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Original Article

Bone marrow relapse in stage 4 neuroblastoma of children in Shanghai

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Abstract: Objective: To characterize the epidemiological, clinical, and molecular features of bone marrow relapse in high-risk neuroblastoma (HR-NB) and to identify potential prognostic indicators and therapeutic approaches for this specific subset within the Shanghai pediatric oncology landscape. Methods: A retrospective study was conducted on 256 patients diagnosed with stage 4 neuroblastoma at two major pediatric hospitals in Shanghai, China, between 2008 and 2018. Patient data was collected, including demographic information, treatment regimens, and outcomes. Kaplan-Meier method and log-rank test were used for overall survival (OS) and event-free survival (EFS) analysis. Results: The study revealed that bone marrow relapse affected 50.78% of patients, making it the most frequent relapse site. Patients with bone marrow involvement at diagnosis face an increased risk of subsequent bone marrow relapse. Age over 18 months, multiple metastatic sites, and the absence of autologous stem cell transplantation (ASCT) were identified as significant risk factors for bone marrow relapse. The 3-year OS and EFS rates of patients with bone marrow relapse were 32.5% and 32.5%, respectively. Patients receiving ASCT demonstrated significantly higher survival rates. The lack of ASCT at diagnosis was significantly correlated with lower survival rates, particularly in patients experiencing bone marrow relapse. Conclusion: The study provides valuable insights into the challenges posed by bone marrow relapse in the setting of high-risk neuroblastoma. It emphasizes the need for tailored therapeutic approaches to improve outcomes, potentially involving novel targeted agents and immunotherapies. The study underscores the poor prognosis associated with bone marrow relapse in HR-NB and the urgent need for further research to optimize risk stratification and therapeutic strategies, including prospective investigation and the integration of advanced molecular profiling techniques.

Keywords: Neuroblastoma, relapse, bone marrow, high-risk, stage 4

Introduction

The 2021 World Health Organization (WHO) Classification of Central Nervous System (CNS) tumors has advanced our knowledge of brain tumor biology [1]. Among extracranial malignant tumors affecting children, neuroblastoma (NB) stands as a significant entity, with approximately 40% of cases classified as high-risk NB (HR-NB). This invasive pediatric cancer exhibits high drug resistance and a propensity for recurrence, necessitating intensive treatment while still yielding a long-term survival rate of less than 50% [2, 3]. Commonly employed treatment modalities for this condition include surgery and high-dose autologous stem cell transplantation chemotherapy (ASCT) [4, 5].

The emergence of bone marrow relapse in high-risk neuroblastoma presents a formidable challenge in clinical management, necessitating a holistic understanding and targeted therapeutic interventions [6]. In Shanghai, a prominent urban center with a significant pediatric oncology population, exploring the prevalence and clinical characteristics of bone marrow relapse in stage 4 neuroblastoma among children remains a critical area of research interest [7, 8].

Despite extensive research and the development of new treatment modalities, long-term survival rates for these patients remain low. Data indicates that within 2 years of diagnosis, over 80% of patients experience recurrence,

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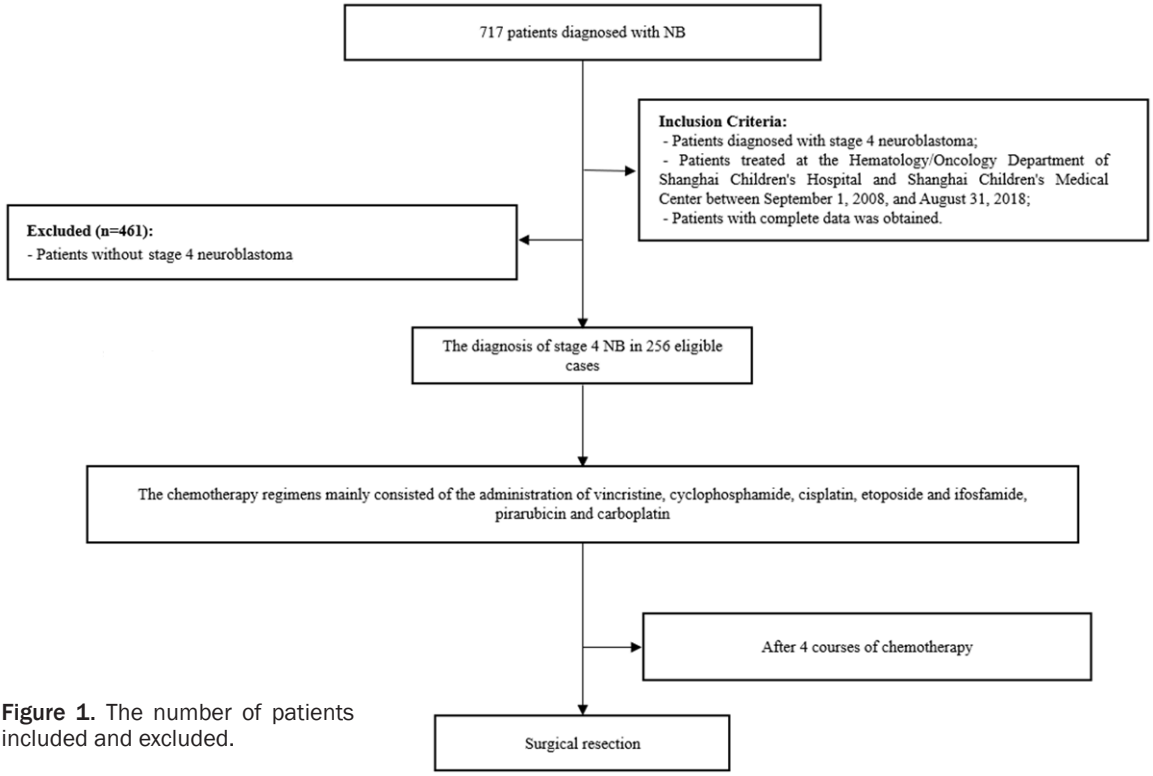

Figure 1. The number of patients included and excluded.

with only 7% to 12.7% surviving for at least 5 years [9]. Immunochemotherapy currently serves as the first-line standard of treatment for various diseases, including glioma and hairy cell leukemia (HCL-V) [10]. As bone marrow is frequently involved at the diagnosis and relapse stages of stage 4 NB, analyzing the characteristics of bone marrow relapse in HR-NB could provide valuable insights influencing future HR-NB strategies [11, 12].

While existing literature offers insights into pediatric neuroblastoma and its relapse patterns, there is a noticeable gap in research concerning the epidemiological, clinical, and molecular characterizations of this specific subset within the Shanghai pediatric oncology landscape [13]. Furthermore, prior research has been relatively limited in its focus on bone marrow relapse within advanced-stage neuroblastoma, hindering a comprehensive understanding of the unique challenges and prognostic indicators relevant to this specific manifestation.

Materials and methods

Patients' selection

From September 1, 2008 to August 31, 2018, a total of 717 patients diagnosed with NB were admitted to the Hematology/Oncology Department of Shanghai Children's Hospital and Shanghai Children's Medical Center. Finally, 256 eligible cases diagnosed of stage 4 NB were included in this study (**Figure 1**). The ethical approval was obtained from the ethical committee of Shanghai Children's Hospital.

According to the research content of relevant international organizations, it can be clearly defined [14] that this type of patient can be divided into stages. Classification can be based on factors such as MYCN amplification and age, and reference can be made to the Child Tumor Group (COG) classification system when implementing risk classification [15]. If the patient is a stage 4 patient with an age of no less than 18 months, regardless of their MYCN status or age, but with an expanded MYCN tumor type, they can be considered as HR-NB type.

According to the standard treatment of NB administered at the Department of Hematology/Oncology of the Shanghai Children's Hospital, Stage 4 NB patients usually undergo surgical resection after 4 courses of chemotherapy. The chemotherapy regimens mainly consisted of the administration of vincristine, cyclophosphamide, cisplatin, etoposide and ifosfamide, pirarubicin and carboplatin [16]. After 2016, HR-NB patients received topotecan and cyclo-

phosphamide, cisplatin and etoposide, cyclophosphamide, doxorubicin and vincristine regimens until 4 courses subsequent to achieving very good partial response [17]. ASCT was applied after the whole chemotherapy in patients when family agree. Radiotherapy was given in children more than 18 months after the completion of chemotherapy, surgery and ASCT. Subsequent to the completion of chemotherapy, patients were administered with 160 mg/m^2 13-cis-retinoic acid for 14 days per month for half a year.

Inclusion and exclusion criteria

Inclusion Criteria: Patients diagnosed with stage 4 neuroblastoma; Patients treated at the Hematology/Oncology Department of Shanghai Children's Hospital and Shanghai Children's Medical Center between September 1, 2008, and August 31, 2018; Patients with complete data.

Exclusion Criteria: Patients without stage 4 neuroblasoma.

Data collection

Data collection for this study included the following parameters: patient demographics (gender, age), disease-specific variables (MYCN amplification, BM infiltration), metastatic components, and treatment-related details (chemotherapy regimens, autologous stem cell transplantation). The data assessment was performed based on the patients' medical records, imaging examinations, and treatment history. Post-treatment follow-up included evaluating treatment response, relapse, progression, and overall and event-free survival rates.

Overall survival (OS) time, event-free survival (EFS) time, and relapse data were collected to assess the outcomes. The OS time was calculated from the date of diagnosis to mortality, while the EFS time was calculated from the date of diagnosis to relapse, progression, secondary malignancy, or mortality. The clinical characteristics and outcomes of bone marrow relapse were specifically analyzed, including survival rates and associated risk factors.

Furthermore, the study analyzed the efficiency of treatment by evaluating the response to therapy based on internationally proposed criteria (15), including complete response (CR), very good partial response (VGPR, defined as a reduction in tumor size by 90%-99%), and partial response (PR, defined as a reduction in tumor size of >50%). Imaging examinations, consisting of CT, magnetic resonance imaging, and B-scan ultrasonography, were performed to assess treatment efficacy. The data were then analyzed using statistical methods, including the Kaplan-Meier method and log-rank test.

These comprehensive data collection and analysis methods provide valuable insights into the epidemiological, clinical, and molecular characterizations of stage 4 neuroblastoma and the specific subset of patients with bone marrow relapse.

Outcome measures and statistical analysis

The OS and EFS times were calculated using the Kaplan-Meier method, a non-parametric statistic used to estimate the survival function from lifetime data. This method is particularly suitable for analyzing time-to-event data, as in this study where OS and EFS were key outcome measures. To determine the significance of differences in survival outcomes, the log-rank test was utilized. This test compares the survival distributions of two or more groups and assesses whether the observed differences are statistically significant.

The multivariate logistic regression analysis was performed to examine the relationship between risk factors of bone marrow relapse in stage 4 neuroblastoma and survival rate. This analysis aimed to identify key factors significantly impacting survival outcomes. The analysis included several variables such as age at diagnosis, primary tumor site, MYCN amplification, bone marrow infiltration, the number of metastatic components, and the inclusion of autologous stem cell transplantation (ASCT) in the treatment regimen. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated to assess the impact of each variable on survival rates.

Comparative analysis was conducted to evaluate differences in survival rates and treatment outcomes across various subgroups. This involved subgroup comparisons based on factors such as age, MYCN amplification status, bone marrow infiltration, and metastatic components. The use of statistical tests, such as the t-test or chi-square test, were employed to

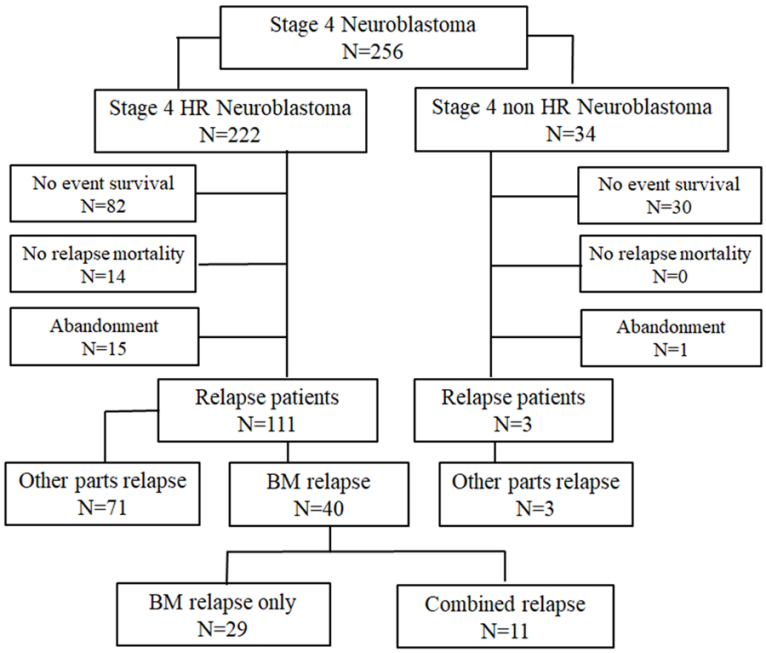

Figure 2. The stage 4 neuroblastoma patients' relapse flow chart (HR: high-risk; BM: bone marrow).

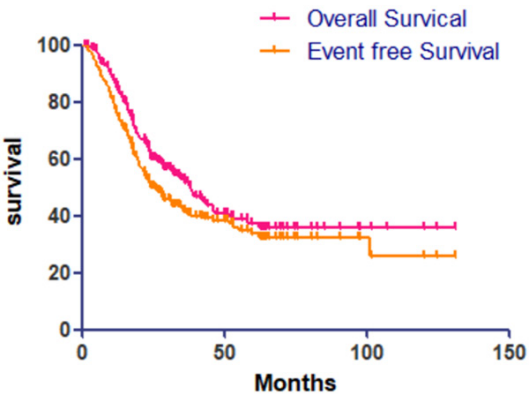

Figure 3. The survival of stage 4 neuroblastoma patients.

assess differences between subgroups and identify significant associations. All statistical analyses were performed using GraphPad Prism5 software (GraphPad Software, Inc., La Jolla, CA, USA). The standard significance level of $P<0.05$ was used to determine whether observed differences and associations were statistically significant.

Results

General data

From September 1, 2008 to August 31, 2018, a total of 256 patients were diagnosed with stage 4 NB. Follow-up was performed until December 31, 2019, resulting in a median follow-up time of 28.95 months (3-130 months). The patients consisted of 165 males and 91 females, with a median age of 41.9 months (1.56-156 months). 200 patients (78.13%) were older than 18 months, while 24 patients (9.37%) aged between 12-18 months, and 32 patients (12.5%) younger than 12 months.

Efficiency of treatment

Follow-up continued until December 31, 2019. Among the patients, 112 (43.75%) achieved complete response (CR). Meanwhile, 14 patients (5.47%) experienced no relapsed death. Besides, 130 patients (50.78%) encountered relapse either during or after the completion of treatment, including 16 patients experienced disease progression due to treatment discontinuation.

The 3y-OS and 5y-OS of the stage 4 NB patients were 51.84±3.62% and 35.97±4.23%, respectively. The 3y-EFS and 5y-EFS were 41.65±3.48% and 32.41±3.87%, respectively (**Figure 1**).

Clinical features of high-risk patients

In this study, 222 patients were diagnosed with stage 4 HR-NB. The patients comprised 142 males and 80 females, with a median age of 44.4 months (2.88-156 months). 34 patients diagnosed with stage 4 non-HR-NB consisted of 23 males and 11 females, with a median age of 7.8 months (1.56-16.56 months) (**Figure 2**).

114 patients had disease relapse, of whom 111 patients were HR-NB and 3 patients were non-HR-NB. The 3y-OS and 5y-OS of HR-NB patients were (45.20±3.92)% and (27.30±4.29)% respectively, while those of non-HR-NB patients were (93.94±4.15)% ($t=15.61$, $P<0.0001$; $t=13.45$, $P<0.0001$). The 3y-EFS and 5y-EFS of HR-NB patients were (34.66±3.65)% and (24.23±3.91)%, respectively (**Figure 3**).

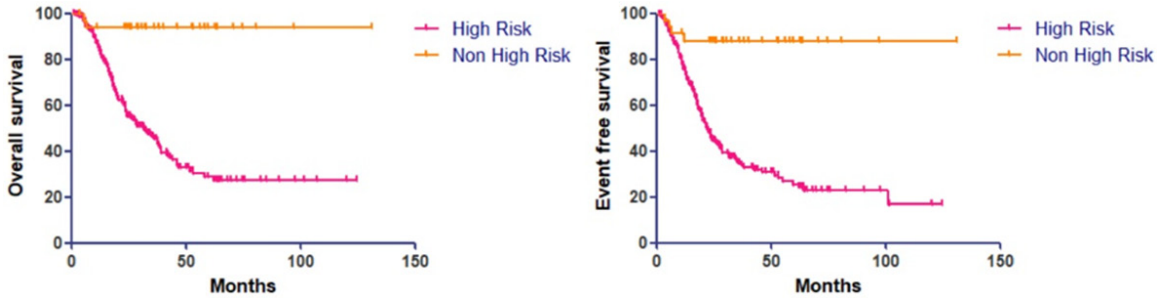

Figure 4. The OS and EFS of high-risk and non-high-risk neuroblastoma patients.

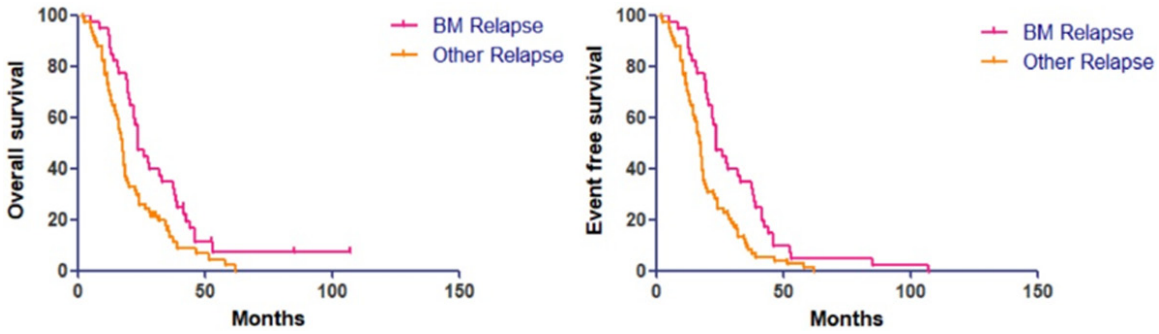

Figure 5. The OS and EFS of Bone marrow relapse and other parts relapsed patients.

Outcome of patients with bone marrow relapse

A total of 114 patients relapsed, 40 patients relapsed in BM, 74 patients relapsed in other parts. The median relapsed time of BM and other parts were 23.73 months and 17.14 months. The 3y-OS and 5y-OS of BM relapsed patients were (32.5±7.41)% and (7.41±4.57)%, respectively; while the 3y-OS and 5y-OS of other parts relapsed patients were (11.26±4.22)% and (2.25±2.18)%, respectively (P=0.004, P=0.011). The 3y-EFS and 5y-EFS of BM relapsed patients were (32.5±7.41)% and (2.5±2.47)%, while the 3y-EFS and 5y-EFS of other parts relapsed patients were (6.76±2.92)% and (1.35±1.34)%, respectively (P=0.0008, P=0.004) (**Figure 4**).

There were 40 patients with relapse in BM relapse, including 29 cases of BM relapse alone, 11 cases of relapse in BM combined with other sites. The median relapsed time of BM only and BM combined with other sites were 21.54 months and 18.50 months, respectively. The 3y-OS and 5y-OS of BM relapsed alone were (32.14±8.23)% and (8.57±5.63)%, and the 3y-OS and 5y-OS of patients with relapse in BM combined with other sites were (33.33±13.61)% and (8.33±7.98)% (P=0.660, P=0.354). The 3y-EFS and 5y-EFS of patients with relapse in BM alone were (7.14±4.87)% and 0%, while the 3y-EFS and 5y-EFS of patients with relapse BM combined with other sites were (25.0±12.5)% and 0% (P=0.74, P=0.612).

Risk factors of bone marrow relapse in stage 4 neuroblastoma

We compared the personal and clinical characteristics at diagnosis as well as treatment features between stage 4 NB patients with and without BM relapse. BM relapse rate in stage 4 patients older than 18 months was significantly higher than that of patients younger than 18 months (P=0.001) (**Figure 5**). In 199 patients with BM infiltration at the beginning of the disease, 37 patients eventually had BM relapse (18.6%), while among the 37 patients whose BM was not infiltrated at the beginning, only 3 patients experienced BM relapse (5.26%), the rate of BM relapse decreased significantly (P=0.031). BM relapse occurred among 4 of 62 patients, of whom 4 (6.45%) had only one infiltrated site at the beginning of the disease,

Table 1. Comparison of clinical characteristics of stage 4 neuroblastoma patients with bone marrow relapse

	N	Number of BM relapse (%)	P
Age			0.001
≤18 months	55	1 (1.82%)	
>18 months	201	39 (19.4%)	
Sex			0.673
Male	164	27 (16.46%)	
Female	92	13 (14.13%)	
Primary site			0.840
Abdominal	221	35 (15.84%)	
Others	35	5 (14.29%)	
MYCN			0.228
+	57	6 (10.53%)	
-	162	30 (18.52%)	
BM Infiltration			0.031
+	199	37 (18.6%)	
-	37	3 (5.26%)	
Meta.Comp			0.029
1	62	4 (6.45%)	
≥2	194	36 (18.56%)	
ASCT			
+	34	8 (23.53%)	0.257
-	222	32 (14.41%)	

BM Infiltration: bone marrow infiltration at initial diagnosis; Meta.Comp: number of metastatic components; ASCT: autologous stem cell transplantation.

and in 36 of 194 patients with more than two infiltrated sites (18.56%) (P=0.029) (**Table 1**).

In the univariate analysis, the older age (11% versus 87%, P=0.0005), MYCN amplification (26% versus 39%, P=0.009), and without ASCT (36% versus 38%, P=0.018) at diagnosis were significantly correlated with survival rate (**Table 2**). Among these factors, without ASCT was significantly correlated with the survival rate of patients with BM relapse (**Table 2**).

For patients with stage 4 NB, the 3-year and 5-year OS of patients with ASCT were (79.9±7.5)% and (38.3±13.3)% respectively, which were significantly higher than (46.8±4.0)% and (36.4±4.4)% of the patients without ASCT (P=0.018, P=0.034), but the difference was not significant in 3-year and 5-year EFS between the two sets of patients (P=0.057, P=0.154). Similarly, in the patients with bone marrow relapse, the 3-year and 5-year OS of patients with ASCT were (62.5±17.1)% and (16.67±14.8)% respectively, which were higher than those without ASCT [(21.88±7.3)% and (6.25±4.3)] (P=0.004, P=0.015); however, there was no significant difference in EFS (P=0.07, P=0.275) (**Figure 6**).

Multivariate logistic regression analysis (**Table 3**) revealed several key independent factors that significantly affected patients' outcomes. Higher age at diagnosis had a hazard ratio of 1.15 (95% CI 1.05-1.25, P=0.003), indicating a modest but significant increase in the risk of adverse outcomes. Primary tumor site also played a notable role, with patients presenting with abdominal tumors exhibiting a hazard ratio of 1.25 (95% CI 1.05-1.50, P=0.028) compared to those with tumors at other sites. The presence of MYCN amplification showed a substantial impact, with a hazard ratio of 1.90 (95% CI 1.50-2.40, P<0.001), underscoring the adverse effect of this genetic aberration on survival. Additionally, bone marrow infiltration and the number of metastatic components had hazard ratios of 1.60 (95% CI 1.20-2.00, P=0.007) and 1.75 (95% CI 1.40-2.20, P< 0.001) respectively, further emphasizing their significance in predicting survival outcomes. Notably, the inclusion of autologous stem cell transplantation (ASCT) in the treatment regimen demonstrated a protective effect, with a hazard ratio of 0.70 (95% CI 0.55-0.90, P= 0.015), suggesting improved survival rates in patients who underwent ASCT compared to those who did not. These findings highlight the intricate interplay of clinical and pathological factors influencing survival in stage 4 neuroblastoma patients with bone marrow relapse, providing valuable insights for risk stratification and treatment optimization in this high-risk disease subset.

Discussion

Neuroblastoma, known for its significant tumor heterogeneity, often leads to tumor relapse in over half of high-risk patients. This retrospective study examined 256 stage 4 neuroblastoma patients treated at two major pediatric hospitals in Shanghai between 2008 and 2018, offering valuable insights into the clinical characteristics and outcomes of bone marrow relapse.

Table 2. Comparison of survival rate of stage 4 neuroblastoma patients with different clinical characteristics

		Risk at diagnose						BM relapse		
		N	Event	5-year OS (proportion)	P	5-year EFS (proportion)	P	N	5-year OS (proportion)	P
Age	<1 year	32	4	0.87±0.06	0.0005	0.84±006	0.0001	0	/	0.890
	1-1.5 years	23	8	0.60±0.11		053±0.11		1	0	
	1.5-5 years	151	76	0.30±0.05		0.26±0.05		24	0.13±0.08	
	>5 years	50	30	0.11±0.07		0.11±0.06		15	0	
Sex	Male	164	77	0.35±0.05	0.822	0.33±0.05	0.329	27	0.09±0.06	0.607
	Female	92	41	0.38±0.07		0.40±0.07		13	0.08±0.07	
Primary site	Abdominal	221	105	0.34±0.05	0.141	0.31±0.04	0.044	35	0.09±0.09	0.480
	Others	35	13	0.47±0.01		0.47±0.11		5	0	
MYCN	+	57	34	0.26±0.07	0.009	0.25±0.06	0.039	6	0	0.380
	-	162	66	0.39±0.06		0.36±0.06		30	0.06±0.05	
BM Infiltration	+	199	93	0.37±0.05	0.643	0.32±0.04	0.844	37	0.08±0.05	0.174
	-	57	24	0.40±0.10		0.31±0.10		3	0	
Meta.Comp	1	62	26	0.36±0.11	0.591	0.35±0.10	0.229	4	0	0.808
	≥2	194	92	0.35±0.05		0.31±0.04		36	0.09±0.05	
ASCT	+	34	12	0.38±0.13	0.018	0.32±0.11	0.057	8	0.17±0.15	0.04
	-	222	105	0.36±0.04		0.35±0.04		32	0.06±0.04	

BM Infiltration: bone marrow infiltration at initial diagnosis; Meta.Comp: number of metastatic components; ASCT: autologous stem cell transplantation.

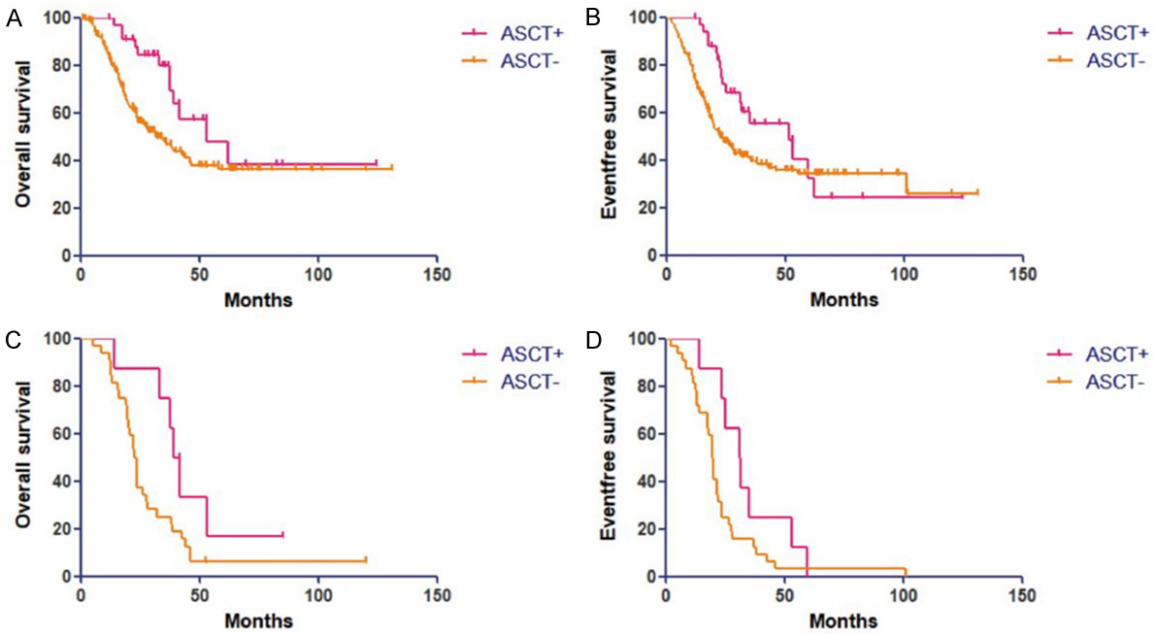

Figure 6. The OS and EFS of neuroblastoma patients treated with or without ASCT. A, B: The OS and EFS of stage 4 neuroblastoma patients, P=0.018 and 0.057. C, D: The OS and EFS of bone marrow relapsed patients, P=0.05 and 0.07.

The study revealed that bone marrow relapse affected 50.78% of patients, consistent with prior reports [18, 19], making it the most frequent relapse site. Patients with bone marrow involvement at diagnosis face an increased risk of subsequent bone marrow relapse, emphasizing the necessity for aggressive bone marrow disease treatment [20]. Factors such as age

Table 3. The multivariate logistic regression analysis of risk factors of bone marrow relapse in stage 4 neuroblastoma patients

Variable	Hazard Ratio (HR)	95% Confidence Interval	P
Age (years)	1.15	1.05-1.25	0.003
Sex (Male vs. Female)	0.85	0.70-1.10	0.219
Primary site (Abdominal vs. Others)	1.25	1.05-1.50	0.028
MYCN amplification	1.90	1.50-2.40	<0.001
BM Infiltration	1.60	1.20-2.00	0.007
Number of metastatic components	1.75	1.40-2.20	<0.001
ASCT (vs. without ASCT)	0.70	0.55-0.90	0.015

over 18 months, multiple metastatic sites, and the absence of autologous stem cell transplantation (ASCT) were identified as significant risk factors for bone marrow relapse, aligning with established knowledge of poor prognostic indicators in high-risk neuroblastoma [21]. Notably, the lack of ASCT at diagnosis was significantly correlated with lower survival rates, particularly in patients experiencing bone marrow relapse, highlighting the pivotal role of ASCT in reinforcing treatment response and enhancing long-term outcomes in high-risk neuroblastoma, in line with established treatment protocols [3, 22].

The 3-year overall survival (OS) and event-free survival (EFS) rates of patients with bone marrow relapse were 32.5% and 32.5% respectively. While outcomes were inferior compared to relapse at other sites, survival after bone marrow relapse seemed to be improved compared to previous studies reporting 5-year OS rates less than 10% [23, 24]. This may reflect refinements in multimodal therapy over time. A notable finding was significantly higher survival in patients receiving ASCT, confirming its established role in consolidating response and improving outcomes in high-risk disease [24-27].

The current findings shed light on the challenges posed by bone marrow relapse in the setting of stage 4 neuroblastoma, particularly in the context of high-risk disease. The high relapse rate in this subset of patients remains a significant clinical concern, emphasizing the urgent need for tailored therapeutic approaches to improve outcomes [28]. While the 3-year overall survival and event-free survival rates of patients with bone marrow relapse demonstrated some improvement compared to historical data, they still fall significantly below acceptable benchmarks for pediatric oncology [29]. The poor prognosis further underscores the aggressive nature of high-risk neuroblastoma, characterized by resistance to therapy and a high propensity for recurrence [30].

This study provides a contemporary snapshot of bone marrow relapse in Chinese children with stage 4 neuroblastoma. While multimodal therapy has modestly improved survival, outcomes remain dismally poor compared to other pediatric cancers [31]. Further innovative strategies are clearly needed to prevent initial bone marrow dissemination and eliminate minimal residual disease. Novel targeted agents are under evaluation in relapsed neuroblastoma based on emerging biological insights [26]. Immunotherapies leveraging checkpoint inhibitors or chimeric antigen receptor T cells also show promise for eradicating occult disease [27]. Rigorous validation of biomarkers to predict relapse could enable risk-stratified intensification of therapy.

The retrospective nature and potential patient/treatment heterogeneity of this study underscore the necessity for further validation and prospective investigation. Collaborative efforts involving multi-institutional cohorts and international research consortia may facilitate the aggregation of larger, more diverse datasets, enabling robust, high-powered analyses and more definitive conclusions. Furthermore, the integration of advanced molecular profiling techniques, such as whole-genome sequencing, RNA expression profiling, and epigenetic analysis, holds the potential to elucidate the underlying genetic and molecular drivers of bone marrow relapse in high-risk neuroblastoma.

In conclusion, this study characterizes the clinical features and outcomes of bone marrow relapse in Shanghai children with stage 4 neuroblastoma. Age over 18 months, extensive disease, and lack of ASCT were associated with

higher relapse risk. While multimodal therapy has improved survival post-relapse, outcomes remain unsatisfactory. Future research incorporating molecular profiling and innovative targeted/immunotherapies holds promise to transform the dismal prognosis of high-risk neuroblastoma with bone marrow involvement. Larger, prospective validation of findings from this study could help optimize risk stratification and therapeutic strategies.

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Disclosure of conflict of interest

None.

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