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ORIGINAL RESEARCH

Low Levels of Natural Killer Cell in Newly Diagnosed Myelodysplastic Syndromes Patients May Confer Poor Prognosis: A Retrospective Cohort Study

Shengping Gong[1], Cong Shi[2]

[1]Cancer Radiotherapy and Chemotherapy Center, the First Affiliated Hospital of Ningbo University, Ningbo, Zhejiang, People's Republic of China; [2]Laboratory of Stem Cell Transplantation, the First Affiliated Hospital of Ningbo University, Ningbo, Zhejiang, 315000, People's Republic of China

Correspondence: Cong Shi, Email shicong5103@sina.com

Background: Immune imbalance appears to have a critical role in tumor growth according to emerging research. Peripheral lymphocyte subsets are considered to reflect the systemic immune response and clinical prognosis. The prognostic value of lymphocyte subpopulations in myelodysplastic syndrome (MDS) patients remains unclear.

Methods: A total of 94 MDS patients were enrolled for the study. X-tile software was performed to determine the prognostic significance of various lymphocyte subpopulations, CD3, CD4, CD8, CD4/CD8 ratio, natural killer cell (NK) and CD19. Among them, the appropriate threshold of NK percent could be found only. Patients were divided into the high NK percent group and the low NK percent group. The prognostic significance was determined by univariate and multivariate Cox hazard models.

Results: MDS patients with lower NK level had significantly shorter overall survival (OS). Based on univariate analysis, male gender ($P = 0.030$), lower HB (<10 g/dl, $P = 0.029$), higher BM blast (>5%, $P < 0.0001$), higher-risk IPSS-R cytogenetic ($P = 0.032$) and lower NK percent ($P < 0.0001$) were significantly associated with shorter OS. Multivariate Cox proportional hazards regression analysis indicated that low NK was also independent adverse prognostic factor for OS in MDS.

Conclusion: Decreased NK level predicts poor prognosis independent of the IPSS-R and provide a novel evaluation factor for MDS patients.

Keywords: myelodysplastic syndrome, lymphocyte subsets, prognostic, IPSS-R, natural killer cell

Background

Myelodysplastic syndrome (MDS) is a group of heterogeneous myeloid clonal diseases that originate from hematopoietic stem cells. They are characterized by ineffective hematopoiesis, which is manifested by morphologic dysplasia in hematopoietic cells and peripheral cytopenia(s). MDS carries a high risk of transforming into secondary acute myeloid leukemia (AML).[1] Due to the heterogeneity of prognosis, current clinical treatment plans for MDS patients primarily rely on the risk stratification provided by various clinical prediction models.[2] In 2012, the Revised International Prognostic Scoring System (IPSS-R) was introduced to risk-stratify MDS patients.[3] The assessment approach primarily focused on the extent of hemocytopenia (anemia, thrombocytopenia, neutropenia, reduced hemoglobin levels), elevated bone marrow blasts, and cytogenetic elements. In recent studies, researchers have extensively examined several potential prognostic predictors for MDS. Our research team has discovered that lower levels of ApoA1 in serum, elevated fibrinogen levels, and an increase in mature monocytes in bone marrow are all linked to a poor prognosis in MDS.[4–6]

Host immune dysregulation is involved in the occurrence and development of MDS.[7] Lymphocytes are crucial immune cells in the body, performing cellular immune effects and immune regulatory functions. They also play a vital role in immune surveillance within the host body and actively participate in the body's hematopoietic process. Notably, the level of absolute lymphocyte count (ALC) has shown a correlation with prognosis, suggesting that it could be used as biomarkers.[8] The detection of lymphocyte subpopulations is the primary method used to assess the quality and quantity

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of lymphocytes. Recent studies have shown that peripheral blood lymphocyte subpopulations can be used to predict the prognosis of breast cancer and renal cell carcinoma.[9,10] However, there is still a lack of evidence regarding the role of lymphocyte subpopulations in disease progression and prognosis of MDS. Therefore, we conducted a retrospective analysis of lymphocyte subsets at diagnosis to accurately determine its meaningful prognostic value in MDS patients.

Materials and Methods

Patients

Data on clinical and follow-up of 94 Patients newly diagnosed with MDS at the First Affiliated Hospital of Ningbo University from 2009 to 2019 were collected. Based on the patient's medical history, peripheral blood cell count, bone marrow morphology, cytogenetics, and other examination results, all patients met the minimum diagnostic criteria for MDS. The diagnosis and classification of MDS and leukemic transformation were determined according to the 2016 World Health Organization (WHO) classification and the 2022 WHO classification.[1,11] All BM morphology diagnostic and classification were interpreted by two experienced and qualified clinical pathologists. The risk stratification of MDS was conducted using IPSS-R.[2] Additionally, any patients who had received any treatment for MDS or immune related conditions were excluded. Before undergoing treatment, all patients underwent laboratory examinations. Symptomatic and supportive treatment was administered to nearly all patients. Peripheral blood samples were collected from 100 healthy donors to be used as controls.

The Ethics Committee of the First Affiliated Hospital of Ningbo University (approval number RS2023142A) approved the retrospective review of these records, in accordance with the Declaration of Helsinki. Informed consent was obtained from all adult subjects, or from parents if the subjects were under 18.

Lymphocyte Subsets Detection

Peripheral blood samples collected from all subjects were anticoagulated using EDTA. The enumeration of lymphocyte subsets was performed using a BD FACSCanto flow cytometer (BD, USA). The enumeration of lymphocyte subsets was performed using the BD Multitest 4-Color TBNK reagent. The antibodies used in this study included CD45 PerCP, CD3 FITC, CD4 APC, CD8 PE, CD19 APC, and natural killer cell (NK) (CD16+CD56) PE. The experimental procedures were conducted following the manufacturer's instructions.

Morphology Analysis

The morphology of MDS myeloid cells was observed by examining Wright-Giemsa stained bone marrow smears. Initially, the overall quality and distribution of the cells were subjectively evaluated using light microscopy at low power (10× objectives). Subsequently, a more detailed analysis was conducted at high power (100× oil objectives) to determine the differential count.

Cytogenetic Analysis

BM cells were collected and cultured in RPMI-1640 medium supplemented with 20% newborn calf serum for 24 hours. R-banded metaphases and their corresponding karyotypes were identified using the International System for Human Cytogenetic Nomenclature (ISCN2016).[12] At least 20 metaphases were analyzed for normal karyotype and at least 10 metaphases were analyzed for abnormal karyotype. The karyotypes were classified into five categories (very good, good, intermediate, poor, and very poor) based on the IPSS-R.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) significantly impacted the survival of patients with MDS.[13] Overall survival (OS) was calculated from the date of initial diagnosis of MDS until the date of death, last follow-up, or acquisition of allo-HSCT. The Kaplan-Meier method was used to analyze OS and compared using the Log rank test. Multivariable analyses were performed using the Cox proportional hazard regression model. Differences in the distribution of continuous variables between categories were

analyzed using the Mann–Whitney *U*-test, and categorical variables were analyzed using the Chi-squared test. The cutoff points were determined using the X-tile software.[14] The optimal cutoff values for differences in survival were determined based on the lowest *P*-value under the Log rank test. A *P*-value below 0.05 was considered statistically significant.

Results

Patient Characteristics

In our cohort, the Tables 1 and 2 describe the baseline characteristics of the study population. The data was obtained over a 10-year period and included 94 MDS patients, comprising of 54 males and 40 females, with a median age of 59 years (range 16–89 years). The median OS for these patients was 14 months (range 0–125 months), and 11 patients (11.7%) progressed to AML. According to the 2016 WHO classification, all patients were classified as follows: 11 (12%) with MDS with single lineage dysplasia (MDS-SLD), 30 (32%) with MDS with multilineage dysplasia (MDS-MLD), 7 (7%) with MDS with ring sideroblasts (MDS-RS), 0 (0%) with MDS with isolated del (5q) (MDS-5q-), 18 (19%) with MDS with excess blasts 1 (MDS-EB1), 22 (23%) with MDS-EB2, and 6 (6%) with unclassifiable MDS (MDS-U). According to the 2022 WHO classification, all patients were classified as follows: 6 (6%) of MDS with SF3B1 mutation (MDS-SF3B1), 0 (0%) of MDS with biallelic TP53 inactivation (MDS-biTP53), 0 (0%) of MDS with fibrosis (MDS-f), 0 (0%) of MDS-5q-, 8 (9%) of MDS with low blasts (MDS-LB), 19 (20%) of MDS with increased blasts 1 (MDS-IB1), 21 (22%) of MDS-IB2 and 40 (43%) of hypoplastic MDS (MDS-h). Furthermore, based on IPSS-R, 90 patients were

Table 1 Comparison of Laboratory Factors Between MDS with Low NK Group and High NK Group in 94 MDS Patients

Variable	Total Patients	Low NK Percent Group (n=22)	High NK Percent Group (n=72)	Statistics	*P value*
Gender (n)	94			$\chi2$=1.354	0.245
Male/Female, n	54/40	15/7	39/33		
Age [years, median (range)**]**	59 (16~89)	50.5 (16~84)	60 (19~89)	Z =−0.934	0.350
BM Blast[%, median (range)]	3.5 (0.0~19.5)	7.25 (0~19.5)	3 (0~18)	Z =−2.058	0.040
Peripheral Blood					
NE [$\times10^9$/L, median (range)]	1.1 (0.1~6.9)	0.8 (0.1~6.9)	1.2 (1.1~4.5)	Z =−1.154	0.249
HB [g/L, median (range)]	8.1 (2.3~14.2)	6.9 (2.5~12.2)	8.2 (2.3~14.2)	Z =−1.630	0.103
PLT [$\times10^9$/L, median (range)]	60.5 (2~332)	33.5 (6~277)	75 (2~332)	Z =−2.791	0.005
ALC [$\times10^9$/L, median (range)]	1.0 (0.3~4.3)	1.0 (0.4~4.3)	1.0 (0.3~3.2)	Z =−0.018	0.985
NK [%, median (range)]	13.2 (1.98~52.8)	6.1 (2.0~7.7)	17.3 (7.9~52.8)	Z =−3.166	0.002
2016 WHO classification				$\chi2$=9.605	0.142
MDS-SLD, % (n/n)	12% (11/94)	0% (0/22)	15% (11/72)		
MDS-MLD, % (n/n)	32% (30/94)	36% (8/22)	31% (22/72)		
MDS-RS-SLD, % (n/n)	1% (1/94)	0% (0/22)	1% (1/72)		
MDS-RS-MLD, % (n/n)	6% (6/94)	0% (0/22)	8% (6/72)		
MDS-5q-, % (n/n)	0% (0/94)	0% (0/22)	0% (0/72)		
MDS-EB1, % (n/n)	19% (18/94)	18% (4/22)	19% (14/72)		
MDS-EB2, % (n/n)	23% (22/94)	41% (9/22)	18% (13/72)		
MDS-U, % (n/n)	6% (6/94)	5% (1/22)	7% (5/72)		
2022 WHO classification				$\chi2$=7.114	0.130
MDS-SF3B1, % (n/n)	6% (6/94)	0% (0/22)	8% (6/72)		
MDS-biTP53, % (n/n)	0% (0/94)	0% (0/22)	0% (0/72)		
MDS-5q-, % (n/n)	0% (0/94)	0% (0/22)	0% (0/72)		
MDS-LB, % (n/n)	9% (8/94)	5% (1/22)	10% (7/72)		
MDS-IB1, % (n/n)	20% (19/94)	18% (4/22)	21% (15/72)		
MDS-IB2, % (n/n)	22% (21/94)	41% (9/22)	17% (12/72)		
MDS-h, % (n/n)	43% (40/94)	36% (8/22)	44% (32/72)		
MDS-f, % (n/n)	0% (0/94)	0% (0/22)	0% (0/72)		

(*Continued*)

Table 1 (Continued).

Variable	Total Patients	Low NK Percent Group (n=22)	High NK Percent Group (n=72)	Statistics	*P value*
IPSS-R cytogenetic risk group				$\chi2$=2.292	0.682
Very good, % (n/n)	2% (2/90)	0% (0/19)	3% (2/71)		
Good, % (n/n)	62% (56/90)	63% (12/19)	62% (44/71)		
Intermediate, % (n/n)	22% (20/90)	16% (3/19)	24% (17/71)		
Poor, % (n/n)	6% (5/90)	11% (2/19)	4% (3/71)		
Very poor, % (n/n)	8% (7/90)	11% (2/19)	7% (5/71)		
IPSS-R risk category				$\chi2$=14.558	0.006
Very low, % (n/n)	8% (7/90)	0% (0/19)	10% (7/71)		
Low, % (n/n)	24% (22/90)	5% (1/19)	30% (21/71)		
Intermediate, % (n/n)	29% (26/90)	42% (8/19)	25% (18/71)		
High, % (n/n)	23% (21/90)	16% (3/19)	25% (18/71)		
Very high, % (n/n)	16% (14/90)	37% (7/19)	10% (7/71)		
IPSS-R score[median (quartile)]	4.0 (1.0~10.0)	5.5 (3.0~10)	4.0 (1.0~10)	Z =−2.755	0.006
Leukemia transformation, % (n/n)	11.7% (11/94)	18% (4/22)	10% (7/72)	$\chi2$=1.167	0.277

Abbreviations: BM, bone marrow; NE, neutrophil; HB, hemoglobin; PLT, platelet; ALC, absolute lymphocyte count; NK, natural kill; MDS-SLD, MDS with single lineage dysplasia; MDS-MLD, MDS with multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single lineage dysplasia; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-5q-, MDS with isolated del (5q); MDS-EB1, MDS with excess blasts 1; MDS-EB2, MDS with excess blasts 2; MDS-U, unclassifiable; MDS-SF3B1, MDS with low blasts and SF3B1 mutation; MDS-biTP53, MDS with biallelic TP53 inactivation; MDS-LB, MDS with low blasts; MDS-IB1, MDS with increased blasts 1; MDS-IB2, MDS with increased blasts 2; MDS-h, hypoplastic MDS; MDS-f, MDS with fibrosis; IPSS-R, Revised International Prognostic Scoring System.

Table 2 Univariate and Multivariate Analyses for Overall Survival in 94 Patients with MDS

Variables	Univariate Analysis for OS		Multivariate Analysis for OS		
	P-value	HR (95% CI)	*P-value*	Exp (B)	HR (95% CI)
Age ≥ 60 (years)	0.447	51.035–90.087	–	–	–
Gender (male)	0.030	34.742–59.910	0.016	3.588	1.263–10.193
HB < 10g/dl	0.029	43.609–79.155	0.195	1.983	0.704–5.586
NE < 0.8×10^9/L	0.293	38.474–84.983	–	–	–
PLT < 100×10^9/L	0.799	43.956–66.144	–	–	–
BM blast > 5%	< 0.0001	17.913–33.871	0.001	4.630	1.943–11.033
IPSS-R, cytogenetic risk group	0.032	61.328–90.765	0.090	2.208	0.274–17.812
NK percent < 7.9%	< 0.0001	11.137–28.388	0.012	3.206	1.295–7.936

Abbreviations: BM, bone marrow; NE, neutrophil; HB, hemoglobin; PLT, platelet; IPSS-R, Revised International Prognostic Scoring System; NK, natural killer cell; OS, overall survival.

divided into the following risk groups: 7 (8%) in very low risk, 22 (24%) in low risk, 26 (29%) in intermediate risk, 21 (23%) in high risk, and 14 (16%) in very high risk. The IPSS-R score ranged from 1.0 to 10.0, with a median of 4.0. Table 1 provide more details. Almost all of the patients received symptomatic and supportive care. Seventy-two patients acquired further treatment, of whom 35 individuals (37%) were treated with intensive chemotherapy, 11 patients 12(%) with hemopoietic stem cell transplantation (HSCT), and 16 patients (17%) with hypomethylating drugs. Some patients received more than one treatment.

X-Tile Analyses

The X-tile algorithm established the appropriate threshold for changes in survival based on the Log rank test, which yielded the lowest *P*-value of 7.9%. The high NK group had a NK percent of ≥ 7.9%, whereas the low NK group had

a NK percent of < 7.9% (Figure 1A). In our cohort, CD4, CD8, and CD19 had no effect on OS in MDS, and no appropriate cutoff values were discovered. The data not shown.

The Correlation of peripheral NK Percent with Clinical and Laboratory Factors

In our cohort, the median NK percent in 94 MDS patients was lower than that in 100 healthy donors (13.6% vs 18.9%, $P = 0.007$; Figure 1B). MDS patients were separated into two groups to investigate the relationship between NK level and other clinical and laboratory characteristics. It revealed that patients with lower NK level had significantly more counts of BM blast ($P = 0.04$), higher IPSS-R score ($P = 0.006$), and lower PLT ($P = 0.005$) than those with higher NK. Additionally, the patients of the decreased NK level with higher risk distribution in terms of IPSS-R ($P = 0.006$). There were no significant differences in other variables between the two groups (Table 1).

Decreased NK Percent Was Associated with Poor Prognosis

We found that a lower level of NK (< 7.9%) was substantially correlated with decreased OS by the use of the Kaplan-Meier survival analysis and the Log rank test. As demonstrated in Figure 1C, the median OS in the lower NK was shorter (46 months vs 125 months, $P < 0.0001$) as compared to that in the high-level equivalent. However, when it comes to the LFS, the difference between the two group was statistically insignificant ($P = 0.123$; Figure 1D).

In univariate analysis, OS was adversely associated with male gender ($P = 0.030$), lower HB (<10 g/dl, $P = 0.029$), higher BM blast (>5%, $P < 0.0001$), higher-risk IPSS-R cytogenetic ($P = 0.032$) and lower NK percent ($P < 0.0001$). The Results of multivariate analyses indicated that a lower proportion of NK (<7.9%, $P = 0.012$), male gender ($P = 0.016$) and higher BM blast ($P = 0.001$) were associated with worse OS. Table 2 presented the results.

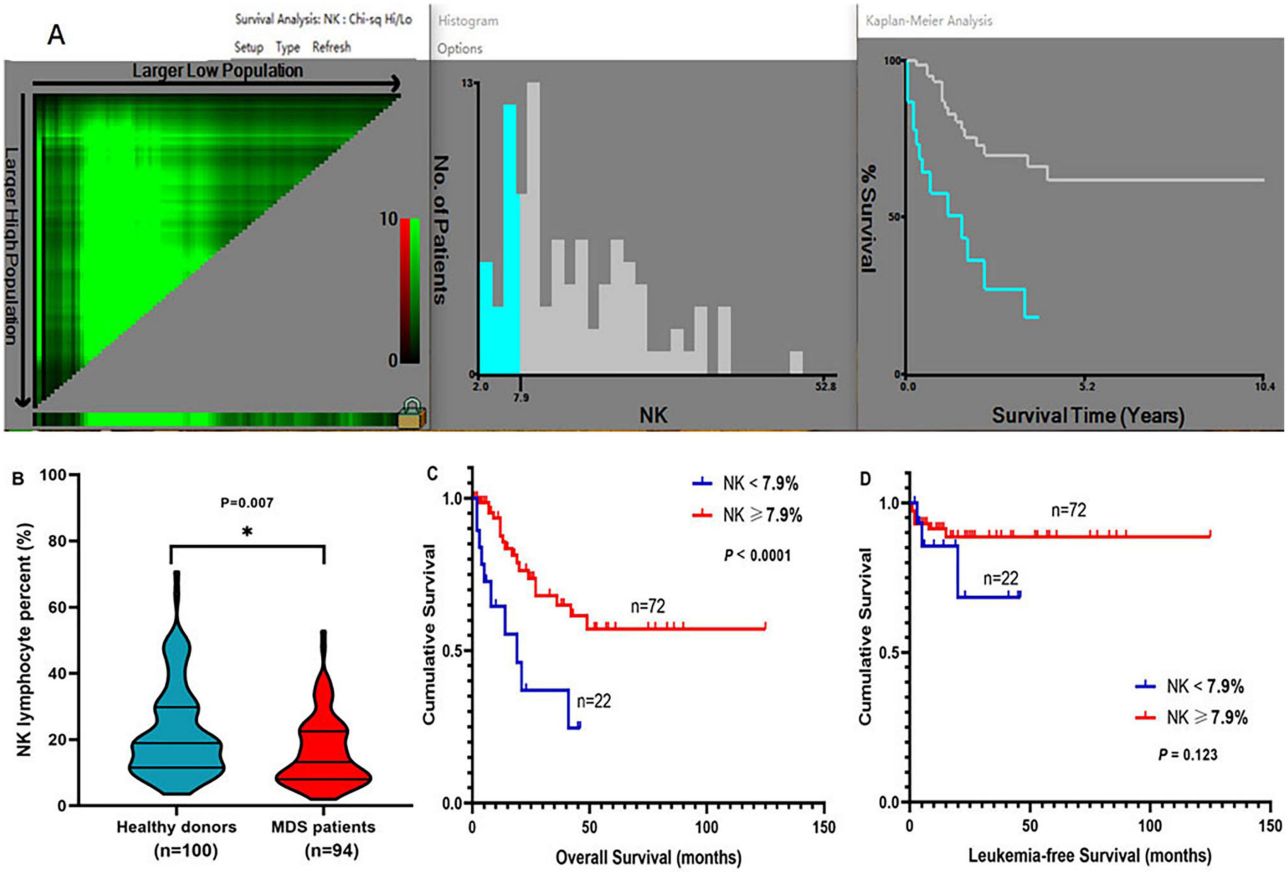

Figure 1 (**A**) X-tile analyses of OS were performed using patients' data to determine the optimal cutoff value for NK percent and the optimal cutoff value for NK percent was 7.9%. (**B**) Compare NK lymphocyte percent between 100 healthy donors and 94 MDS patients (*$P < 0.05$). (**C**) Overall survival of 94 patients with primary MDS was stratified by NK < 7.9% vs NK ≥ 7.9% ($P < 0.0001$). (**D**) Leukemia-free survival of 94 patients with primary MDS was stratified by NK < 7.9% vs NK ≥ 7.9% ($P = 0.123$).

Discussion

MDS is a group of highly heterogeneous diseases. Its pathogenesis involves epigenetic alterations, aberrant gene expression, changes in the hematopoietic microenvironment and other factors. Among them, immune disorders play a crucial role in the occurrence and development of MDS. Immune disorders can decrease the body's immune surveillance function and disrupt immunological homeostasis. Through immunological modulation, T lymphocytes can suppress hematopoietic stem cells and encourage the emergence and growth of MDS.[15] The findings of this study demonstrate that, in comparison to healthy subjects, MDS patients have lower proportions of NK in peripheral blood lymphocyte subpopulations. This study employed statistical analysis on 94 newly diagnosed MDS patients to further assess the clinical utility of lymphocyte subpopulations. X-tile software was utilized to determine the ideal critical values of each indicator of lymphocyte subpopulation, and the Kaplan-Meier method was used to compare the results. Based on the obtained results, due to impaired hematopoiesis, we showed that pretherapy NK ratio at low level was associated with higher BM blast, higher IPSS-R scores, and lower PLT. Decreased NK ratio was found to be a poor prognostic factor for MDS in univariate analysis and to be an independent risk factor affecting the overall survival time of MDS patients in multivariate analysis. Due to the samples limitation, the difference of LFS between the two group was statistically insignificant, but the patients with low NK cells were at higher risk of transforming into AML.

Disease progression is caused by the immunological microenvironment, which also plays a dynamic role in immune escape and malignant clonal proliferation. It also mediates bone marrow failure.[16] A shift in the immunological milieu, such as an overabundance of inflammatory substances in the bone marrow, damages hematopoietic stem cells functionally, which opens the door for clonal hematopoiesis and MDS to begin. An essential component of the immunological microenvironment are immune cells. The immune system is crucial to the onset and progression of MDS; this includes immunological escape, decreased regulatory T cells, increased pro-apoptotic cytokines, malfunctioning B cells, and NK cells, among other things.[17] The body's immunological status is indicated by changes in T, B, and NK lymphocyte subpopulations as well as by dynamic changes in peripheral blood lymphocyte subpopulations, which might represent the systemic immune status.

Research has demonstrated the prognostic and predictive value of systemic or local immune markers in tumor patients,[18] and that low peripheral blood CD4+/CD8+ ratios and CD3+ T cell counts are inversely connected with overall survival in patients with renal cell carcinoma.[10] Patients with low peripheral blood B lymphocyte counts prior to therapy for nasopharyngeal cancer had a poor prognosis.[19] A reported study demonstrated that favorable prognostic role of NK cells in head and neck squamous cell carcinoma.[20] In additional, colon cancer patients with lower NK cell percentages had shorter OS than those with higher percentages, and NK cell percentage was one of the independent prognostic factors.[21] MDS is impacted by NK cell-mediated cytotoxicity prior to therapy somatic cells, indicating that MDS patients' NK cells might be a target for treatment.[22] The findings of this study demonstrate that decreased NK levels are independent risk factors and that low levels of NK cells among peripheral blood lymphocyte subsets of newly diagnosed MDS patients suggest a poor prognosis and a short OS. Other lymphocyte subpopulation indicators, however, do not statistically significantly affect prognosis. Our study has certain limitation. First, a retrospective study was done in this case, which is prone to selection bias and confounding factors. In addition, this study did not detect the absolute count of lymphocyte subpopulations in patients, which cannot accurately reflect the body's immune status. Second, there were very few cases among the gathered data that developed into leukemia, making it difficult to assess the correlation between lymphocyte subpopulation levels and the likelihood that MDS will develop into leukemia. To support additional research, more samples must be gathered. Finally, the overall conclusion was significantly limited by the study design, sample size and the methodological limitations, the multi-center and more large-scale cohort replication would benefit the findings.

Conclusions

Peripheral blood has the advantages of quick capture, straightforward processing, and dynamic monitoring as the primary source of immune cells in the tumor microenvironment. The association between immune cell alterations and objective clinical responses in MDS patients will be the subject of clinical investigations that will shed light on the various immune

system components and their roles in the prognosis of MDS. This study analyzed the relationship between the proportion of peripheral blood lymphocyte subpopulations and disease prognosis in patients with MDS, and provided data for further research on tumor prediction and prognostic immunological indicators that are effective in treatment.

Abbreviations

MDS, Myelodysplastic syndromes; OS, Overall survival; LFS, Leukemia-free survival; IPSS-R, Revised International Prognostic Scoring System; AML, Acute myeloid leukemia; IPSS, International Prognostic Scoring System; WHO, World Health Organization; BM, Bone marrow; allo-HSCT, Allogeneic hemopoietic stem cell transplantation; ISCN2016, International System for Human Cytogenetic Nomenclature (2016); NE, Neutrophil; HB, Hemoglobin; PLT, Platelet; ALC, Absolute lymphocyte count; NK, Natural killer cell; MDS-SLD, MDS with single lineage dysplasia; MDS-MLD, MDS with multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single lineage dysplasia; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-EB, MDS with excess blasts; MDS-U, MDS with unclassifiable; MDS-SF3B1, MDS with low blasts and SF3B1 mutation; MDS-biTP53, MDS with biallelic TP53 inactivation; MDS-LB, MDS with low blasts; MDS-IB1, MDS with increased blasts 1; MDS-IB2, MDS with increased blasts 2; MDS-h, Hypoplastic MDS; MDS-f, MDS with fibrosis.

Data Sharing Statement

Data from the First Affiliated Hospital of Ningbo University back the study's findings. Nevertheless, these data are not openly accessible, as they were employed with authorization specifically for this analysis. Nonetheless, if you seek to access and obtain approval from the First Affiliated Hospital of Ningbo University, the authors can provide the data upon request. If so, the first author should be contacted if one requests access to the study's data.

Ethics Clearance and Participation Consent

Each patient provided written informed consent, and it was documented. In accordance with the principles outlined in the Helsinki Declaration, the Ethics Committee of the First Affiliated Hospital of Ningbo University has granted approval for Project (RS2023142A). To provide the co-authors access to the data, the consent request was expanded to include all of them.

Author Contributions

All authors made a significance contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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