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Severe malnutrition evaluated by patient-generated subjective global assessment results in poor outcome among adult patients with acute leukemia

A retrospective cohort study

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Abstract

To evaluate nutritional status in adult patients with acute leukemia (AL) using patient-generated subjective global assessment (PG-SGA) and to investigate the influence of nutritional status on prognosis.

We observationally investigated 68 adult patients with newly diagnosed AL who received PG-SGA at the First Hospital of Jilin University between May 2013 and July 2015. Clinical features, chemotherapy regimens, biochemical indexes, body composition, complete remission (CR) rate, minimal residual disease (MRD), survival time, and side-effects of chemotherapy were compared between patients with and without severe malnutrition.

Mean PG-SGA scores of the total patients were 6.1 ± 4.0, and 19 of 68 (27.9%) patients had severe malnutrition (PG-SGA score ≥ 9). Patients with acute myeloid leukemia (AML) had higher scores than those with acute lymphocytic leukemia (ALL; $P = .011$) and high-risk patients had higher scores regardless of whether they had AML or ALL (AML, $P = .012$; ALL, $P = .043$). Univariate analysis showed that severe malnutrition was correlated with age ($P = .041$), transferrin ($P = .042$), Karnofsky Performance Status score ($P = .006$), and C-reactive protein (CRP) ($P = .018$). Multivariate analysis demonstrated that severe malnutrition was associated with CRP (hazard ratio [HR] = 1.020, 95% confidence interval [CI]: 1.002–1.039, $P = .026$). No difference was found in CR rate ($P = .831$) between patients with and without malnutrition, but those who were severely malnourished had higher MRD ($P = .048$ in AML patients, $P = .036$ in ALL patients) and more gastrointestinal side-effects ($P = .014$). Severe malnutrition was also associated with inferior overall survival (HR = 0.243, 95% CI: 0.063–0.945, $P = .041$) but not with event-free survival (HR = 0.808, 95% CI: 0.338–1.934, $P = .663$).

Severe malnutrition defined by PG-SGA in adult patients with de novo AL may result in poor outcome.

Abbreviations: AL = acute leukemia, ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, BMI = body mass index, CR = complete remission, EFS = event-free survival, MRD = minimal residual disease, OS = overall survival, PG-SGA = patient-generated subjective global assessment.

Keywords: acute leukemia, adult patients, nutritional status, patient-generated subjective global assessment, severe malnutrition

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1. Introduction

A high prevalence of malnutrition has been found in patients with cancer, present in 40% to 80% of cases.[1] It has been suggested that malnutrition is one of the main causes of medical complications and even death.[2] Many studies have focused on patients with solid tumors, but leukemia has seldom been investigated. Owing to a higher survival rate and gradually appearing side-effects of malnutrition during growth stages, most studies have been among children rather than adults with leukemia. At present, there is no "gold standard" for the diagnosis or classification of malnutrition.[3,4] Various nutritional evaluation tools such as body mass index (BMI), weight loss, biochemical indexes, and body composition are applied in different studies, yielding inconsistent results.[5–10] This situation is a main factor limiting leukemia-related nutritional research.

Patient-generated subjective global assessment (PG-SGA) is a widely used nutritional screening tool designed especially for patients with cancer.[11,12] It is highly recommended by the American Society for Parenteral and Enteral Nutrition and Anti-Cancer Association of China. PG-SGA consists of 2 parts, one

Table 1

Average scores of PG-SGA among clinical features.

	Cases	Average scores ($\bar{x} \pm s$)	P
Age			
<60 years	60	5.8±3.8	.083
≥60 years	8	8.4±4.9	
Type of acute leukaemia			
ALL	17	4.0±3.2	.011
AML	51	6.8±4.0	
Sex			
Male	35	5.6±3.7	.300
Female	33	6.6±4.2	
Initial leukocyte count			
<50×10⁹/L	56	5.9±3.9	.478
≥50×10⁹/L	12	6.8±4.2	
Risk category			
AML			
Low risk	36	6.2±3.4	.012
High risk	15	8.8±5.1	
ALL			
Low risk	3	2.0±1.0	.043
High risk	14	4.4±3.4	
Onset to admission time			
≤7 days	11	4.5±2.7	.137
>7 days	57	6.4±4.1	

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, PG-SGA = patient-generated subjective global assessment.

completed by patients and the other completed by medical staff, and includes the indexes such as weight loss history, dietary intake, stress score, and physical examination to qualitatively and quantitatively evaluate nutritional status. A high score indicates a higher risk of malnutrition and critical need of nutrition support. PG-SGA has a high degree of inter-rater reproducibility and high sensitivity and specificity when compared with other validated nutrition assessment tools that have been proved in patients with solid tumor.[13–15] The indexes in PG-SGA are easily collected in patients with leukemia; however, the efficiency of PG-SGA and its relevance with prognosis are unknown.

Our hospital has evaluated nutritional status using PG-SGA in adult patients with newly diagnosed acute leukemia (AL) since 2013. In the current study, we reviewed data of these patients to investigate the feasibility of PG-SGA as a tool to evaluate nutritional status, and to explore the correlation between nutritional status and prognosis.

2. Materials and methods

2.1. Patients

In this retrospective study, adult patients with newly diagnosed AL in the First Hospital of Jilin University who met the inclusion criteria were enrolled between May 2013 and July 2015. Inclusion criteria were: patients more than 18 years old with a new morphological and immunological diagnosis of acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL), and with nutritional status evaluated using PG-SGA before drug administration. Exclusion criteria were: patients with a history of myelodysplastic syndrome or myeloproliferative disease, a history of other malignant tumors, those who did not receive treatment after diagnosis, patients with acute promyelocytic leukemia, and those who received allogeneic hematopoietic stem cell transplantation in follow-up treatment. All patients

were followed-up until December 31, 2015. All participating patients gave their written informed consent prior to enrollment in the study. This study was approved by the ethics committee of the First Hospital of Jilin University and conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Nutritional data collection

Biochemical indexes such as albumin, C-reactive protein (CRP), transferrin, and triglyceride were detected before therapy using blood tests. Body composition characteristics such as body fat ratio, muscle mass, water fraction, and basal metabolism were measured using a body composition analyzer (InbodyS10, Seoul, Korea), and anthropometric measures such as body weight and nondominant hand grip were measured by trained nurses in our department.

2.3. PG-SGA score classification

PG-SGA was carried out using a questionnaire for the assessment of nutritional status.[16] A doctor and a nurse are required to complete the questionnaire together, with strict quality control. In our study, any disagreement was resolved by a third party. According to PG-SGA nutritional triage recommendations, patients scoring 0 to 1 are considered well nourished; a score of 2 to 3 points indicates suspected malnutrition, 4 to 8 points indicates moderate malnutrition, and 9 points or more indicates severe malnutrition, which requires improved symptom management and/or nutrient intervention options.[14] Patients were divided into a severe malnutrition and a non-severe malnutrition group according to PG-SGA score.

2.4. Clinical data collection and analysis

We collected information of clinical features such as age, sex, risk category, and Karnofsky Performance Status (KPS); chemotherapeutic regimens; complete remission (CR) rate; minimal residual disease (MRD); side-effects of chemotherapy; overall survival (OS), and event-free survival (EFS). MRD was detected by flow cytometry (MACS Quant; Germany) on the 14th day after induction therapy in AML patients and on the 14th and 28th day in ALL patients. Risk category and remission status were based on the 2016 National Comprehensive Cancer Network guideline. ALL patients were divided into high-risk and low-risk groups. AML patients with no response after induction chemotherapy were classified into the high-risk group. To facilitate the data analysis, low- and moderate-risk AML patients were included in the low-risk group.

Treatments for AML patients have been previously described.[17] For ALL patients older than 35 years, chemotherapy followed the 2008 China Acute Lymphocytic Leukemia Group protocol;[18] treatment in the remaining patients followed the 2008 Chinese Children's Leukemia Group–ALL protocol.[19]

Univariate analysis was conducted for age, sex, type of leukemia, risk category, initial leukocyte count, and onset to admission time. Univariate and multivariate analysis was carried out using biochemical indexes, body composition factors, and anthropometric measures between the severe and non-severe malnutrition groups. Induction remission rate, MRD, and survival time were compared between the 2 groups. In both univariate and multivariate analysis, the missing data (Table S3, http://links.lww.com/MD/C83) were deleted because of the small sample size.

Table 2

General characteristics, chemotherapy regimens, biochemical indexes, body composition, and anthropological measurements between 2 PG-SGA groups.

PG-SGA group	Non-severe malnutrition, PG-SGA:0–8	Severe malnutrition, PG-SGA ≥9	P
	N=49	N=19	
Age, years	40.7±14.2	48.8±15.1	.041
KPS	90.8±8.1	84.2±9.6	.006
Sex			
Male	26	9	.673
Female	23	10	
Type of AL			
AML	34	17	.067
ALL	15	2	
Comorbidities			
Yes	13	7	.402
No	36	12	
Pre-existing infection			
Yes	20	12	.098
No	29	7	
Subtypes of AML			
M1	1	0	.450
M2	14	4	
M4	10	9	
M5	8	4	
M6	1	0	
Subtypes of ALL			
T-ALL	11	1	.496
B-ALL	4	1	
Regimens of AML			
IA	17	8	.539
DA	17	9	
D+CAG	4	4	
Regimens of ALL			
CALLG 2008	9	1	.787
CCLG-ALL 2008	7	1	
Pre-albumin, g/L	0.18±0.07	0.16±0.05	.281
Albumin, g/L	36.0±5.1	33.8±5.6	.127
C-reactive protein, mg/L	10	33.85	.018
Transferrin, g/L	2.0±1.0	1.6±0.3	.042
Triglyceride, mmol/L	1.1	1.11	.773
Total cholesterol, mmol/L	3.7±2.0	3.1±0.8	.292
Blood sugar, mmol/L	5.9±1.2	6.4±1.9	.186
HDL, mmol/L	0.9±0.4	0.9±0.2	.517
LDL, mmol/L	1.8±0.6	1.7±0.4	.500
Protein quality, kg	9.35	8.75	.288
Body fat ratio, %	21.5±9.0	20.8±8.0	.800
Nonfat mass, kg	48.9±10.0	48.0±11.3	.761
Muscle mass, kg	45.9±9.8	45.3±10.7	.834
Water fraction, %	38.8±1.0	39.2±0.9	.274
Basal metabolism, Kcal	1425.9±206.2	1406.4±243.2	.758
Weight, kg	62.7±13.1	61.8±12.3	.806
BMI, kg/m^2	22.7±4.2	22.3±3.1	.719
Nondominant hand grip, kg	26.6±9.9	22.9±9.8	.167

Data of CRP, triglyceride and protein quality are presented in the form of a median.

AL = acute leukemia, CALLG = China Acute Lymphocytic Leukemia Group, CCLG = Chinese Children's Leukemia Group, HDL = high-density lipoprotein, KPS =Karnofsky Performance Status, LDL = low-density lipoprotein, PG-SGA = patient-generated subjective global assessment.

2.5. Statistical analysis

Statistical analyses were carried out using SPSS version 21.0 (IBM Corp., Armonk, NY). The χ^2, nonparametric, and t-test were used, as appropriate, to make comparisons between groups. General linear regression was applied to find correlations between nutritional status (defined by PG-SGA) and clinical features. OS was measured from diagnosis to the date of death or until the last follow-up if the patient remained alive or dropped out of the study. EFS was measured from diagnosis to the date of induction failure, disease relapse, or death (whichever occurred first), or until the last follow-up if no events occurred. Survival time was analyzed using the Kaplan–Meier log-rank test. Multivariate analysis was carried out by Cox regression. Statistical significance was set at the $P < .05$ level.

3. Results

A total of 68 adult patients with newly diagnosed AL met the study criteria, comprising 35 men and 33 women. There were 51 patients with AML and 17 with ALL. Mean age was $43.0±14.8$ years (19–83 years). Median follow-up time was 8.25 months (1–30 months) to the end of follow-up; 44 of 68 (64.7%) patients remained alive, 16 (23.5%) died, and 7 (11.8%) dropped out. About 26 patients had events that terminated EFS.

3.1. Correlations between clinical features and PG-SGA score

Average PG-SGA scores were lower in ALL patients than those in AML patients, with statistical significance ($4.0±3.2$ vs. $6.8±4.0$, $P=.011$). In both AML and ALL patients, average PG-SGA scores were higher in high-risk patients than low-risk patients (AML, $8.8±5.1$ vs. $6.2±3.4$, $P=.012$; ALL, $4.4±3.4$ vs. $2.0±1.0$, $P=.043$). There were no evident differences in terms of age, sex, initial leukocyte count, and onset to admission time (Table 1).

3.2. Comparison of general characteristics, biochemical indexes, body composition, and anthropometric measures between patients with and without severe malnutrition

According to PG-SGA score, 44 (64.7%) patients were malnourished and 19 (27.9%) were severely malnourished. Compared with those who were not severely malnourished, patients with severe malnutrition had significantly higher average age and CRP levels, as well as lower transferrin and KPS scores. No differences were found for other clinical features, such as sex, comorbidities, and AL subtype (Table 2). In the severe malnutrition group, 10 patients had pneumonia, 4 had gastroenteritis, and 8 had upper respiratory tract infection. In the other group, 8 patients had pneumonia, 2 had gastroenteritis, and 6 had upper respiratory tract infection, with coinfection in some patients. There was no evident difference between the 2 groups. According to multivariate analysis, only CRP was associated with severe malnutrition (Table 3). These results indicated that high CRP level may serve as a predictor of severe malnutrition.

3.3. Comparison of induction remission rate, MRD, and side-effects between groups

No significant difference was found between the 2 nutritional groups for CR rate (12/18 in severe malnutrition patients vs. 34/49 in non-severe malnutrition patients, $\chi^2=0.045$, $P=.831$; 1 patient in the severe malnutrition group was not evaluated). However, in AML and ALL patients, distinctions were found in terms of MRD. On the 14th day after chemotherapy in AML patients and the 14th day of chemotherapy in ALL patients, MRD was higher in the severe malnutrition group than in their counterparts in the other group (Table 4).

There was a significantly higher incidence of gastrointestinal side-effects in patients with severe malnutrition ($\chi^2 = 6.058$, $P = .014$). There were no statistically significant differences for other chemotherapy-related side-effects (Table 5).

3.4. Effects of severe malnutrition on survival time

The mean OS of the 68 patients was 22.0 ± 1.7 months; the median OS was not achieved (Fig. S1A, http://links.lww.com/MD/C83). The mean EFS was 17.7 ± 1.8 months and the median EFS was 16.0 ± 2.6 months (Fig. S1B, http://links.lww.com/MD/C83). As shown in Fig. S2A and B, http://links.lww.com/MD/C83 patients with severe malnutrition had significantly worse OS (log-rank = 0.030), and EFS tended to be poor in these patients, with no statistical significance (log-rank = 0.240). According to Cox regression, nutritional status, induction remission status, and risk category were independent factors influencing OS (hazard ratio [HR]: 0.243, 95% confidence interval [CI]: 0.063–0.945, $P = .041$; Table S1, http://links.lww.com/MD/C83), and patients with severe malnutrition had inferior outcomes. No distinct differences were found in EFS between the 2 nutritional groups (HR: 0.808, 95% CI: 0.338–1.934, $P = .663$; Table S2, http://links.lww.com/MD/C83); only risk category was associated with EFS.

4. Discussion

Diagnosis of malnutrition is a serious problem in patients with tumor including leukemia. Previous studies have showed that the influence of BMI on survival time differs from each other,[5–9] and other indexes such as weight and albumin are also unstable.[10] PG-SGA is highly recommended by nutritionists and can be easily applied in leukemia patients. Thus, we aimed to evaluate the nutritional status of adult patients with AL using PG-SGA and to investigate the influence of nutritional status on prognosis.

In our study, a high prevalence of malnutrition was found in AL patients. A total 64.7% of patients were diagnosed with malnutrition, and there were 27.9% of patients with severe malnutrition who were in critical need of nutritional support, which is slightly more than the proportion of children and young adults,[20] whose nutritional regulation and compensation capacities are stronger.

The clinical features were compared using PG-SGA score. These results indicated that ALL patients had better nutritional status than AML patients. Myeloid hematopoietic cells are abnormally proliferated in AML, which could decrease the levels of neutrophils, erythrocytes, and platelets, thus leading to infection, anemia, and hemorrhage. At the same time, anorexia, gastrointestinal function disorders, and stomatitis—all related to poor appetite—result in less food intake and weight loss, which can be severe. These developments may be the reason why these patients tend to have poor nutritional status. A previous study came to the same conclusion.[21] In high-risk patients, average PG-SGA scores were significantly higher, which indicated that nutritional status was associated with risk category. Several studies among patients with solid cancers have reached the similar conclusion.[22,23] Leukemia cells in high-risk patients tended to be more progressive than those in patients with lower risk, which indicates that progressiveness influenced the function of major organs and might be related to malnutrition and lead to poor outcomes. There was no evidence of differences in other clinical characteristics; however, patients aged more than 60 years and patients with onset to admission time of more than 7 days tended to have higher scores.

Table 3

Multivariate analysis of all indexes between 2 PG-SGA groups.

	95% CI			
	Lower	Upper	HR	P
Age	0.962	1.054	1.007	.769
C-reactive protein	1.002	1.039	1.020	.026
Transferrin	0.275	2.327	0.801	.683
KPS	0.886	1.025	0.953	.192
Constants			14.232	.447

CI = confidence interval, HR = hazard Ratio, KPS = Karnofsky Performance Status, PG-SGA = patient-generated subjective global assessment.

It has been reported that PG-SGA scores are influenced by the types and stages of tumor, KPS score, comorbidities, and whether patients have received nutritional support.[23] Based on our data, age, KPS score, CRP level, and transferrin were associated with severe malnutrition in univariate analysis. However, in multivariate analysis, only CRP level was associated with severe malnutrition. CRP is one of the most sensitive and recurrent markers of inflammation. The association between CRP as an indicator of inflammation and nutritional status has been previously reported by others.[20,24–28] High-risk disease may not only increase metabolic demands on the host, leading to malnutrition, but it may also result in increased production and release of proinflammatory cytokines that in turn raise the production of CRP.[29] Thus, elevated CRP levels might be related to both infection and severity of disease. Based on our data, there was an evident difference in CRP and risk category, but not incidence of infection between the 2 groups. Moreover, in patients without pre-existing infection, there was no difference in terms of CRP levels between the 2 groups (data not shown). Therefore, severity of disease might be the main cause of elevated CRP; however, the exact mechanism requires further investigation. No difference was found in other nutritional indexes.

Effects of severe malnutrition evaluated by PG-SGA on efficacy and survival time were also analyzed. No difference was found in CR rate; nevertheless, there was a significantly higher incidence of gastrointestinal side-effects in patients with severe malnutrition, which may be correlated with rapid proliferation and a high need for nutrients in the gastrointestinal mucosa. These results are consistent with those of other studies.[14,30] Though no difference was found in the CR rate, MRD was higher in the severe malnutrition group, which indicates that although severe malnutrition had no significant influence on initial disease relief, there were still differences in deep remission. This might be related to metabolism of chemotherapy drugs.[31,32] The levels of

**Table 4**

MRD of AML and ALL patients in the 2 groups.

PG-SGA groups	Non-severe malnutrition, %	Severe malnutrition, %	P
AML	2	8.71	.048
ALL1	1.28	1	.036
ALL2	0.20	0.06	.672

MRD in AML was detected on the 14th day after chemotherapy.
MRD in ALL1 was detected on the 14th day of chemotherapy, although the median was higher in non-severe malnutrition patients than severe malnutrition patients, the latter one had higher rank (19.23 vs. 27.17).
MRD in ALL2 was detected on the 28th day of chemotherapy.
ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MRD = minimal residual disease, PG-SGA = patient-generated subjective global assessment.
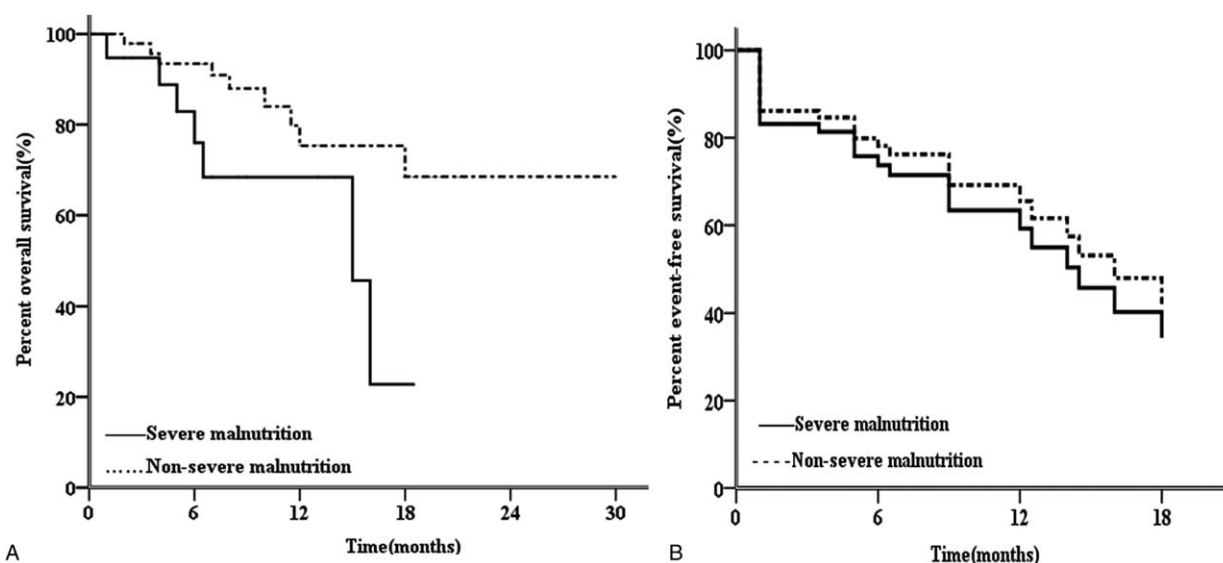
Figure 1. Comparison of survival time between the 2 groups after multivariate analysis. (A) Comparison of overall survival between severe malnutrition and non-severe malnutrition group after multivariate analysis. (B) Comparison of event-free survival between severe malnutrition and non-severe malnutrition group after multivariate analysis.

MRD detected on the 28th day of chemotherapy in ALL patients were indistinct between the 2 groups; however, only 2 ALL patients had severe malnutrition. The results clearly require further study with a larger number of patients. To our knowledge, MRD has not been previously analyzed to find a correlation with nutritional status. OS and EFS were compared between the 2 groups; univariate analysis indicated that patients with severe malnutrition had shorter survival time. In addition to nutritional status, the type of AL, age, initial leukocyte count, and risk category were all considered in assessing the influence of nutritional status on survival time. The results indicated that de novo patients who did not have severe malnutrition had superior prognosis than those who were severely malnourished. Because AL subtypes, therapeutic regimen, and CR rate were not different between the 2 groups (Tables 3 and 4), the difference in OS might be correlated with a higher level of MRD and worse risk category in severely malnourished patients; however, no marked difference was found in EFS (Fig. 1A and B). Our results are in accordance with those of previous studies;[6,7,11] but disagree with the findings of others.[5,8] BMI and weight were widely used in studies focusing on the influence of nutritional status on survival time; however, the same conclusions were not reached in these studies, suggesting that these indexes may be unreliable for assessing severe malnutrition.

As far as we are aware, this is the first study to evaluate the correlation between nutritional status and prognosis in adult patients with AL. Owing to the limited sample size, prospective studies with a larger number of patients are clearly required.

In conclusion, malnutrition is commonly seen in leukemia patients and PG-SGA can be used as an efficient tool to evaluate nutritional status. CRP was an independent risk factor of severe malnutrition. Although there was no difference in CR rate between the 2 groups, our study suggests that severely malnourished patients have more side-effects of chemotherapy, higher levels of MRD, and shorter survival time. Thus, for patients with severe malnutrition, nutrient support might be needed before or during chemotherapy. Whether nutrient support can improve survival time and decrease side-effects requires further clinical investigation.

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Table 5

Comparison of chemotherapy side-effects between the 2 groups.

PG-SGA groups	Non-severe malnutrition	Severe malnutrition	P
Documented infection	43	17	1.000
Notable hemorrhage	6	3	.702
Gastrointestinal side-effects	15	12	.014
PLT transfusion, μ	4.3±3.1	5.1±4.0	.591
RBC transfusion, μ	8.8±5.1	10.6±4.6	.355

PG-SGA = patient-generated subjective global assessment, PLT = platelet, RBC = red blood cell.

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