

The Prognostic value of the controlling nutritional status score in patients with myelodysplastic syndrome

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Abstract

Purpose

To evaluate the prognostic value of the controlling nutritional status score (CONUT) in patients with myelodysplastic syndrome (MDS).

Methods

The clinical data of 81 newly diagnosed MDS patients treated with decitabine in the hematology ward of our hospital from October 2009 to September 2020 were analyzed retrospectively. According to the ROC curve of overall survival (OS), the best cut-off value of CONUT was obtained. MDS patients were divided into high CONUT score group and low CONUT score group according to the best cut-off value, and their clinical characteristics and survival were analyzed.

Results

Among the 81 patients with MDS, there were 32 cases in the high CONUT score group and 49 cases in low CONUT score group. Compared with the low CONUT group, the high CONUT group had lower levels of hemoglobin, lymphocyte count, albumin and total cholesterol ($P = 0.037, < 0.001, 0.009, < 0.001$). The median OS of low and high CONUT groups were 11.0 and 17.2 months ($P = 0.017$). According to the results of univariate and multivariate survival analysis of OS, thrombocytopenia, high CONUT score, medium and high risk IPSS-R score were independent prognostic factors.

Conclusion

High CONUT score is associated with low hemoglobin in patients with MDS. High CONUT score indicates poor OS and it is an independent prognostic factor in patients with MDS.

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of bone marrow disorders associated with ineffective hematopoiesis with an increased risk of transforming into acute myeloid leukemia [AML], manifesting as morphologic dysplasia in hematopoietic elements and peripheral cytopenia. The median age of MDS patients is about 70 years old, and the incidence rate increases with age. The incidence rate of people over 60 years old reached 35/100000[1].

Patients with MDS are highly heterogeneous, so it is particularly important to classify the prognosis of the disease. The traditional risk stratification of MDS is based on disease-related factors, such as cytogenetics, percentage of bone marrow primordial cells, hemoglobin, platelet and neutrophil count.

Some prognostic risk scores, such as the World Health Organization classification-based Prognostic Scoring System (WPSS) and the revised International Prognostic Scoring System (IPSS-R), have been used to stratify related risks. Clinically, appropriate treatment is often selected according to this.

However, considering the prognosis only according to the IPSS-R score will ignore the basic function of the patient, so there is an urgent need for a scoring standard to evaluate the patient's own conditions and prognosis, so as to formulate a more comprehensive treatment plan.

In patients with MDS, the prognostic value of nutritional status has not been paid attention to. The controlling nutritional status score (CONUT), counted from total lymphocyte counts, serum albumin, and total cholesterol levels, is an easy-to-use tool to assess nutritional status, and has been confirmed to have an inversely correlated prognostic value for several solid tumors, heart diseases and hematological malignancies [2-5].

This study retrospectively analyzed the initial CONUT score and clinical characteristics of 81 patients with MDS, and discussed the prognostic value of CONUT score in the survival of patients with MDS. Further analyze the prognostic factors based on OS with other prognostic factors, in order to provide basis for a new prognostic model of MDS

Research Object And Research Method

Patients

This study enrolled 81 patients with MDS in the Hematology Department of our hospital from October 2009 to September 2020. The patients were classified according to the MDS classification standard revised by WHO in 2016. Inclusion criteria: ☐MDS patients newly diagnosed by hemogram, myelogram and Cytogenetics; ☐ Age \geq 18 years old; ☐ The first-line treatment was decitabine alone or decitabine combined with chemotherapy, and at least two courses of treatment were completed.

The baseline clinical data of patients were recorded, including age, gender, WHO classification, hemoglobin (Hb), platelet count (PLT), absolute neutrophil count (ANC), total lymphocyte count (TLC), albumin (Alb), total cholesterol (T-Cho), IPSS-R score.

CONUT score

The CONUT score is calculated by serum albumin, total cholesterol and total lymphocyte count (Table 1). The total score is 0-12, 0-1 is normal, 2-4 is mild, 5-8 is moderate and 9-12 is severe.

According to the ROC curve of overall survival (OS), the best cut-off value of CONUT score was 5.5 (area under the curve [AUC] :0.604, 95% confidence interval [95% CI]: 0.456-0.753, sensitivity 44.4%, specificity 77.8%). According to the cut-off value, the patients were divided into 32 cases in high CONUT group (CONUT > 5.5) and 49 cases in low CONUT group (CONUT < 5.5).

Table 1, The controlling nutritional status score

Alb(g/dL)	3.5-4.5	3.0-3.4	2.5-2.9	<2.5
Alb score	0	2	4	6
TLC(μm^3)	≥ 1600	1200-1599	800-1199	<800
TLC score	0	1	2	3
T-cho(mg/dL)	>180	140-180	100-139	<100
T-cho score	0	1	2	3
CONUT score	0-1	2-4	5-8	9-12
CONUT grade	normal	mild	moderate	severe

Efficacy evaluation and follow-up

The curative effect was evaluated according to the curative effect standard of MDS international working group. Overall survival (OS) was defined as the time from diagnosis to death or to the end of follow-up. The deadline for follow-up is December 1, 2020. All patients are followed up from the date of diagnosis, and the dead patients are followed up to the date of death. Follow up data were obtained from inpatient medical records or telephone contact with patients and their families.

Statistical analysis

Overall survival was analyzed using the Kaplan–Meier method and compared between groups through univariate analysis using the log-rank test. Cox proportional hazards regression model was used for multivariate analyses of the OS outcomes. Differences in treatment regimens were evaluated using the chi-square test. The cut-off point of *p*-value for statistical significance was set to 0.05. Statistical analyses were performed using IBM Corp. 2018. IBM SPSS Statistics for Windows, Version 21. Armonk, NY.

Result

General clinical characteristics of patients

Among 81 patients with MDS, there were 25 cases of MDS-EB-I, 30 cases of MDS-EB-II, 8 cases of MDS-SLD, 16 cases of MDS-MLD and 2 cases of MDS-U. The median age was 64 (18-82) years, including 46 males and 35 females. The median number of ANC at initial diagnosis was $1.19 (0.08-66) \times 10^9 / L$, median Hb was 76.5 (43.0-134.0) g/L, and median PLT was $47.5 (3.0-814.0) \times 10^9 / L$. The median Alb was 34.9 (20.8-48.1) g/L and the median TLC was $1.18 (0.21-23.62) \times 10^9 / L$, the median T-Cho was 3.3 (1.31-7.0) mmol/L. There were 13 patients with low risk IPSS-R score (1.5-3 points), 25 patients with medium risk (3.5-4.5 points), 26 patients with high risk (5-6 points) and 17 patients with very high risk (> 6 points). All patients received first-line treatment based on decitabine. The median follow-up time was 13.1 (2.1-

115.7) months, and the median OS was 13.8 months (95% CI 9.2-18.5). 18 patients survived and 63 died. The clinical features are shown in Table 2.

Table 2. Clinical features of 81 patients with MDS

Clinical features	CONUT ≥ 5.5 (n=32)	CONUT < 5.5 (n=49)	ALL (n=81)	P-value
Gender (male)%	20 (62.5)	26 (53.1)	46 (56.8)	0.402
Median age (range) years	64 (18-80)	63 (28-82)	64 (18-82)	0.996
Median ANC (range) $\times 10^9/L$	1.34 (0.19-51.7)	1.06 (0.08-66)	0.94 (0.08-66)	0.578
Median Hb (range) g/L	71.0 (45.0-116.0)	81.5 (43.0-134.0)	76.5 (43.0-134.0)	0.037
Median PLT (range) $\times 10^9/L$	39.5 (10.0-814.0)	58.0 (3.0-285.0)	47.5 (3.0-814.0)	0.171
WHO classification				
MDS-SLD	4	4	8	
MDS-MLD	8	8	16	
MDS-EB-I	11	14	25	
MDS-EB-II	9	21	30	
MDS-U	0	2	2	
Median Alb (range) g/L	37.4 (28.2-48.1)	31.35 (20.8-40.7)	34.9 (20.8-48.1)	< 0.001
Median To-cho (range) mmol/L	3.62 (2.4-7.0)	2.86 (1.31-4.96)	3.3 (1.31-7.0)	< 0.001
Median TLC (range) $\times 10^9/L$	1.4 (0.38-23.62)	0.805 (0.21-3.351)	1.18 (0.21-23.62)	0.009

Clinical characteristics of each group after grouping according to CONUT score

Among the 81 patients with MDS, there were 32 cases in the high CONUT score group and 49 cases in the low CONUT score group. Among the 32 patients with high CONUT score, there were 11 cases of MDS-EB-I, 9 cases of MDS-EB-II, 4 cases of MDS-SLD and 8 cases of MDS-MLD. The median age was 64 (18-80) years, including 20 males and 12 females. The median number of ANC at initial diagnosis was 1.34 (0.19-51.7) $\times 10^9/L$, median Hb was 71.0 (45.0-116.0) g/L, and median Plt was 39.5.0 (10.0-814.0) $\times 10^9/L$. The median Alb was 37.4 (28.2-48.1) g/L and the median TLC was 1.4 (0.38-23.62) $\times 10^9/L$, the median T-Cho was 3.62 (2.4-7.0) mmol/L. There were 3 low-risk patients, 9 medium-risk patients, 12 high-risk patients and 8 very high risk patients with IPSS-R score.

Among the 49 patients with low CONUT score, there were 14 cases of MDS-EB-I, 21 cases of MDS-EB-II, 4 cases of MDS-SLD, 8 cases of MDS-MLD and 2 cases of MDS-U. The median age was 63(28-82) years, including 26 males and 23 females. The median number of ANC at initial diagnosis was 1.06 (0.08-66) $\times 10^9/L$, median Hb was 81.5 (43.0-134.0) g/L, and median PLT was 58.0 (3.0-285.0) $\times 10^9/L$. The median Alb was 31.35 (20.8-40.7) g/L and the median TLC was 0.805 (0.21-3.351) $\times 10^9/L$, the median T-Cho was 2.86 (1.31-4.96) mmol/L. There were 10 low-risk patients, 16 medium-risk patients, 14 high-risk patients and 9 very high risk patients with IPSS-R score. Compared with the low CONUT score group, Hb, T-Cho, TLC and Alb in the high CONUT score group decreased significantly (P values were 0.037, < 0.001 , 0.009 and < 0.001 , respectively).

survival analysis

Among the 81 patients, 18 survived and 63 died. 14 patients (28.5%) survived in the low CONUT score group and 4 patients (12.5%) survived in the high CONUT score group; 35 cases (71.4%) died in the low score group and 28 cases (87.5%) died in the high CONUT score group. $\chi^2=2.893$ $P=0.089$

The median overall survival time in the high CONUT score group was 11.0 months (95% CI 7.42-14.6), and the median OS in the low CONUT score group was 17.2 months (95% CI 13.3-21.1) $\chi^2 = 5.745$, $P = 0.017$ (Figure 1).

Analysis of prognostic factors

The age, gender, hemoglobin, platelet count, neutrophil count, IPSS-R score and CONUT score of MDS patients at the initial diagnosis were included in the univariate prognosis analysis based on OS. The results showed that thrombocytopenia, high CONUT score, medium and high-risk IPSS-R score at the initial diagnosis were associated with poor OS (P values were 0.033, 0.018 and 0.006, respectively). Further, the factors related to OS in univariate analysis were put into multivariate analysis. The results showed that the above three items were still poor prognostic factors of OS (P values were 0.026, 0.038 and 0.016 respectively) (Table 3).

Table 3. Univariate and multivariate prognostic analysis of MDS patients based on OS

Risk factors	Univariate analysis		multivariate analysis	
	HR [95%CI]	<i>P</i>	HR[95%CI]	<i>P</i>
Age>60 years	0.933[0.555-1.569]	0.794		
Gender	0.870[0.517-1.463]	0.599		
Hb[100g/L	0.919[0.483-1.748]	0.797		
PLT≤100×10 ⁹ /L	0.537[0.303-0.952]	0.033	0.546[0.313-0.953]	0.026
ANC≤0.8×10 ⁹ /L	1.359[0.701-2.636]	0.364		
CONUT[5.5	1.828[1.108-3.018]	0.018	0.52[0.292-0.926]	0.038
Low-risk IPSS-R	3.086[1.387-6.862]	0.006	2.715[1.208-6.106]	0.016

Discussion

Myelodysplastic syndrome (MDS) is a clonal bone marrow stem cell disease, which has higher prevalence rate in elderly patients. It is often accompanied by comorbidities, organ dysfunction and poor general conditions. Therefore, in MDS patients, it is not only necessary to carry out traditional prognosis grouping for patients, but also to individualized assessment of patients' own conditions.

CONUT score is a simple and completely objective tool to evaluate nutritional status. It can be determined by routine measurement parameters. It includes albumin, lymphocyte count and total cholesterol, reflecting the nutritional, immune and caloric status of patients. It has been confirmed that CONUT score can indicate the prognosis of a variety of diseases, including solid tumors and hematological malignancies, such as diffuse large B-cell lymphoma, multiple myeloma, adult T-cell leukemia / lymphoma, etc. [6–8]. There are few reports on the CONUT score in patients with MDS. Sakurai A's study found that in patients treated with Azacitidine, high CONUT score is closely related to the poor prognosis of MDS and AML with bone marrow dysplasia [9].

The CONUT score was composed of serum albumin, total cholesterol and lymphocyte count. Albumin is often used as a general index of nutritional evaluation, which widely reflects the balance between protein synthesis and catabolism. A multicenter study showed that pre transplant hypoalbuminemia was associated with poor OS in AML and MDS patients undergoing allogeneic transplantation [10].

Dyslipidemia in MDS is characterized by tumor wasting diseases, and lipid reduction is associated with HMGcoAR and LDL-R gene expression [11]. Studies have shown that the cholesterol level in MDS patients is significantly lower than that in the normal control group, and decreases progressively with the progress of the disease, especially in EB type [12], and the total cholesterol level is significantly lower in IPSS-R

high-risk group or very high-risk group, while the TC level in patients relieved by demethylation treatment is significantly higher than that before treatment [13].

Previous studies have shown that the low lymphocyte count level at the initial diagnosis of low-risk MDS is associated with poor prognosis [14], and the decrease of NK cells in high-risk MDS patients is associated with poor prognosis [15]. In patients treated with decitabine, lymphocyte count can be used as the standard to evaluate the efficacy [16]. Although the mechanism of action remains to be further studied, there is more and more evidence that the immune homeostasis of patients with MDS has changed [17].

In this study, according to the ROC curve, we determined that the cut-off value of CONUT score was 5.5, and the patients were divided into two groups, including 32 cases with high CONUT score and 49 cases with low CONUT score. There was no significant difference in WHO classification between the two groups. Compared with the low score group, the hemoglobin, total cholesterol, lymphocyte count and albumin in the high CONUT score group were significantly reduced. In addition, we found that high CONUT score was associated with poor OS. The median overall survival time in the high CONUT score group was 11.0 months and 17.2 months in the low CONUT score group. There was significant difference between the two groups.

Our results showed that thrombocytopenia, high CONUT, medium and high risk IPSS-R scores at initial diagnosis were associated with poor OS. Further, the factors related to OS in univariate analysis were put into Multivariate analysis. The results showed that the above three factors were still independent adverse prognostic factors of OS.

The traditional risk stratification of MDS is based on disease-related factors and does not include the patient's physical fitness and tolerance to drug treatment into the score. The CONUT score evaluates the patient's nutritional status and plays an important role in establishing a more detailed prognosis evaluation for MDS patients.

Declarations

*Funding:*Not applicable

*Conflicts of interest/Competing interests:*The authors declare that they have no conflict of interest.

*Availability of data and material:*The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable

*Authors' contributions:*Xin ZHOU and Jun XIA provided the conception and design of the study. Jin QIAN and Jing WANG collected and assembled the data and wrote the article. Feng CHENG and Hong-feng GUO participated in data analysis and interpretation. All authors finally approved the manuscript.

Ethics approval: The Institutional Review Board of the Wuxi People's Hospital approved this study in accordance with the Helsinki Declaration. The requirement for informed consent was waived owing to the retrospective design of data collection.

Consent to participate: Not applicable

Consent for publication: Not applicable

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<https://doi.org/10.3324/haematol.2014.118679>

Figures

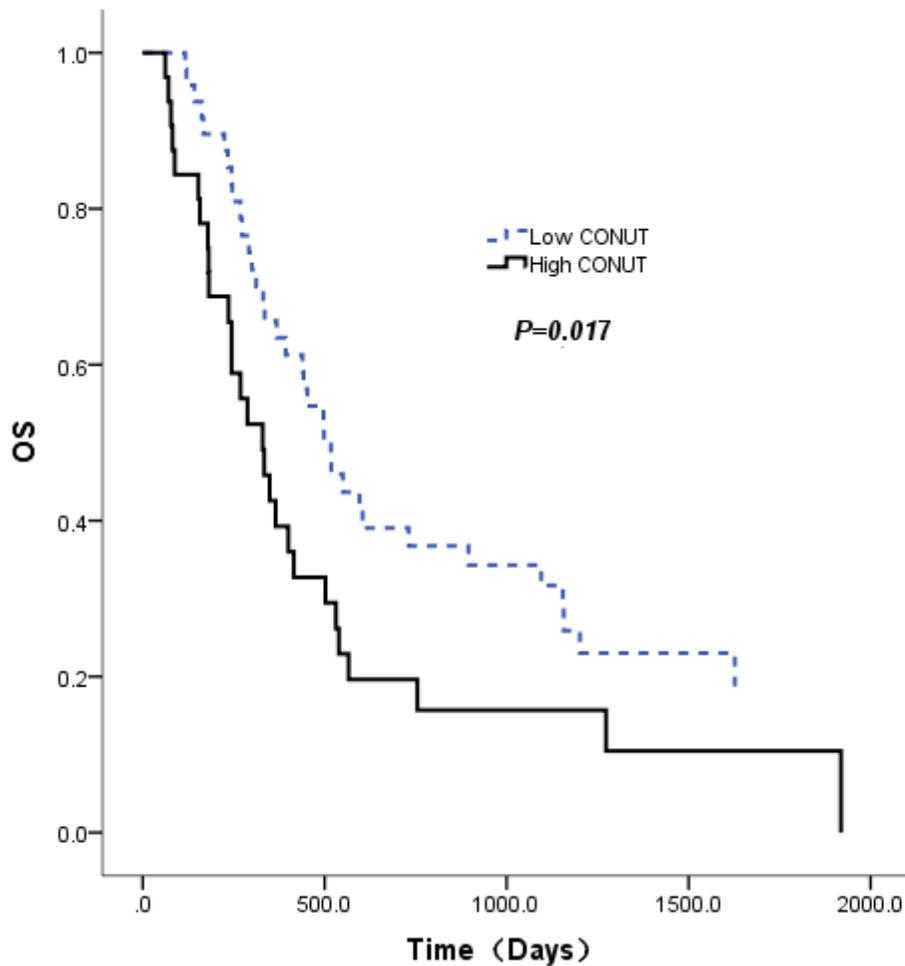


Figure 1

Overall survival curve of MDS patients in low and high CONUT score groups