predictor for poorer survival. In addition, our study also showed that surgery before PN initiation had an independently favorable survival association. Postsurgical prolonged poor enteral intake is conceivably a less severe PN indication than other more severe enteral compromises, such as bowel obstruction.

Significant aberrations in energy metabolism are common in cancer patients and the standard predictive equation may not accurately predict the resting energy expenditure (REE) of cancer patients, especially gastrointestinal cancer patients [18, 19]. Total energy expenditure (TEE) is often uniformly estimated at 25–30 kcal•kg$^{-1}$•day$^{-1}$ for all cancer patients, regardless of cancer type or body composition [1]. By this estimate, TEE will be overestimated in obese patients and underestimated in severely malnourished patients. The majority of our study cohort had a BMI over 25 and the values of PN calories by IBW were higher than that by actual weight. Calorie calculation in PN support may be even more inaccurate for patients with unstable metabolic conditions, such as those with significant weight change. These findings reflect the shortcomings of the current practice. PN prescriptions need to take into account individual energy factors, including cancer type and burden, energy reserve, body composition and level of systemic inflammation [20]. More accurate TEE measurement, such as REE by indirect calorimetry and physical activity by wearable devices, might be needed for patients with unstable metabolism [1].

Non-PN energy delivery is often unaccounted for in PN planning. A higher percentage of non-PN calories was negatively associated with survival. The non-PN calories in our study were exclusively from dextrose. This may indicate that non-PN dextrose resulted in an inappropriately high proportion of dextrose calories that could have been avoided by PN planning that considered non-PN calories. Our finding that a higher calories-to-AA ratio was significantly related to worse survival

(univariate analysis) supports this explanation. The optimal nitrogen supply for cancer patients has not been determined and the recommendations of experts range between a minimum protein supply of 1 g•kg$^{-1}$•day$^{-1}$ and a target supply of 1.2–2 g•kg$^{-1}$•day$^{-1}$ [21]. Our study supports a higher target protein supply in cancer patients, as suggested by some experts [22]. Further studies on the optimal AA mixture and percentage of calorie support by AAs (i.e. calories-to-AA ratio) in cancer patients are warranted.

**Table 3.** Multivariate analysis of clinical characteristics and survival*

| Variable | Multivariate analysis | |
|---|---|---|
| | HR [95% CI] | *P*-value |
| Stage | | |
| Local | Reference | |
| Advanced | 2.04 [1.35–3.09] | <0.001 |
| Surgery[a] | | |
| No | Reference | |
| Yes | 0.48 [0.35–0.66] | <0.001 |
| Weight stability[b] | | |
| Stable | Reference | |
| Unstable | 1.41 [1.05–1.9] | 0.023 |
| AA per IBW, g•kg$^{-1}$•day$^{-1}$ | 0.59 [0.37–0.95] | 0.029 |
| Non-PN calories (%) | 1.04 [1.01–1.07] | 0.011 |
| PN Indication | | |
| Non-obstruction | Reference | |
| Obstruction | 1.75 [1.07–2.01] | 0.017 |

AA, amino acid; IBW, ideal body weight; PN, parenteral nutrition; CI, confidence interval; HR, hazard ratio.
*The multivariate analysis included 382 patients with complete weight data.
[a]Surgery within 2 weeks prior to PN initiation.
[b]Stable, <2.5% weight change; unstable, ≥2.5% weight change. Fifty-five patients with missing weight data are excluded in this group.

Our study cohort was large and had a comprehensive data record, which allowed us to analyse the effects of nutritional factors (energy reserve, weight stability and PN calories and energy balance), along with many confounding factors. The adverse association of nutritional disturbances with survival was illustrated through the severity of a low baseline energy reserve and weight changes. Our findings of the impact of non-PN calorie percentage and calories-to-AA ratio on survival in colorectal-cancer patients receiving PN are novel and provide important evidence for nutritional guidelines and future study targets. Our study has several limitations. Data collection, due to its retrospective nature, was limited to availability and a consistent time frame. The acuity of weight change was different among the study subjects. Baseline weight was the mean value of 3-month weight records before PN. This may underestimate the severity of weight changes. Infection is a known risk for survival in cancer patients receiving PN. However, information about concurrent infection as well as the causative pathogen was not obtained due to logistic reasons in this retrospective review. In addition, data of oral intake were unavailable to our analysis, which, as a result, could not include all confounders. Limitation of data availability also restricted our analysis to include some

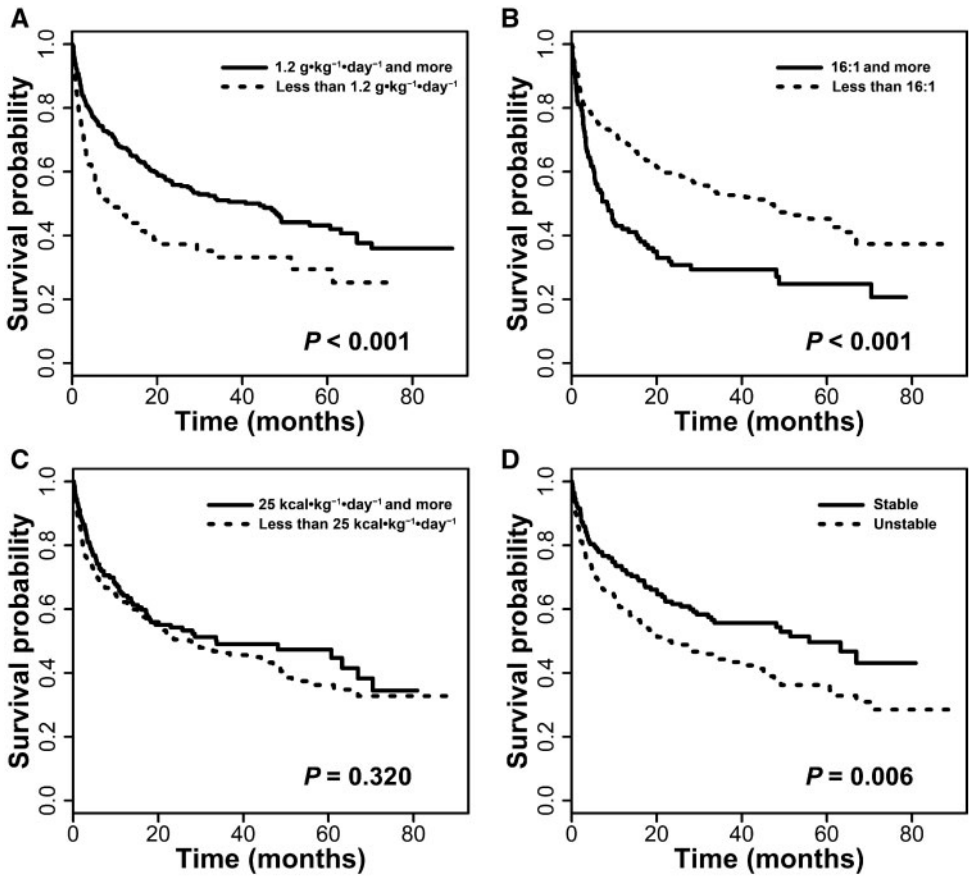


**Figure 1.** Kaplan–Meier curves by weight stability or PN characteristics. (**A**) Parenteral nutrition amino acid by IBW (g•kg$^{-1}$); (**B**) parenteral nutrition calorie-to-amino acid ratio (kcal: g); (**C**) parenteral nutrition calorie by IBW (kcal•kg$^{-1}$); and (**D**) weight stability.

**Table 4.** Association between weight stability and clinical characteristics*

| Variable | Weight stability[a] | | P-value |
|---|---|---|---|
| | Stable ($n = 167$) | Unstable (n = 215) | |
| Cancer stage | | | |
| Advanced | 136 (81.4%) | 168 (78.1%) | 0.428 |
| Local | 31 (18.6%) | 47 (21.9%) | |
| Surgery[b] | | | |
| No | 56 (33.5%) | 111 (51.6%) | <0.001 |
| Yes | 111 (66.5%) | 104 (48.4%) | |
| Chemotherapy[c] | | | |
| No | 143 (85.6%) | 152 (70.7%) | <0.001 |
| Yes | 24 (14.4%) | 63 (29.3%) | |
| PN indication | | | |
| With bowel obstruction | 51 (30.5%) | 69 (32.1%) | 0.746 |
| Without bowel obstruction | 116 (69.5%) | 146 (67.9%) | |

PN, parenteral nutrition.
*The analysis included 382 patients with complete weight data.
[a]Stable, <2.5% weight change; unstable, ≥2.5% weight change.
[b]Surgery within 2 weeks prior to PN initiation.
[c]Receiving chemotherapy within 1 month prior to parenteral nutrition initiation.

of the cancer-specific characteristics, such as tumor molecular features as well as disease-free survival.

## Conclusions

Metabolic disturbances, including a low baseline energy reserve and weight instability, were associated with worse survival in colorectal-cancer patients receiving PN. Maintaining adequate nutritional reservation and stability shall be a strategic goal of PN intervention. The severity of the nutritional disturbances may help in survival prediction, justifying PN use in advanced cancer patients. Diligent routine monitoring of weight is highly recommended. Non-PN calories may impact PN calories and energy balance, and should be considered in PN prescription. Future studies on optimal PN calorie support and energy balance in cancer patients are warranted.

## Authors' contribution

W.L., A.Q. and S.C.Y. conceived of the study and participated in its design and coordination. W.L., A.Q., E.L., J.Y. and T.C. performed data collection. W.L., A.Q., S.Z., J.Z.L., J.Y., E.B. and S.C.Y. performed the statistical analyses and interpretation. W.L. and A.Q. drafted the manuscript. K.V. and L.C. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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## Conflicts of interest

None declared.

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