Published in final edited form as:

Head Neck. 2011 November ; 33(11): 1561–1568. doi:10.1002/hed.21640.

PRETREATMENT NUTRITIONAL STATUS AND LOCOREGIONAL FAILURE IN PATIENTS WITH HEAD AND NECK CANCER UNDERGOING DEFINITIVE CONCURRENT CHEMORADIATION THERAPY

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Abstract

Background—This study was carried out to determine if markers of nutritional status predict for locoregional failure following intensity-modulated radiation therapy (IMRT) with concurrent chemoradiotherapy (CCRT) for squamous cell carcinoma of the head and neck (SCCHN).

Methods—We performed a retrospective chart review of 78 patients with SCCHN who received definitive CCRT. We compared patient factors, tumor characteristics, and nutritional status indicators between patients with and without locoregional failure.

Results—Fifteen of 78 patients (19%) experienced locoregional failure. Median follow-up for live patients was 38 months. On univariate analysis, pretreatment percentage of ideal body weight (%IBW) ($p < .01$), pretreatment hemoglobin ($p = .04$), and treatment duration ($p < .01$) were

significant predictors of failure. On multivariate analysis, pretreatment %IBW ($p = .04$) and treatment time ($p < .01$) remained statistically significant.

Conclusions—Although treatment time is an accepted risk factor for failure, differences in outcome for patients with head and neck cancer undergoing definitive CCRT based on pre-treatment %IBW should be examined further.

Keywords

nutrition; ideal body weight; concurrent chemoradiation therapy; squamous cell carcinoma of the head and neck; percutaneous endoscopic gastrostomy tube

Approximately 36,000 new cases of head and neck cancer were expected to occur in the United States in 2009 with an estimated 7600 deaths.¹ Although the addition of chemotherapy to radiation therapy has improved outcomes, approximately 50% to 60% of these patients are expected to experience treatment failure within 2 years.²

We retrospectively reviewed outcomes of 78 patients with squamous cell carcinoma of the head and neck (SCCHN) at Roswell Park Cancer Institute, to evaluate outcomes following intensity-modulated radiation therapy (IMRT) with definitive concurrent chemoradiotherapy (CCRT).³ We found that total treatment time and baseline hemoglobin level were significant predictors for locoregional failure.

Interventions to target anemia have been unsuccessful in cancer patient populations.^{4–11} Based on the futility of anemia interventions, Prosnitz et al¹² suggest that hemoglobin level should serve as a “biologic staging parameter” rather than as a target parameter. This concept of hemoglobin as simply a surrogate marker of patients’ overall biology caused us to consider targeting interventions to more fundamental biological markers such as nutritional status. Inui¹³ noted that efforts to maintain or improve nutritional status, especially if nutritional state is correlated to anemia, may be helpful in minimizing treatment interruptions.

Noting this possible link between anemia, treatment time, and nutritional status, we hypothesized that nutritional markers may also predict outcomes following concurrent chemoradiation therapy for advanced SCCHN. This analysis was performed to determine if differences in nutritional status were independent predictors of locoregional failure in our previously described cohort of 78 patients.

PATIENTS AND METHODS

This retrospective review of head and neck cancer patients at Roswell Park Cancer Institute was approved by the institutional review board (IRB). All patients who were definitively treated with IMRT and CCRT between August 2004 and September 2007 were included in this study. The total patient population consisted of 78 patients. All patients were offered a percutaneous endoscopic gastrostomy (PEG) tube as a routine supportive measure near the initiation of therapy.

Treatment

This cohort was previously described in great detail.³ Of note, during our current review, it was determined that 1 patient refused his last radiation treatment and therefore received only 68 Gray (Gy). In our initial analysis, he was coded as having completed treatment within 56 days. However, given that the prescribed 70 Gy was not completed within 56 days, he was reclassified as having completed therapy in >57 days for this analysis. All other patients were treated with IMRT to 70 Gy in 35 daily fractions to the high dose target volume and 56 Gy to the elective target volume. All patients received concurrent chemotherapy. The most commonly prescribed regimen was cisplatin 100 mg/m² on days 1, 22, and 43 of radiotherapy. Following completion of chemoradiation therapy, all patients underwent a complete head and neck examination, including flexible laryngoscopy every 2 months for year 1, every 3 to 4 months for year 2, every 6 months for years 3 to 4, and then annually thereafter. A positron emission tomography (PET) or CT scan was used to evaluate initial response to therapy.

Outcomes Collected

From the medical chart, the following patient information was collected: age at diagnosis, sex, tumor site, tumor classification, lymph node stage, insertion/removal date of PEG tube, duration of radiotherapy, height, and weight. Weight measurements were collected for the time period directly before the start of treatment (within 4 weeks) and after the end of treatment (within 4 weeks). Ideal body weight (IBW) was calculated using the Hamwi formula (IBW = 106 lbs for 5 ft tall and 6 lbs/inch for each inch >5 ft for men and 100 lbs for 5 ft tall and 5 lbs/inch for each inch >5 ft for women).¹⁴ Laboratory values extracted from charts included values for hemoglobin and albumin at pretreatment (directly before therapy was initiated), mid-treatment (median point of therapy), immediate posttreatment (directly after therapy ended), and posttreatment (2 months after therapy ended).

Treatment failure was defined as any disease in the primary disease site or neck that was not eradicated by therapy and included both persistent disease (viable disease noted within 6 months of completion of therapy) and recurrent disease (viable disease noted beyond 6 months of completion of therapy). Viable disease was either pathologically confirmed or confirmed by diagnostic enhancement on CT scan.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (version 16, SPSS, Chicago, IL). Because of the small sample size, Fisher's exact test was used to examine categorical variables, and the Mann–Whitney *U* test was used to examine continuous variables. Differences for these variables were compared between patients with locoregional failure and those without. For differences within groups concerning laboratory value changes through treatment period, Friedman's Test was used.

Duration of radiation therapy and PEG tube feeding were examined in terms of days from onset of therapy or insertion of PEG tube to the end of therapy or removal of feeding tube. PEG days were dichotomized based on the median number of days of PEG feeding for the patient population that did not have locoregional failure. Additionally, radiation therapy was

dichotomized based on the results of McCloskey et al.³ and Rades et al.¹⁵ Both studies showed that radiation treatment interruptions of >1 week were significant predictors of locoregional failure. Treatment duration was therefore categorized into clinically relevant categories of ≤56 days or >57 days.

IBW was examined for each participant as the percentage of calculated IBW at both pretreatment and posttreatment time periods. Pre- and post-percentages of IBW were categorized into normal and below normal based on clinical significance as follows: ≥90% IBW as normal and <90% IBW as below normal for both men and women.¹⁶ Actual weight loss and percentage of weight loss during treatment were also calculated, evaluated as clinically significant or severe based on published criteria and compared between groups.^{17,18} This criterion is noted in Table 1.

Serum values for albumin and hemoglobin were categorized into normal and below normal based on clinical norms as follows: albumin of ≥3.5 g/dL as normal and <3.5 g/dL as below normal for both men and women; hemoglobin of ≥12 g/dL for women and ≥14 g/dL for men as normal; and hemoglobin <12 g/dL for women and <14 g/dL for men as below normal.¹⁹ Our previous report used a baseline hemoglobin level cutoff point of 12 g/dL for both men and women.

Odds ratios (OR) were calculated and 95% confidence intervals (CIs) were estimated with unconditional logistic regression for the main effect of variables, such as body weight and laboratory values on treatment failure status. Potential confounders for a multivariate model were examined and were included if they met the inclusion level of $p = .10$. All tests were 2-sided, with a p value of <.05 considered statistically significant.

RESULTS

Patient characteristics are provided in Table 2. Median follow-up for those still alive ($n = 59$) was 38 months. The median age of this cohort was 62 years and 71% of the patients were male. A total of 53 patients (68%) had nodal (N) positive disease as follows: 14% were N1, 35% were N2, 41% were N3, and 10% were N4. Fifteen of 78 patients (19%) experienced locoregional failure. These included: 6 primary site failures, 5 regional neck failures, and 4 failures in both the primary site and regional lymph nodes. All but 1 failure occurred in the high dose target volume.

There were no differences between patients who had disease recurrence and those who did not based on age, sex, lymph node or tumor stage/classification, and disease site. There was a statistically significant difference between these groups based on duration of radiotherapy and on pretreatment hemoglobin values. For all of the other time periods collected, there were no differences between groups based on a comparison of median hemoglobin values (data not shown).

Within groups, based on sex, there were some statistically significant differences in repeated measures of hemoglobin. Because of the retrospective nature of the study, there were missing values for time points other than pretreatment hemoglobin. For women without locoregional failure, median hemoglobin levels went from 13.50 g/dL (pretreatment) to

12.20 g/dL (mid-treatment) to 11.20 g/dL (immediate posttreatment) to 12.20 g/dL (posttreatment) ($p < .01$). There were no statistically significant differences for hemoglobin levels of women with locoregional failure, although all hemoglobin levels for this group were below normal except for the median value at posttreatment, which was 13.00 g/dL.

For men, whose disease did not recur, hemoglobin levels went from 13.60 g/dL (pretreatment) to 12.00 g/dL (mid-treatment) to 11.80 g/dL (immediate post-treatment) to 12.40 g/dL (posttreatment), and this variability was statistically significant ($p < .01$). For men with locoregional failure, hemoglobin levels went from 12.60 g/dL (pretreatment) to 11.65 g/dL (mid-treatment) to 10.60 g/dL (immediate posttreatment) to 9.80 g/dL (posttreatment), and this decline was also statistically significant ($p = .03$).

All patients received a PEG tube prior to the start of therapy except for 3 patients who refused and for 1 patient who required total parenteral nutrition. Differences in nutritional status between patients with and without treatment failure are shown in Table 3. There were no differences based on number of days that the PEG tube was used between the 2 groups. There was a statistically significant difference in clinically relevant percentage of IBW between those patients with treatment failure and those without for pretreatment weight and a marginal statistical significance for posttreatment weight. The median percentage of IBW for the entire group at pretreatment was approximately 114% and was approximately 103% at posttreatment. Overall, the median percentage of weight loss for the cohort during radiation treatment was approximately 9%. The majority of patients met the criteria for clinically significant or severe weight loss during the treatment time period. There was no difference between the pretreatment albumin values of patients with and without treatment failure. Although the median value of serum albumin decreased during therapy, the decline was not statistically significant between groups or within groups (data not shown). The median values of serum albumin remained within the clinically accepted normal range for all treatment time periods and between groups.

Univariate analyses examining locoregional failure as the outcome revealed the following statistically significant predictors: pretreatment percentage of IBW ($p < .01$), pretreatment hemoglobin ($p = .04$) and duration of radiation therapy ($p < .01$). Univariate analysis results for posttreatment percentage of IBW were marginally significant ($p = .06$). There were 9 patients who moved from $>90\%$ IBW pretreatment to $<90\%$ IBW posttreatment and of these patients, only 1 patient had prolonged treatment duration (57 days) and locoregional failure. There were 16 patients whose body weight was $<90\%$ IBW at both pretreatment and posttreatment and of these patients 43% had prolonged treatment duration and locoregional failure. Therefore, we used pretreatment percentage IBW as our independent exposure for weight status in the multivariate model. Additional logistic regression models were developed for pre-treatment hemoglobin levels and for treatment duration. Confounders selected for these models included age, pretreatment hemoglobin, treatment duration, and pretreatment percentage of IBW.

Both the crude and adjusted estimates for these models are shown in Table 4. Compared with patients whose IBW percentage was $\geq 90\%$ at pretreatment, patients whose body weight was $<90\%$ of IBW at baseline had a 4-fold risk of locoregional failure in a model that

controlled for treatment duration and pre-treatment hemoglobin. Additionally, compared with patients whose treatment duration was not prolonged, patients who had prolonged treatment duration (≥ 57 days) had an 8-fold risk of locoregional failure. Whereas the risk estimate of locoregional failure was increased for patients whose pretreatment hemoglobin levels were low compared with those whose levels were in the clinically normal range, it did not reach statistical significance. If pretreatment IBW is removed as a covariate from the model the risk estimate increases, but remains insignificant.

All analyses were rerun (data not shown) with the patient who received only 68 Gy categorized as having completed therapy within 56 days; there were no changes in the statistical significance of any analyses.

DISCUSSION

In the current analysis with extended follow-up of this cohort, treatment time and pretreatment hemoglobin levels remained significant on univariate analysis. In addition to these factors, percentage of IBW at pretreatment was statistically significant on univariate analysis. On multivariate analysis only treatment time and percentage of IBW at pretreatment remained as significant predictors of locoregional failure. The current analysis did use different cutoff points for the dichotomized hemoglobin variable, and included weight status as a covariate in the predictive model as outlined by our a priori analytical strategy. To date, nutrition assessment or intervention is not part of a consistent universal standard of care for patients with cancer undergoing radiation treatment and the impact of either on patient outcomes such as treatment failure is unknown.^{20,21}

Here, we describe the nutritional status of this cohort as they moved through treatment. The median percentage of IBW for the entire cohort was clinically adequate (100% IBW ± 10%) at approximately 114% at pretreatment and 103% at posttreatment; however, the loss of weight for the majority of patients over the course of treatment represented a significant or severe weight loss based on accepted clinical criteria.^{17,18} There is evidence that patients lose an additional 10% of body weight during radiotherapy^{22–25} and our experience was similar.

Nutritional Status in Head and Neck Cancer: Is IBW a Rational Marker?

On multivariate analysis we found that patients whose body weight was <90% of IBW had a 4-fold risk of locoregional failure in a model that controlled for treatment duration and pre-treatment hemoglobin. Weight loss, a prominent sign of malnutrition, may negatively affect cancer prognosis as a result of decreased response to therapy and increased complications and toxicities to treatment.^{16,26,27} It is likely that many patients with head and neck cancer have underlying chronic malnutrition at presentation. Chronic malnutrition may be attributed to the malignancy and its complications, such as dysphagia and/or to tobacco and alcohol abuse exacerbated by poor nutritional habits.

IBW is a valid measure to use for the interpretation of one's nutritional status as being severely mal-nourished to being morbidly obese.²⁸ Percentage of IBW was shown to be a simple, inexpensive, and reliable indicator for the early detection of malnutrition.²⁹ Laaban

et al³⁰ suggested that a multiparameter approach that includes percentage of IBW, ranked as either < or 90%, should be systematically performed in patients with chronic obstructive pulmonary disease with acute respiratory failure to identify malnutrition in these patients. Gerard et al³¹ showed that percentage of IBW <90% was an independent prognostic factor of survival in patients with acquired immunodeficiency syndrome. Limitations of IBW include an inability to detect differences in body composition, relevant biochemical markers, and changes in energy expenditure or functions of body systems that are important estimates in the determination of malnutrition.^{32,33}

Baseline percentage of IBW categorized as clinically relevant for malnutrition (<90%) was the only weight status parameter that was a significant predictor of recurrence. Essentially the majority of patients lost a significant amount of weight throughout their course of therapy despite their weight status starting point. Categorizing the starting weight status in a way that suggests that someone is already underweight, possibly malnourished, or with early cachexia before further significant weight loss occurs may be more clinically relevant. Key information that was missing from this retrospective review was the amount of unplanned weight loss that occurred in these patients prior to the initiation of treatment. More than 50% of patients with advanced head and neck cancer have significant weight loss and potential for cachexia.^{23,34} It has been suggested that cachexia should be considered for a cancer patient with more than a 5% weight loss in the previous 6 months before diagnosis.^{13,35}

For other indicators of nutritional status, such as albumin levels, we did not see a difference between groups. We did not have values for all patients for all time periods; these omissions may have limited our power to detect differences. Additionally, serum albumin levels are sensitive to dilution effects and can be affected by the primary disease, by the treatment, and by related conditions rather than by malnutrition.³² In a report of nutrition intervention by Capuano et al,³⁶ however, all surviving patients who were noncompliant with nutrition intervention had decreased serum prealbumin levels, but patients who were compliant were able to maintain their levels. Compared with the compliant group, prealbumin levels were statistically significantly lower in the non-compliant group at 1 month after treatment ended.³⁶

What Is the Value of PEG Tube?

Our data show that, on multivariate analysis, percentage of IBW prior to treatment was a significant predictor of failure. The fact that IBW prior to treatment predicts for failure raises questions about the therapeutic benefit of standard PEG tube placement during treatment.

Moreover, although 95% of this cohort had a prophylactic PEG tube placed, the cohort lost a clinically significant or severe amount of weight during therapy. In a retrospective review of 140 patients with head and neck cancer receiving radiotherapy, Munshi et al³⁷ reported that 37% of the cohort lost at least 5 kg of body weight with prophylactic tube or with tube placement during treatment. Characteristics of the patients who lost >5 kg included a Karnofsky performance status score < 80 and a treatment regimen providing combination CCRT with a total dose of >60 Gy.³⁷ We did not include a comparison of performance status scores in our study because data were not consistently reported for all patients.

Although we are sure that our cohort lost a significant amount of weight despite the use of prophylactic feeding tubes, we cannot be sure of how much weight would have been lost if patients did not receive these feeding tubes.

It is also possible that individualized nutrition intervention before, during, and after radiotherapy may affect clinical outcomes differently. In our institution, the patients with head and neck cancer undergoing CCRT were not followed by a nutritionist after the PEG tube was placed. In a recent report, patients with head and neck cancer undergoing CCRT who were compliant with a nutritional intervention program, which included counseling throughout therapy, did not lose significant amounts of weight compared with noncompliant patients who suffered a weight loss of >20%.³⁶ These authors reported a positively significant correlation between weight loss percentage and outcomes including infection, early mortality, hospital readmission, and survival.³⁶ Other studies have shown a positive impact from individualized nutrition intervention on clinical outcomes of patients with head and neck cancer undergoing radiotherapy.^{38–40}

There is evidence that patients with poor baseline performance status, receiving aggressive hyperfractionated or combined-modality therapy techniques, and nasopharyngeal, hypopharyngeal, or base of tongue primary tumor site, may be at greater risk for adverse outcomes. Cady et al⁴¹ argued that perhaps these are the very patients who should be selected for a prophylactic feeding tube. Despite such data, the patient selection criteria for prophylactic feeding tubes remain undefined.⁴¹ Furthermore, differences in clinical practices, such as the inclusion of individualized nutrition intervention during radiotherapy, make it difficult to compare outcomes between studies.⁴¹

Caveats

It is possible that both hemoglobin levels and IBW status are simply markers of the physiologic imbalance related to cancer and/or therapy. Consequently, manipulation of either may not result in improved outcomes. Increasing weight loss despite tube feeding intervention may represent cachexia, which involves an increase in tissue catabolism, impaired anabolism along with the release of tumor-derived catabolic factors, neuroendocrine dysfunction, and the presence of inflammatory cytokines.^{42,43} Cachexia is not overturned by nutrition support alone and requires the use of anti-cachexia agents to reverse the proteolysis, lipolysis, anorexia, inappropriate increased resting energy expenditure, and the acute phase response.³⁵

Additionally, there are several limitations of this study related to the study design. The retrospective collection of exposures and other information can be problematic and our sample size may have limited the power to detect differences with only 19% of the original cohort of 78 patients having locoregional failure. Furthermore, some patients had missing laboratory data and were excluded from those specific analyses; however, we did have recorded height and weight for all time points, for all patients.

Future Directions

Several questions are suggested by our findings. First, is IBW a predictor of failure in other cohorts with head and neck cancer? Can the poor prognosis of low IBW be ameliorated by

nutritional intervention? What should be the criteria for prophylactic PEG tube placement? Finally, is the malnutrition that we see in patients with head and neck cancer undergoing CCRT an early sign of cachexia? If this is true, should we consider pharmacologic (with or without nutritional) treatment interventions for this group of patients to improve adverse clinical outcomes?

CONCLUSIONS

Our results show an association between pretreatment percentage of IBW and locoregional failure of head and neck cancer following CCRT. Weight status may have accounted for some of the variance seen in pretreatment hemoglobin as a predictor of failure on multivariate analysis in this examination. We suggest that the IBW status of patients with head and neck cancer prior to initiation of CCRT should be examined in other currently available databases. A prospective examination of nutritional status indicators and cachexia markers for these patients may reveal the potential impact of nutrition interventions on treatment outcomes.

Acknowledgments

Contract grant sponsor: National Cancer Institute; contract grant number: R25-CA-114101.

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Table 1

Clinical definitions of significant and severe weight loss.*

Time period	Significant weight loss, %	Severe weight loss, %
1 wk	1-2	>2
1mo	5	>5
3 mo	7.5	>7.5
6mo	10	>10
Unlimited time	10-20	>20

* See Blackburn et al¹⁷ and Fogt et al¹⁸

Table 2

Descriptive characteristics of cohort by failure status.

Characteristic	Subjects		p value
	Locoregional failure		
	No <i>n</i> = 63 (81%) No. (%)	Yes <i>n</i> = 15 (19%) No. (%)	
Median age in years at diagnosis (range), y	62 (37-78)	62 (47-81)	.92
Sex			.54
Male	44 (70)	12 (80)	
Female	19 (30)	3 (20)	
Lymph node stage treated			1.00
N0	20 (32)	5 (33)	
N+	43 (68)	10 (67)	
Primary tumor stage			.57
1 or 2	32 (51)	6 (40)	
3 or 4	31 (49)	9 (60)	
Disease site condensed (<i>n</i> = 74)			.36
Hypopharynx/oropharynx	39 (65)	7 (50)	
Larynx	21 (35)	7 (50)	
Radiation therapy duration, days			<.01
56	56 (89)	8 (53)	
57	7(11)	7 (47)	
PEG insertion			.48
No	2 (3)	1 (7)	
Yes	60 (97)	14 (93)	
Other	1 patient with total parenteral nutrition		
PEG days [†]			1.00
142	22 (49)	2 (50)	
142	23 (51)	2 (50)	
Pretreatment hemoglobin, g/dL			.045
12 (females), 14 (males)	36 (57)	4 (27)	
<12 (females), 14 (males)	27 (43)	11 (73)	

Abbreviations: PEG, percutaneous endoscopic gastrostomy tube; g/dL, grams per deciliter.

* Fisher's exact test (2-tailed) was used to examine differences for categorical variables; Mann-Whitney U test (2-tailed) was used to examine differences for continuous variables.

[†]Based on median number of PEG days of patients without recurrence.

Table 3

Nutritional status of cohort by failure status.

Characteristic	Subjects		<i>p</i> value
	Locoregional failure		
	No <i>n</i> = 63 (81%) Median or no. (%)	Yes <i>n</i> = 15 (19%) Median or no. (%)	
Percentage of IBW preradiation therapy	114%	99%	.09
Percentage of IBW postradiation therapy	103.4%	88%	.07
Weight loss (lbs) during radiation therapy	14.3	13.9	.97
Percentage of weight loss during radiation therapy	9.1%	10.3%	.57
Pretreatment percentage of IBW			.01
90%	54 (86)	8 (53)	
<90%	9 (14)	7 (47)	
Post-treatment percentage of IBW			.07
90%	46 (73)	7 (47)	
<90%	17 (27)	8 (53)	
Clinical stage of weight loss during radiation therapy			.72
Not clinically relevant	13 (21)	2 (13)	
Significant or severe weight loss	50 (79)	13 (87)	
Pretreatment albumin (<i>n</i> = 75), g/dL			.21
3.50	59 (95)	11 (85)	
<3.50	3 (5)	2 (15)	

Abbreviations: IBW, ideal body weight; lbs, pounds; g/dL, grams per deciliter.

* Fisher's exact test (2-tailed) was used to examine differences for categorical variables; Mann-Whitney U test (2-tailed) was used to examine differences for continuous variables.

Table 4

Risk of treatment failure by selected exposures.

Exposure	Locoregional failure: Yes/No	Crude OR (95% CI)	Adjusted OR (95% CI)
Pretreatment percentage IBW			
90%	8/54	1.00	1.00
<90%	7/9	5.25 (1.53-18.06) $p < .01$	4.35 (1.05-18.0) $p = .04^*$
RT duration, days			
56	8/56	1.00	1.00
57	7/7	7.00 (1.94-25.26) $p < .01$	8.25 (1.75-39.04) $p < .01^{\dagger}$
Pretreatment hemoglobin, g/dL			
12 (females), 14 (males)	4/36	1.00	1.00
<12 (females), 14 (males)	11/27	3.67 (1.05-12.78) $p = .04$	2.09 (0.52-8.36) $p = .30^{\ddagger}$

Abbreviations: IBW, ideal body weight; g/dL, grams per deciliter; OR, odds ratio; CI, confidence Interval; RT, radiation therapy.

* Odds ratio was adjusted by age, pretreatment hemoglobin, and treatment duration.

 † Odds ratio was adjusted by age, pretreatment hemoglobin, and pretreatment percentage of IBW. ‡ Odds ratio was adjusted by age, pretreatment percentage of IBW, and treatment duration.