Pediatric Blood & Cancer

WILEY

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology

RESEARCH ARTICLE

Treatment and Outcome of Children With Neuroblastoma in India: Report From the InPOG-NB-18-01 India Neuroblastoma Registration Study

Jyothi Muni Reddy[1] | Yamini Krishnan[2] | Veerendra Patil[3] | Ramandeep Singh Arora[4] | Arpita Bhattacharya[5] | Faisal Guru[6] | Shruti Kakkar[7] | Manas Kalra[8] | Amita Mahajan[9] | Sangeetha Mudaliar[10] | Venkataraman Radhakrishnan[11] | Revathi Raj[12] | Sirisha Rani[13] | Nikita Patel[14] | Shakeel Modak[15] | Vikramjit S. Kanwar[16]

[1]St. John's Medical College Hospital, Bengaluru, India | [2]MVR Cancer Centre and Research Institute, Kozhikode, India | [3]Basavatarakam Indo American Cancer Hospital, Hyderabad, India | [4]Max Super Specialty Hospital, New Delhi, India | [5]Tata Medical Center, Kolkata, India | [6]Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India | [7]Dayanand Medical College Hospital, Ludhiana, India | [8]Sir Ganga Ram Hospital, New Delhi, India | [9]Indraprastha Apollo Hospital, New Delhi, India | [10]Bai Jerbai Wadia Hospital for Children, Mumbai, India | [11]Cancer Institute, Adyar, Chennai, India | [12]Apollo Hospital, Chennai, India | [13]Rainbow Children's Hospital, Hyderabad, India | [14]INPHOG Research Foundation, Gurugram, India | [15]Memorial Sloan-Kettering Cancer Center, New York, New York, USA | [16]Nanavati Max Super Specialty Hospital, Mumbai, India

Correspondence: Jyothi Muni Reddy (jyothimunireddy@yahoo.co.in)

Received: 6 March 2026 | **Revised:** 23 April 2026 | **Accepted:** 15 May 2026

Keywords: India | neuroblastoma | registry | survival

ABSTRACT

Aim: To describe the clinical, management, and outcome profile of childhood neuroblastoma (NB) in India and identify barriers to optimal management.

Methods: Retrospective (InPOG-NB-18-01) analysis of NB in children under 15 diagnosed between June 2016 and August 2021 across 14 centers, with prospective follow-up for survival outcomes.

Results: A total of 320 children with NB were included, with a median age of 29 months (interquartile range [IQR]: 14–55 months) and a male:female ratio of 1.36:1. Nuclear imaging for staging and *MYCN* amplification testing were performed in 60.3% and 72.5% of cases, respectively. International Neuroblastoma Risk Group (INRG) staging was L1, L2, M, and MS in 39 (12.2%), 89 (27.8%), 175 (54.7%), and 17 (5.3%), respectively. The INRG risk groups were Very low risk, Low risk, Intermediate risk, and High risk in 48 (15%), 29 (9%), 47 (14.7%), and 168 (52.5%) children, respectively, with 28 (8.8%) unknown due to diagnostic limitations. Over half of patients had high-risk neuroblastoma (HR-NB), and of those, only 55 (32.4%) underwent high-dose chemotherapy with autologous stem cell rescue (HDCT/ASCR), and one (0.6%) received anti-GD2 immunotherapy. The 3-year overall survival (OS) and event-free survival (EFS) for the entire cohort was 60% (54.1%–66.5%) and 50.2% (44.4%–56.7%), respectively. Risk factors for

Abbreviations: ^{18}F-FDG PET/CT, [fluorine-18]fluorodeoxyglucose positron emission tomography/computed tomography; AIR, annual incidence rate; EFS, event-free survival; HDCT/ASCR, high-dose chemotherapy with autologous stem cell rescue; HIC, high-income countries; HR-NB, high-risk-neuroblastoma; INPHOG, Indian Pediatric Hematology Oncology Group; INRG, International Neuroblastoma Risk Group; INRGSS, International Neuroblastoma Risk Group Staging System; KM, Kaplan–Meier; LDH, lactate dehydrogenase; LMIC, low- and middle-income countries; NB, neuroblastoma; OMAS, opsoclonus–myoclonus–ataxia syndrome; OS, overall survival; SCC, spinal cord compression.

Previous Presentation: This article contains data that were presented in part as a poster at the 55th Annual Congress of the International Society of Paediatric Oncology (SIOP), October 11–14, 2023, Ottawa, Canada.

poor EFS included age ($p < 0.001$), INRG risk group ($p < 0.001$), *MYCN* amplification ($p < 0.001$), ferritin levels ($p = 0.04$), and lactate dehydrogenase levels ($p < 0.001$).

Conclusions: Lack of accurate diagnostic risk stratification may contribute to poor outcomes of patients with NB in India. Suboptimal outcomes are primarily seen in HR-NB, with limited access to HDCT/ASCR and anti-GD2 immunotherapy.

1 | Introduction

While neuroblastoma (NB) is the most common extracranial solid tumor in children in the United States and other high-income countries (HIC), there is relatively little data on the treatment and outcome of children with NB in India, a low- and middle-income country (LMIC) [1]. While the United States has a reported annual incidence rate (AIR) of 11.7 cases per million children aged 0–14 years, the AIR for NB in India is only 4.3–5.8, which may reflect reporting bias, as according to the national Hospital-Based Cancer Registry (2021) in India, only 3.6% of children between the ages of 0 and 14 years diagnosed with malignancies are reported to have NB [2–5]. Three major referral centers in India treating patients with NB reported 144, 103, and 85 patients, over study periods of 13, 15, and 17 years, respectively, with the majority (86%–99%) presenting at an advanced stage [6–8]. This multi-institutional study was designed to aggressively register children with NB from across India to determine the spectrum of disease seen in India. It was hypothesized that lower stage NB tumors had previously been under-recognized, and that only a fraction of high-risk patients survived long enough to receive medical care; thus, a comprehensive NB registry could determine the current status of NB outcomes in India [9, 10]. In addition, with recent advances in the management of high-risk NB (HR-NB), we wanted to determine their impact on outcomes of NB in India [11].

2 | Methodology

This retrospective, multi-institutional, registry study, enhanced by prospective outcome data collection, aimed to determine the real-world occurrence, management, and outcomes of pediatric NB in India and identify barriers to optimal therapy. It was designed by a committee of pediatric oncologists from across India, peer-reviewed nationally and internationally, and registered with the Indian Pediatric Hematology Oncology Group (INPHOG) [12]. Fourteen institutions across India (Northern India = 6, Southern India = 6, Eastern India = 1, Western India = 1) participated, including four academic, seven private, one government, and two charitable institutions, each with Institutional Ethics Committee approval. The study was also registered with the Clinical Trials Registry—India (No. CTRI/2020/01/023088).

Data from children under 15 years of age diagnosed with NB between June 1, 2016, and August 31, 2021, were submitted online using a custom-designed Google Form. The study included all consecutive patients with biopsy-proven disease confirmed via the primary tumor site or bone marrow/metastatic site. Data included clinical features, biochemistry, imaging, pathology, cytogenetics, and treatment details. While treatment protocols were not uniform across centers, the treatment aligned with national guidelines and was adapted to local resource availability. The International Neuroblastoma Risk Group Staging System (INRGSS) was used for staging and risk stratification, to determine therapy, across all participating centers [13]. However, those with incomplete International Neuroblastoma Risk Group (INRG) criteria were not assigned a risk group, and imaging modalities used across centers were heterogeneous and determined by resource availability, thereby impacting staging accuracy. Treatment of low-risk/very low-risk NB primarily included surgery, except for Stage MS, which was managed with observation alone, with neoadjuvant chemotherapy reserved for those with life-threatening symptoms. Intermediate-risk NB treatment included neoadjuvant chemotherapy followed by surgery and, if required, adjuvant chemotherapy. High-risk NB (HR-NB) management included induction chemotherapy followed by surgery, high-dose chemotherapy with autologous stem cell rescue (HDCT/ASCR), radiotherapy, and maintenance therapy (anti-GD2 immunotherapy and/or cis-retinoic acid). Chemotherapy regimens followed in different centers were noted, but details of drug doses and schedules were not collected. Follow-up data were collected prospectively until August 31, 2025, to analyze survival outcomes.

Barriers to optimal treatment were quantified as the proportion of children who did not receive intended standards of care. Diagnostic barriers included *MYCN* testing, appropriate staging, and risk stratification. Therapeutic barriers included treatment refusal/abandonment and absence of HDCT/ASCR and anti-GD2 immunotherapy for HR-NB.

Univariate analysis, including measures of central tendency, frequency distribution, and dispersion, was employed to interpret cohort characteristics. For event-free survival (EFS), time to event was calculated from the date of diagnosis to the first occurrence of relapse, progressive disease, or death from any cause; patients who were lost to follow-up or abandoned treatment were censored at the date of last contact. Similarly, for overall survival (OS) analysis, survival was calculated from the date of diagnosis to the date of death from any cause, or to the last follow-up, and patients who were lost to follow-up were considered as censored. Median follow-up was calculated using the reverse Kaplan–Meier method. EFS and OS were estimated using the Kaplan–Meier (KM) method, with survival probabilities presented at 3 years along with 95% confidence intervals. The log-rank test was used to compare EFS and OS rates across subgroups, including age groups (≤18 vs. >18 months), primary site, INRG stage, lactate dehydrogenase (LDH) levels, ferritin levels, *MYCN* amplification status, and risk group. Log-rank test with a *p*-value less than 0.05 was considered statistically significant.

3 | Results

A total of 320 children were registered in the InPOG-NB-18-01 study.

3.1 | Clinical Profile

Median age at diagnosis was 29 months (interquartile range [IQR]: 14–55 months), with 80.6% of children being under 5 years of age. Three children were diagnosed in the neonatal period. Male predominance was observed (male:female ratio = 1.36:1). The adrenal gland (63.8%) was the most common primary site. Over half of the cohort (52.5%) was stratified as high risk based on the presence of Stage M in children above 547 days and/or *MYCN* amplification. Opsoclonus–myoclonus–ataxia syndrome (OMAS) was present in 21 children (6.6%), of whom 19/21 (90.5%) had localized or locoregional disease. Spinal cord compression (SCC) was seen in 20 (6.25%), of whom 11 (55%) had metastatic disease. The clinical profile of this cohort is summarized in Table 1.

TABLE 1 | Descriptive statistics of the cohort ($n = 320$).

Patients' characteristics	*n* (%)
Age	
≤18 months (547 days)	110 (34.4%)
18 months to 4 years	148 (46.2%)
5–9 years	47 (14.7%)
>10 years	15 (4.7%)
Gender	
Male	184 (57.5%)
Female	136 (42.5%)
Primary site[a]	
Adrenal—upper abdomen	204 (63.8%)
Cervical paraspinal	12 (3.8%)
Thoracic paraspinal	35 (10.9%)
Pelvic—mid/lower abdomen	62 (19.4%)
Brain	3 (0.9%)
Skull	3 (0.9%)
Orbit	1 (0.3%)
INRG staging	
L1	39 (12.2%)
L2	89 (27.8%)
M	175 (54.7%)
MS	17 (5.3%)
INRG risk group	
Very low risk	48 (15%)
Low risk	29 (9%)
Intermediate risk	47 (14.7%)
High risk	168 (52.5%)
Not assigned	28 (8.8%)

[a]As reported, but probably represents metastatic sites from an occult primary.

3.2 | Diagnostic Profile

Screening ultrasonography was performed in 178 children (55.6%). Cross-sectional imaging was performed in 252 (78.75%) children, the modality being CT (computed tomography) scan in 210 (65.6%), MRI (magnetic resonance imaging) in 30 (9.4%), and both in 12 (3.8%) children. Nuclear imaging for staging was performed in 193 children (60.3%), with ^{18}F-FDG PET/CT ([fluorine-18]fluorodeoxyglucose positron emission tomography/computed tomography) ($n = 163$, 50.9%) being the most common modality, followed by I-131 MIBG (metaiodobenzylguanidine) ($n = 14$, 4.4%), with 16 (5%) children undergoing both. Due to the lack of commercial availability of I-123 MIBG in India, I-131 MIBG is used for the staging evaluation of NB.

Urinary vanillylmandelic acid (VMA) testing was performed in 105 (32.8%) children and was abnormal in 64 (61%) of those tested. *MYCN* amplification was tested for in 232 (72.5%) and found to be amplified in 63 (27.2%) of those tested. Pathology was classified as unfavorable in 191 (59.7%), favorable in 102 (31.9%), and not defined in 27 (8.4%). Among those in whom *MYCN* amplification was tested, 139 also had LDH/ferritin tested, which was found to be strongly associated with *MYCN* amplification on chi-square analysis ($p < 0.001$). A subset of children in whom *MYCN* amplification was not tested, *and* who were not Stage M with age greater than 18 months, had unknown risk status ($n = 28$). Of these, while serum LDH or ferritin testing could identify high-risk NB (HR-NB), only 17/28 children were tested, of whom 11/17 had elevated LDH and/or ferritin, none of whom were treated as HR-NB. The detailed diagnostic and treatment profile of our cohort is given in Table 2.

3.3 | Treatment Profile

For low-risk NB, surgery was the primary modality of treatment. Chemotherapy was reserved for life-threatening symptoms. Chemotherapy protocols used included the SIOPEN LINES protocol in 85.7% ($n = 12$) of the centers, that is, a combination of carboplatin and etoposide, and the CCG-3891 protocol ($n = 2$). The intermediate-risk NB were treated on a variety of protocols that included COG (Children's Oncology Group) ANBL0531 ($n = 10$), SIOPEN LINES ($n = 4$), and CCG3891 protocol ($n = 2$). Two centers used more than one protocol based on the physicians' discretion. The most common protocol used for high-risk neuroblastoma in the majority of the participating centers was the HR-NBL1-SIOPEN protocol ($n = 13$, 93%). One center used the CCG3891 protocol in the majority of their patients (~90%).

Among 39 children with INRG L1 stage disease, 35 (89.75%) were classified as very low-risk NB, three (7.7%) were classified as HR-NB due to *MYCN* amplification, and one could not be assigned a risk group. Among the HR-NB, two underwent primary surgical resection, and one received only chemotherapy; none underwent HDCT/ASCR. Out of the remainder (36), 28 (77.8%) underwent primary surgical resection (gross-total = 27; subtotal = 1). Three

TABLE 2 | Diagnostic and treatment characteristics of the cohort (n = 320).

Patients' characteristics	*n* (%)
VMA	
Normal	41 (12.8%)
Abnormal	64 (20%)
Missing	215 (67.2%)
LDH[a]	
<750 IU/L	124 (38.75%)
≥750 IU/L	63 (19.69%)
Missing	133 (41.56%)
Ferritin[a]	
<120 ng/mL	42 (13.1%)
≥120 ng/mL	71 (22.2%)
Missing	207 (64.7%)
MYCN status	
Not amplified	169 (52.8%)
Amplified	63 (19.7%)
Missing	88 (27.5%)
Imaging	
USG	178 (55.6%)
CT scan	222 (69.4%)
MRI	42 (13.1%)
^{18}F-FDG PET/CT	179 (55.9%)
MIBG	30 (9.4%)
Pathology	
Favorable	102 (31.9%)
Unfavorable	191 (59.7%)
Missing	27 (8.4%)
Primary surgery	
Biopsy	241 (75.3%)
Subtotal resection	15 (4.7%)
Gross total resection	64 (20%)

Note: A total of 96 out of 241 (39.8%) children who underwent biopsy as primary surgery were subject to delayed resection of the tumor: 5/79 (6.3%) children who underwent upfront tumor resection and 5/96 (5.2%) who underwent delayed tumor resection were subject to second-look surgeries.

Abbreviations: ^{18}F-FDG PET, [fluorine-18]fluorodeoxyglucose positron emission tomography; CT, computed tomography; VMA, vanillylmandelic acid.

[a]Threshold values for LDH (≥750 IU/L) and ferritin (≥120 ng/mL) were defined using the SIOP-PODC Adapted Risk Stratification and Treatment Guidelines: Recommendations for Neuroblastoma in Low- and Middle-Income Settings [17].

among the 28 received adjuvant chemotherapy. Among the eight who did not undergo upfront resection, one received neoadjuvant chemotherapy followed by surgery, five received chemotherapy only, and three were on expectant management.

Among 89 children with L2 disease, 29 (32.6%) were classified as low risk, 39 (43.8%) as intermediate risk, and five (5.6%) as high risk (due to MYC-N amplification), while 16 (18%) children could not be risk-stratified. Overall, 76 (85.4%) received chemotherapy. Upfront resection was performed in 26 children (29.2%), followed by adjuvant chemotherapy in 17. The majority of children (N = 59) received neoadjuvant chemotherapy, with 40 undergoing delayed resection. One out of five children with high-risk L2 disease underwent HDCT/ASCR.

Metastatic disease was present in 175 (54.7%) children, of whom 159 (90.8%) were classified as high risk, eight (4.6%) as intermediate risk, and the remainder could not be risk-stratified. In the metastatic HR-NB cohort, 54 children (34%) underwent HDCT/ASCR. Cis-retinoic acid was used as maintenance therapy in all patients, whereas anti-GD2 immunotherapy was administered to one patient.

Among 17 children with INRG Stage MS, 12 (70.6%) were classified as very low risk, one (5.9%) was high risk, and four (23.5%) could not be assigned a risk group. Twelve (70.6%) received chemotherapy, two (11.8%) received radiotherapy in addition to chemotherapy, and five (29.4%) were observed.

Out of a total of 168 children identified to have HR-NB (across all stages of the disease), 57 children were ineligible for HDCT/ASCR due to treatment abandonment (12), opting for palliative therapy upfront (8), and due to progressive/refractory disease (37). Of the remainder (111), only 55 (50%) underwent HDCT/ASCR, and one (0.9%) underwent immunotherapy.

3.4 | Outcomes

Of 21 children with OMAS, 17 (81%) children survived. While one child with L2 disease relapsed, two children with metastatic disease and one child with complications secondary to SCC succumbed. Of 20 children with SCC, 14 (70%) survived. Five children with metastatic disease had relapse (1), progressive disease (2), and refractory disease (2), while one succumbed to complications associated with SCC.

Median follow-up duration using the reverse KM method was 38 months (IQR: 17–60). The 3-year overall survival (OS) and event-free survival (EFS) for the entire cohort was 60% (54.1%–66.5%) and 50.2% (44.4%–56.7%), respectively. The 3-year OS for INRG stages L1, L2, M, and MS was 100%, 76.4% (67.2%–86.8%), 41.5% (33.7%–51.1%), and 72.8% (53.1%–99.8%), respectively. The corresponding 3-year EFS was 96.4% (89.8%–100%), 72.4% (63%–83.1%), 28.6% (22%–37.2%), and 58.7% (34.3%–100%). Kaplan–Meier curves for the cohort are given in Figure 1. The 3-year EFS and OS of the HR-NB cohort were 27.4% (20.8%–36.2%) and 40.3% (32.4%–50.2%), respectively. Excluding children who were ineligible for HDCT/ASCR, the survival of those who underwent transplant versus those who did not were 3-year EFS 44.8% (32.8%–61.2%) versus 29.7% (18.7%–47.1%) (p = 0.43), respectively, and 3-year OS 57.6% (44.8%–74%) versus 46.6% (33.5%–64.9%) (p = 0.54), respectively (Figure S1). There was no difference in the rate of relapses (52.7% vs. 46.4%, p = 0.5) and non-relapse mortality (9% vs. 16%, p = 0.27) between the two groups.

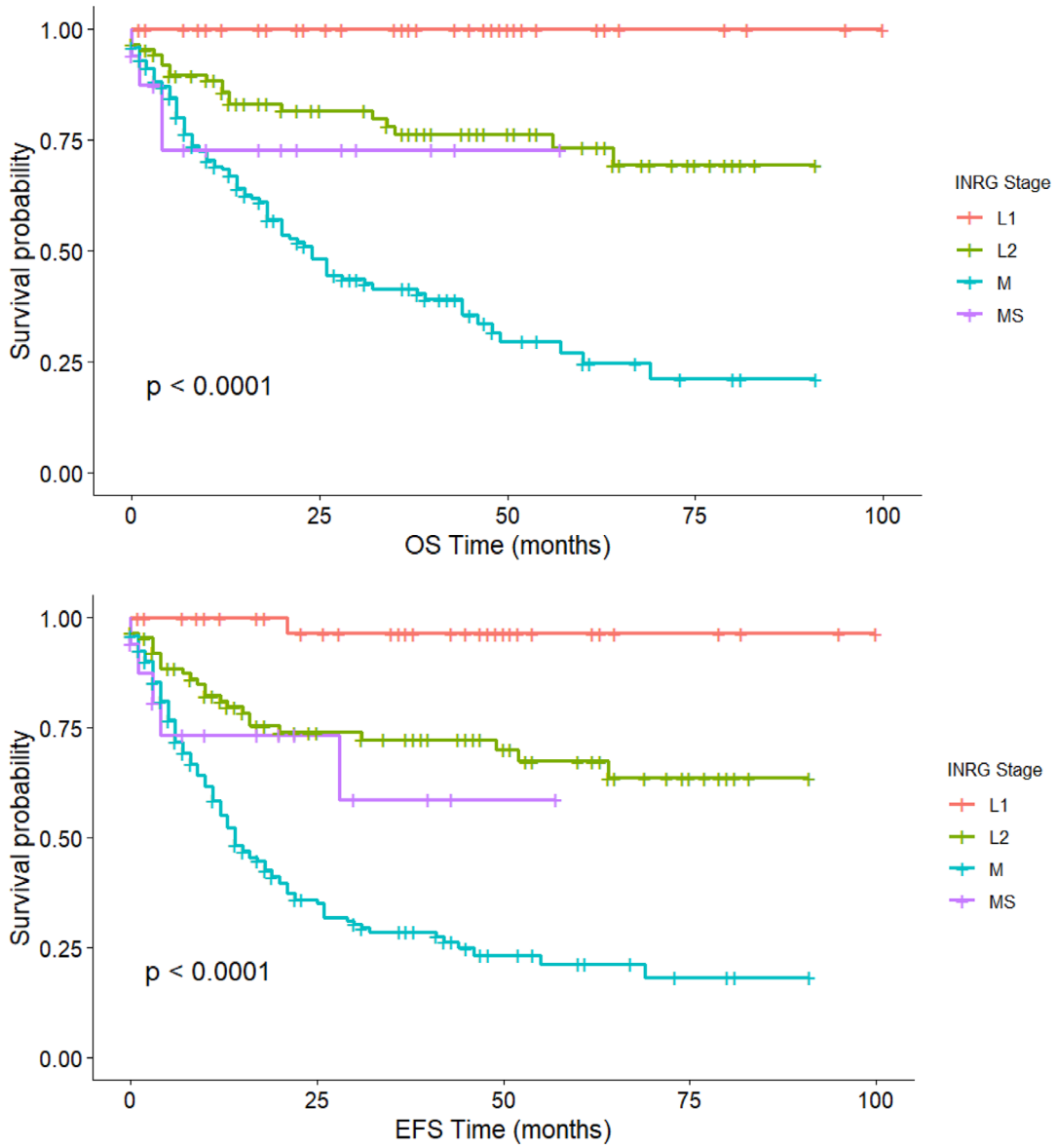

FIGURE 1 | Overall survival (OS) and event-free survival (EFS) of the cohort based on International Neuroblastoma Risk Group (INRG) staging.

3.5 | Prognostic Factors

Children aged more than 18 months had worse survival compared with those aged ≤18 months ($p < 0.001$), with 3-year OS of 54.1% versus 71.8% and 3-year EFS of 42.3% versus 66.7%. Using the INRG staging system, patients with Stage M disease had the worst survival ($p < 0.001$). The 3-year OS was 41.5%, and EFS was 28.6%. Survival outcomes differed significantly by INRG risk group ($p < 0.001$), with those classified as very low/low risk having excellent outcomes (3-year OS: 97.2%; EFS: 93.3%), whereas those in the high-risk group had worse survival (OS: 40.3%; EFS: 27.4%). Patients with *MYCN*-amplified tumors, ferritin levels ≥120 ng/mL, and LDH levels ≥750 U/L had significantly lower EFS compared with those without amplification ($p < 0.001$), lower ferritin levels ($p = 0.04$), and lower LDH levels ($p < 0.001$), respectively. No significant differences in survival were observed between adrenal and extra-adrenal primary sites for either OS or EFS. Survival based on patient and disease characteristics is summarized in Table 3.

3.6 | Barriers to Optimal Treatment

Barriers to treatment identified in our analysis are shown in Figure 2. More than three-fourth presented with advanced (i.e., locoregional or metastatic) disease. Less than two-third had nuclear imaging for staging, and 8.8% ($n = 28$) could not be assigned a risk group due to inadequate diagnostic data. Among the 168 (52.5%) patients classified as high-risk NB, only a third received HDCT/ASCR, and less than 1% received anti-GD2 immunotherapy. Seventeen (5.3%) children abandoned therapy either at diagnosis or before treatment completion (12 in HR-NB group).

TABLE 3 | Three-year OS and EFS according to patient and disease characteristics.

		3-year OS (95% CI)		3-year EFS (95% CI)	
Overall cohort	**n**	**60 (54.1–66.5)**	***p*-value***	**50.2 (44.4–56.7)**	***p*-value***
Age					
≤18 months (547 days)	110	71.8 (62.8–82.1)	**<0.01**	66.7 (57.5–77.5)	**<0.001**
>18 months	210	54.1 (46.8–62.5)		42.3 (35.5–50.4)	
Site					
Adrenal	204	59 (51.4–67.6)	0.42	47.3 (40.1–55.8)	0.19
Extra-adrenal	116	61.2 (52.2–71.8)		54.5 (45.6–65.2)	
Gender					
Female	136	59.7 (51.2–69.7)	0.89	52.4 (44.1–62.3)	0.63
Male	184	60.1 (52.2–69)		48.3 (40.7–57.3)	
INRG staging**					
L1	39	100	**<0.001**	96.4 (89.8–100)	**<0.001**
L2	89	76.4 (67.2–86.8)		72.4 (63–83.1)	
M	175	41.5 (33.7–51.1)		28.6 (22–37.2)	
MS	17	72.8 (53.1–99.8)		58.7 (34.3–100)	
INRG risk group**					
Very low risk/Low risk	77	97.2 (93.5–100)	**<0.001**	93.3 (87.1–100)	**<0.001**
Intermediate risk	47	75.4 (62.3–91.2)		74.9 (62.4–89.9)	
High risk	168	40.3 (32.4–50.2)		27.4 (20.8–36.2)	
MYCN status					
Not amplified	169	74.5 (67.5–82.3)	**<0.001**	67.5 (60.1–75.7)	**<0.001**
Amplified	63	41.3 (29.3–58.1)		34.4 (23.7–49.9)	
Unknown	88	40.9 (29.2–57.2)		24.5 (15.5–38.5)	
Ferritin level					
<120	42	65.2 (51.3–82.8)	0.05	54 (39.7–73.5)	**0.04**
≥120	71	40.2 (28.6–56.6)		34.5 (24.2–49.3)	
LDH level					
<750	124	68.6 (59.7–78.7)	**<0.001**	57.6 (48.6–68.2)	**<0.001**
≥750	63	33.2 (21.4–51.4)		20.6 (12.1–34.9)	

Note: *Survival distributions were compared using the log-rank test, and corresponding *p*-values are shown. **Survival estimates for some categories should be interpreted cautiously, as these subgroups included small numbers of patients, resulting in wide confidence intervals.

Abbreviations: CI, confidence interval; EFS, event-free survival; INRG, International Neuroblastoma Risk Group; LDH, lactate dehydrogenase; OS, overall survival.

4 | Discussion

The cure rates for neuroblastoma (NB) in India in published literature have been consistently lower compared to data from HIC [1, 6–8]. The challenges of limited diagnostic facilities, delayed diagnosis, socioeconomic constraints, treatment-related factors, and abandonment have been previously documented. A literature review by Kulkarni and Marwaha over a decade ago emphasized the predominance of advanced stage at presentation in their analysis of studies across India, as well as a high proportion of upfront refusal for treatment (18.7%) and subsequent abandonment (21.3%) [14]. A single-center hospital database review of pediatric solid tumors from Western India identified 389 children under 15 years with NB presenting over a 5-year period (2012–2016), with a mean age of 3.9 years, a male-to-female ratio of 2:1, with 72.5% children under 5 years, an age distribution similar to our study, but there was no separate outcome analysis for NB [15]. Similarly, a single-center review from South India looked at 85 patients, which showed the same pattern of advanced disease at presentation and overall poor outcome [8].

The various challenges of tumor-related, treatment-related, and social factors, including inaccurate diagnosis and resource limitations in LMICs, have been extensively narrated by van Heerden and colleagues [16]. The InPOG-NB-18-01 India neuroblastoma registration and biology study was initially designed to capture registration and follow-up data with accurate risk stratification

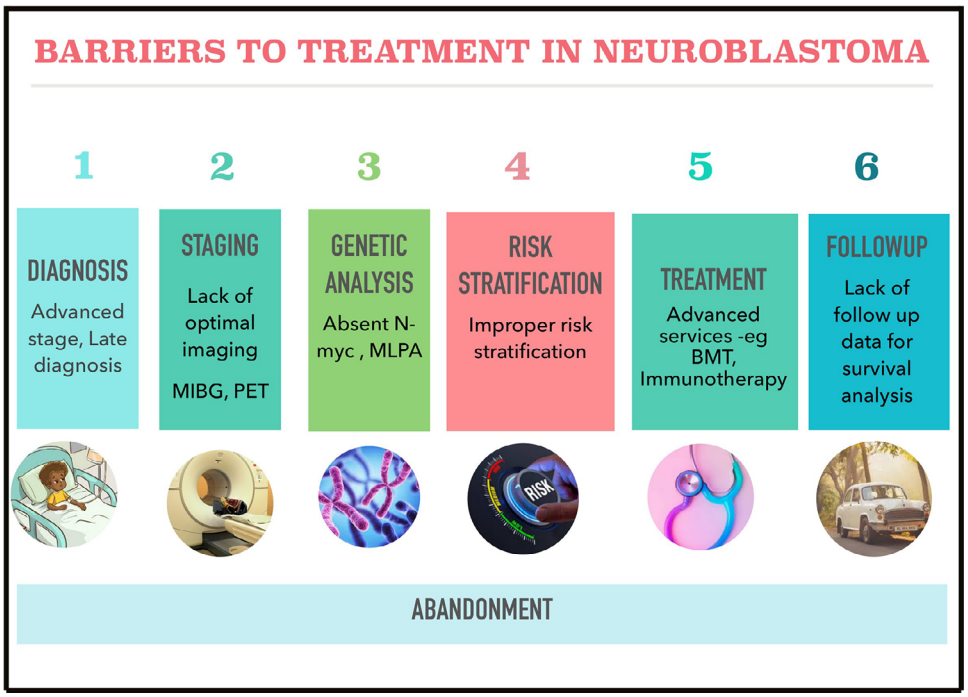

FIGURE 2 | Barriers to treatment in neuroblastoma.

using genomic analysis with next-generation sequencing, pathology review, *MYCN* amplification, and 11q23 status [9, 10]. This ambitious multicenter study was planned to look at a model of diverse stakeholder involvement to advance childhood cancer care and research in the field of NB in India. The study faced barriers in specimen accrual, such as transport delay, quality of samples sent to the central laboratory, and after several months, only four samples could be analyzed. Due to these issues, the study was closed and amended to the current retrospective analysis that aims to describe the treatment and outcomes of NB and identify barriers to better survival in Indian children [11]. The study population was well distributed throughout India. Among the 14 centers, 42.8%, 42.8%, 7.2%, and 7.2% were from the north, south, west, and east of the country, respectively, which gave us a reasonably diverse perspective from across the entire country.

The value of serum LDH and ferritin has been well recognized in risk-stratifying children with neuroblastoma for a long time [17, 18]. It is also well known that using genomic tools in LMIC is often difficult, and an adapted INRG classification primarily using serum LDH and ferritin levels may be more appropriate in this setting. We performed our analysis using MYC-N amplification and/or an age cutoff of greater than 18 months for Stage M to categorize as HR-NB. Ferritin values of ≥120 ng/mL and LDH ≥750 U/L were found to be strongly correlated with HR-NB in the cohort. A more recent analysis of children with NB less than 21 years of age studied a total of 14,501 children from the INRG Data Commons diagnosed between 1990 and 2014 from Children's Oncology Group, International Society of Paediatric Oncology European Neuroblastoma Research Network, German Pediatric Oncology and Hematology Group, and Japan Children's Cancer Group confirmed that LDH ≥1400 IU/L, and serum ferritin ≥30 ng/mL would be more optimal cutoffs as previously proposed by Moroz and colleagues [19].

Only a minority of patients underwent testing for urinary catecholamines, presumably because the diagnosis was often evident (especially in patients with metastatic disease, 32.8% of the total), and it would not impact risk stratification [17, 20]. Despite resource constraints, 72.5% of the patients in our cohort underwent *MYCN* amplification testing. It raises the question as to whether efforts should still be made to perform this testing uniformly at specialty centers or whether a more simplified staging system should be adopted, as discussed previously. Imaging studies were primarily ultrasound, CT scan, and/or ^{18}F-FDG PET/CT scan. In common with many other studies, MIBG staging was used in a minority of patients (9.9%) [14, 15]. Whether ^{18}F-FDG PET/CT adequately stages metastatic NB is also a question that still remains unanswered, but is worthy of further study [21]. An age cutoff of 18 months (547 days) at diagnosis was used, as age is a powerful predictive factor, but there are data that for metastatic disease in NB, 12 months (365 days) may be a more appropriate cutoff if genomic data are not available [22]. Given the delay in diagnosis that often occurs in LMIC, Chantada and colleagues have also questioned how age cutoffs should be considered in an LMIC setting in determining risk category for pediatric solid tumors [23].

While the outcomes for L1 and L2 neuroblastoma in this cohort are comparable to those reported in HIC, outcomes for metastatic disease were inferior and comparable to other Indian studies, even in patients with HR-NB who received HDCT/ASCR [6–8, 14, 24, 25]. In our cohort, survival outcomes of patients with HR-NB who underwent HDCT/ASCR were not statistically improved compared to those who did not, confirming that anti-GD2 immunotherapy plays a critical role in this group [26]. Barriers to optimal outcomes identified included lack of proper staging and risk stratification, and inadequacies in the treatment modalities employed, reflecting limitations in access to treatment and financial coverage. A survey to evaluate global inequities

in access to anti-GD2 immunotherapy for HR-NB revealed that only 21% of LMIC centers had access, as opposed to 93% in HIC, and this was attributed to drug non-availability and financial constraints. Cost analysis showed a full treatment course of anti-GD2 immunotherapy would cost $142,695–$610,800, depending on the product [27, 28]. Overall, LMICs such as India face challenges with most clinical trials beyond basic registration studies, which constitutes an additional barrier. Van Heerden and colleagues reviewed the landscape of clinical trials for NB in LMIC, in which only six of 138 (4.3%) of LMIC in 2020 participated in NB trials [29].

5 | Strengths and Limitations

Limitations of the study include the retrospective design, though follow-up data were prospectively collected, and heterogeneity in diagnostic modalities and treatment protocols used across centers, and incomplete data on disease biology, leading to potential inaccuracies in staging and outcome analysis. Despite these limitations, this study is the first large-scale multi-institutional study from India that captured real-world data from diverse geographic locations and settings, such as government, private, and academic institutions. This study also identified healthcare gaps, such as access to optimal diagnostic facilities and therapies such as HDCT/ASCR and anti-GD2 immunotherapy, that contribute to poor outcomes in HR-NB, and this information can be incorporated into national advocacy efforts and health policies.

6 | Conclusion

In conclusion, our study expands and builds on previously published data from India on childhood NB risk categories and outcomes. Optimizing risk stratification of children with NB in India, improving access to specialized centers for therapy that can administer HDCT/ASCR, and reducing the crushing financial burden associated with anti-GD2 immunotherapy could impact outcomes of this challenging disease. We are currently looking at participating in a future pilot study to apply ACNRG (Adaptive Clinical Neuroblastoma Risk Groups) criteria to risk-stratify NB patients, and we are cautiously optimistic that despite past challenges, this will let us implement meaningful prospective therapeutic studies for NB in India under the aegis of INPHOG.

Acknowledgments

The authors extend their gratitude to the INPHOG neuroblastoma subcommittee members and study protocol reviewers for their guidance in conducting this registry study.

Ethics Statement

This study was designed by a committee of pediatric oncologists from across India, peer-reviewed nationally and internationally, and registered with the Indian Pediatric Hematology Oncology Group (INPHOG). Fourteen institutions across India participated, including four academic, seven private, one government, and two charitable institutions, each with Institutional Ethics Committee approval. The study was also registered with the Clinical Trials Registry—India (No. CTRI/2020/01/023088).

No written consent has been obtained from the patients, as this retrospective, multi-institutional registry study includes no patient-identifiable data.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. J. Van Heerden, N. Abraham, J. Schoeman, D. Reynders, E. Singh, and M. Kruger, "Reporting Incidences of Neuroblastoma in Various Resource Settings," *JCO Global Oncology* 7 (2021): 947–964.

2. P. Yan, F. Qi, L. Bian, et al., "Comparison of Incidence and Outcomes of Neuroblastoma in Children, Adolescents, and Adults in the United States: a Surveillance, Epidemiology, and End Results (SEER) Program Population Study," *Medical Science Monitor* 26 (2020): e927218.

3. R. Swaminathan, R. Rama, and V. Shanta, "Childhood Cancers in Chennai, India, 1990–2001: Incidence and Survival," *International Journal of Cancer* 122, no. 11 (2008): 2607–2611.

4. R. S. Arora, T. O. Eden, and G. Kapoor, "Epidemiology of Childhood Cancer in India," *Indian Journal of Cancer* 46, no. 4 (2009): 264.

5. ICMR – NCDIR, "Cancers in childhood. Clinicopathological Profile of Cancers in India: A Report of the Hospital Based Cancer Registries," ICMR – NINE, 2021, https://ncdirindia.org/All_Reports/HBCR_2021/Default.aspx.

6. S. Agarwala, A. Mandelia, S. Bakhshi, et al., "Neuroblastoma: Outcome Over a 14 Year Period From a Tertiary Care Referral Centre in India," *Journal of Pediatric Surgery* 49, no. 8 (2014): 1280–1285.

7. D. Bansal, R. K. Marwaha, A. Trehan, et al., "Profile and Outcome of Neuroblastoma With Conventional Chemotherapy in Children Older Than One Year: a 15-Years Experience," *Indian Pediatrics* 45, no. 2 (2008): 135–139.

8. V. Radhakrishnan, A. Raja, M. Dhanushkodi, T. S. Ganesan, G. Selvaluxmy, and T. G. Sagar, "Real World Experience of Treating Neuroblastoma: Experience From a Tertiary Cancer Centre in India," *Indian Journal of Pediatrics* 86, no. 5 (2019): 417–426.

9. V. S. Kanwar, A. Bhattacharya, G. Chinnaswamy, et al., "Indian Neuroblastoma Registration and Biology Study InPOG NB18-01 a Model of Diverse Stakeholder Involvement to Advance Childhood Cancer and Research in India," *Pediatric Hematology Oncology Journal* 4, no. 2 (2019): S7.

10. V. S. Kanwar and R. S. Arora, "Neuroblastoma in India: Closing the Gap," *Indian Journal of Medical and Paediatric Oncology* 43, no. 03 (2022): 294–295.

11. V. Kanwar, R. Arora, and A. Bhattacharyya, "INPOG-NB-18-01: Retrospective Survey of "Real World" Outcomes of Pediatric Neuroblastoma in India," *Pediatric Blood & Cancer* 70 (2023): S304.

12. R. S. Arora, R. Raj, A. Mahajan, N. Radhakrishnan, G. Chinnaswamy, and S. Banavali, "Collaborative Cancer Research: Progress Report From the Indian Pediatric Oncology Group," *Lancet Child & Adolescent Health* 5, no. 4 (2021): 239–240.

13. S. L. Cohn, A. D. Pearson, W. B. London, et al., "The International Neuroblastoma Risk Group (INRG) Classification System: an INRG Task Force Report," *Journal of Clinical Oncology* 27, no. 2 (2009): 289–297.

14. K. P. Kulkarni and R. K. Marwaha, "Outcome of Neuroblastoma in India," *Indian Journal of Pediatrics* 80, no. 10 (2013): 832–837, https://doi.org/10.1007/s12098-012-0948-9.

15. S. S. Qureshi, M. G. Bhagat, S. A. Kembhavi, et al., "A Cross-sectional Study of the Distribution of Pediatric Solid Tumors at an Indian Tertiary Cancer Center," *Indian Journal of Cancer* 55, no. 1 (2018): 55–60.

16. J. van Heerden and M. Kruger, "Management of Neuroblastoma in Limited-resource Settings," *World Journal of Clinical Oncology* 11, no. 8 (2020): 629–643.

17. N. S. Parikh, S. C. Howard, G. Chantada, et al., "SIOP-PODC Adapted Risk Stratification and Treatment Guidelines: Recommendations for Neuroblastoma in Low- and Middle-Income Settings," *Pediatric Blood & Cancer* 62 (2015): 1305–1316.

18. V. Moroz, D. Machin, B. Hero, et al., "The Prognostic Strength of Serum LDH and Serum Ferritin in Children With Neuroblastoma: a Report From the International Neuroblastoma Risk Group (INRG) Project," *Pediatric Blood & Cancer* 67 (2020): e28359.

19. W. B. London, G. Villanueva, D. Shyr, et al., "Adaptive Clinical Neuroblastoma Risk Groups—Tailoring Treatment in Low-and Middle-Income Countries: an International Neuroblastoma Risk Group Project," *JCO Global Oncology* 11 (2025): e2500349.

20. D. Bansal, S. Totadri, and G. Chinnaswamy, "Management of Neuroblastoma: ICMR Consensus Document," *Indian Journal of Pediatrics* 84, no. 6: 446–455.

21. L. Feng, S. Li, C. Wang, and J. Yang, "Current Status and Future Perspective on Molecular Imaging and Treatment of Neuroblastoma," *Seminars in Nuclear Medicine* 53, no. 4 (2023): 517–529.

22. M. S. Irwin, A. Naranjo, F. F. Zhang, et al., "Revised Neuroblastoma Risk Classification System: a Report From the Children's Oncology Group," *Journal of Clinical Oncology* 39 (2021): 3229–3241.

23. G. Chantada, A. Fandiño, J. Manzitti, et al., "Late Diagnosis of Retinoblastoma in a Developing Country," *Archives of Disease in Childhood* 80 (1999): 171–174.

24. K. Venkatakrishnan, P. Srinivasan, G. Das, et al., "Autologous Stem Cell Transplantation for High-Risk Neuroblastoma—A Real-World Evidence From a Tertiary Cancer Care Center in Southern India," *Indian Journal of Hematology & Blood Transfusion* 42, no. 2 (2026): 386–394.

25. R. Jain, R. Hans, S. Totadri, et al., "Autologous Stem Cell Transplant for High-Risk Neuroblastoma: Achieving Cure With Low-Cost Adaptations," *Pediatric Blood & Cancer* 67, no. 6 (2020): e28273.

26. B. H. Kushner, I. Ostrovnaya, I. Y. Cheung, et al., "Lack of Survival Advantage With Autologous Stem-cell Transplantation in High-Risk Neuroblastoma Consolidated by Anti-GD2 Immunotherapy and Isotretinoin," *Oncotarget* 7, no. 4 (2016): 4155–4166.

27. N. Roy Moulik, C. Dhamne, and R. S. Arora, "Immunotherapy in Pediatric Oncology in India: a Nationwide Survey Assessing Practices, Perceptions, and Barriers among Pediatric Oncologists," *Indian Pediatrics* 63, no. 4 (2026): 301–302.

28. R. Papyan, J. Hoveyan, M. Guscott, et al., "The Price of Survival: Global Inequities in Anti-GD2 Immunotherapy for Neuroblastoma," *Pediatric Blood & Cancer* 73, no. 4 (2026): e70152.

29. J. Van Heerden, M. Kruger, T. M. Esterhuizen, and W. Pinxten, "Neuroblastoma: the Basis for Cure in Limited-resource Settings," *Pediatric Blood & Cancer* 68, no. 7 (2021): e28923.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information: pbc70431-sup-0001-figureS1.docx