# Adaptive Clinical Neuroblastoma Risk Groups—Tailoring Treatment in Low- and Middle-Income Countries: An International Neuroblastoma Risk Group Project

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## ABSTRACT

**PURPOSE** Risk/treatment stratification for children with neuroblastoma (NB) relies on clinical, histologic, and genomic factors. However, most children with cancer live in low- and middle-income countries (LMIC), where access to advanced methods for stratification is limited. To address this unmet need, we developed a novel risk/treatment classification, the Adaptive Clinical Neuroblastoma Risk Groups (ACNRG) using clinical prognostic biomarkers.

**PATIENTS AND METHODS** A survival tree regression analysis of the International Neuroblastoma Risk Group (INRG) Data Commons (N = 14,501, diagnosed 1990-2014) was performed using univariate Cox regression models (age, International Neuroblastoma Staging System, serum lactate dehydrogenase [LDH], and serum ferritin) of event-free survival (EFS), separately for test and validation sets. Within each terminal node of the survival tree, the proportion of patients by initial treatment assignment and outcome achieved on that treatment were used to subjectively assign risk/treatment intensity (low-, intermediate-, and high-risk). For additional validation, the ACNRG was descriptively compared with INRG classification. Guidelines were developed for determining INRGs Staging System (INRGSS) in LMIC, using the minimum essential versus optimal imaging/biopsy procedures.

**RESULTS** Twelve statistically, clinically significant unique pretreatment risk groups of INRGSS/age/LDH/ferritin were identified (5-year EFS): low—L1/any/any/any (92% ± 0.5%); intermediate—L2/<18 months/<1,400/any (88% ± 1%), MS/any/<1,400/any (86% ± 1.5%), M/<12 months/<1,400/any (76% ± 2.3%); intermediate/high—L2/<18 months/≥1,400/any (73% ± 4.7%), L2/≥18 months/<1,400/<30 (68% ± 3.4%), L2/≥18 months/<1,400/≥30 (59% ± 3.7%), MS/any/≥1,400/any (52% ± 6.3%); high—L2/≥18 months/≥1,400/any (46% ± 4.7%), M/12-18 months/<1,400/any (64% ± 4.1%), M/<18 months/≥1,400/any (60% ± 1.6%), M/≥18 months/any/any (28% ± 0.8%). The concordance and discordance rates of ACNRG versus INRG were 86.6% and 13.4%, respectively (n = 8,152 nonmissing-data intersection).

**CONCLUSION** The ACNRG classification, using easily obtained clinical markers, is highly prognostic. The ACNRG could transform risk and treatment stratification, improve accuracy of treatment intensity decisions, and potentially improve outcome, for the large number of children with NB in LMIC. Prospective validation of the ACNRG classification is planned in a pilot trial.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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## INTRODUCTION

For over 3 decades, determination of treatment intensity for patients newly diagnosed with neuroblastoma (NB) has been based on factors prognostic of poor outcome.[1-4] In high-income countries, low-risk patients typically undergo surgery and observation, intermediate-risk patients receive chemotherapy and surgery, and high-risk patients receive

## CONTEXT

**Key Objective**

Is it possible to create a novel, data-driven risk/treatment stratification (low-, intermediate-, and high-risk) for children newly diagnosed with neuroblastoma (NB), using only clinical (not resource-intensive genomic or pathologic) biomarkers at diagnosis, to address an unmet need in low- and middle-income countries (LMIC)?

**Knowledge Generated**

Using data from 14,501 patients in the International Neuroblastoma Risk Groups (INRGs) Data Commons, the Adaptive Clinical Neuroblastoma Risk Groups (ACNRG) stratification was developed and validated, limited to *clinical* biomarkers highly prognostic of event-free survival: age, INRGs Staging System stage, serum lactate dehydrogenase, and serum ferritin. We present a user-friendly table of 12 statistically and clinically distinct biomarker-/outcome-defined risk groups. Concordance of ACNRG versus INRG stratification was 86.6%. Adaptive guidelines were developed to optimize disease staging procedures in LMIC within available resources.

**Relevance**

The novel ACNRG stratification and adaptive staging guidelines have immediate implications for more feasible and improved stratification/assignment of appropriate treatment intensity for children with NB in LMIC. Appropriate treatment intensity balances minimization of toxicity and late effects with maximum potential therapeutic benefit.



intensive multimodality therapy including surgery, myeloablative chemotherapy with stem-cell transplantation, radiation, and immunotherapy. Risk classification in high-income countries[5] is based on age, International Neuroblastoma Risk Groups (INRGs) Staging System (INRGSS),[6] *MYCN* status,[7,8] histologic category, mitosis-karyorrhexis index (MKI), grade of tumor differentiation,[2,9] ploidy, 1p aberration, 11q aberration,[10] degree of resection, and whether the patient is symptomatic.[5,11-17] The INRG classification[18] facilitates eligibility and comparison of risk-based clinical trials conducted in different regions of the world, and uses age, INRGSS, *MYCN* status, histologic category, grade of tumor differentiation, ploidy, and 11q aberration.

Ninety-percent of the world's children (approximately 2 billion) live in low- and middle-income countries (LMIC), where 56% (224,000) of the world's 397,000 children with cancer are diagnosed annually.[19-22] Suboptimal/delayed diagnosis, risk stratification, or treatment may occur because of limited resources and unavailable infrastructure.[23] Access to testing for genomic and histopathologic prognostic factors in LMIC is limited by lack of funding, technology, or expertise. Our objective was to develop a prognostic stratification for patients newly diagnosed with NB in LMIC, using lower cost and easily obtainable clinical factors, to guide treatment decisions.[24,25] Age, a powerful prognostic factor, is an evidence-based choice for risk stratification in LMIC.[26] In 1971, a 12-month cutoff discriminated younger (better outcome) from older (worse outcome) patients[27]; subsequent analyses demonstrated 547 days (18 months) as a more optimal cutoff.[28-30] INRGSS M is also highly prognostic of poor outcome[6]; with adaptation to available modalities, disease staging is feasible in LMIC.[31] Although not currently used in NB risk stratification, the prognostic ability of serum lactate dehydrogenase (LDH) and ferritin has long been known[25,32-35]; these markers can be obtained from a blood test. Per the SIOP-PODC adapted guidelines,[23] LDH and ferritin are used in South Africa to guide risk stratification and treatment.[36] The absence/presence of symptoms guides treatment in INRGSS MS.[13] Histologic category, MKI, grade of tumor differentiation, ploidy, 1p, 11q, and other segmental chromosome aberrations are more challenging and costly in LMIC, while degree of surgical resection[23] has widely variable results. Thus, these factors were not considered for a LMIC classification.

Our goal was to determine whether a risk stratification of *clinical* factors age, INRGSS stage, LDH, and ferritin, named the Adaptive Clinical Neuroblastoma Risk Groups (ACNRG), could be developed to inform decisions about treatment intensity for patients newly diagnosed with NB in LMIC.

## PATIENTS AND METHODS

A total of 14,501 children from the INRG Data Commons (INRGDC)[18] met INRG eligibility criteria: confirmed diagnosis of NB, ganglioneuroblastoma, or ganglioneuroma, maturing; age 21 years or younger at diagnosis; diagnosis between 1990 and 2014; and known event-free survival (EFS) and overall survival (OS). Data were from the Children's Oncology Group (COG; n = 9,589, 66.1%), International Society of Pediatric Oncology European Neuroblastoma Research Network (n = 2,504, 17.3%), German Pediatric Oncology and Hematology Group (n = 1,938, 13.4%), and Japan Children's Cancer Group (n = 470, 3.2%). Informed consent was obtained for trial enrollment per guidelines of each consortium. The INRGDC has approval from the University of Chicago Institutional Review Board. INRG data are publicly available.[37]

To define the minimum essential versus optimal imaging and biopsy protocols that balance diagnostic precision with resource availability in LMIC, a consensus flow diagram to determine INRGSS was developed by expert treating physicians in LMIC.

### Statistical Considerations

The primary end point was time from diagnosis until first event (relapse, progression, secondary malignancy, or death from any cause), censored on the date of last contact if no event. OS time was a secondary end point (event = death from any cause). Five-year Kaplan-Meier point estimates of EFS and OS are reported, with standard errors per Greenwood.[38,39] Age at diagnosis (<547 days, ≥547 days; <365, 365-546 days), LDH (<1,400, ≥1,400 IU/L), and serum ferritin (<30, ≥30 ng/mL; optimal cutoffs per Moroz et al[35]) were analyzed as binary variables, while International Neuroblastoma Staging System (INSS; 1, 2, 3, 4s, 4) was analyzed categorically. INSS was available in the INRGDC for most patients, while INRGSS was not. For clinical utility, INSS stage was retroactively mapped to INRGSS: 1/2a→L1, 2b/3→L2, 4s→MS, 4→M. Kaplan-Meier EFS/OS curves were generated, and comparisons made using one-sided log-rank tests.

Survival tree regression with recursive partitioning was performed using univariate Cox proportional hazards regression modeling of EFS, testing age, INSS stage, LDH, and ferritin,[40-43] including checks for proportional hazards. The



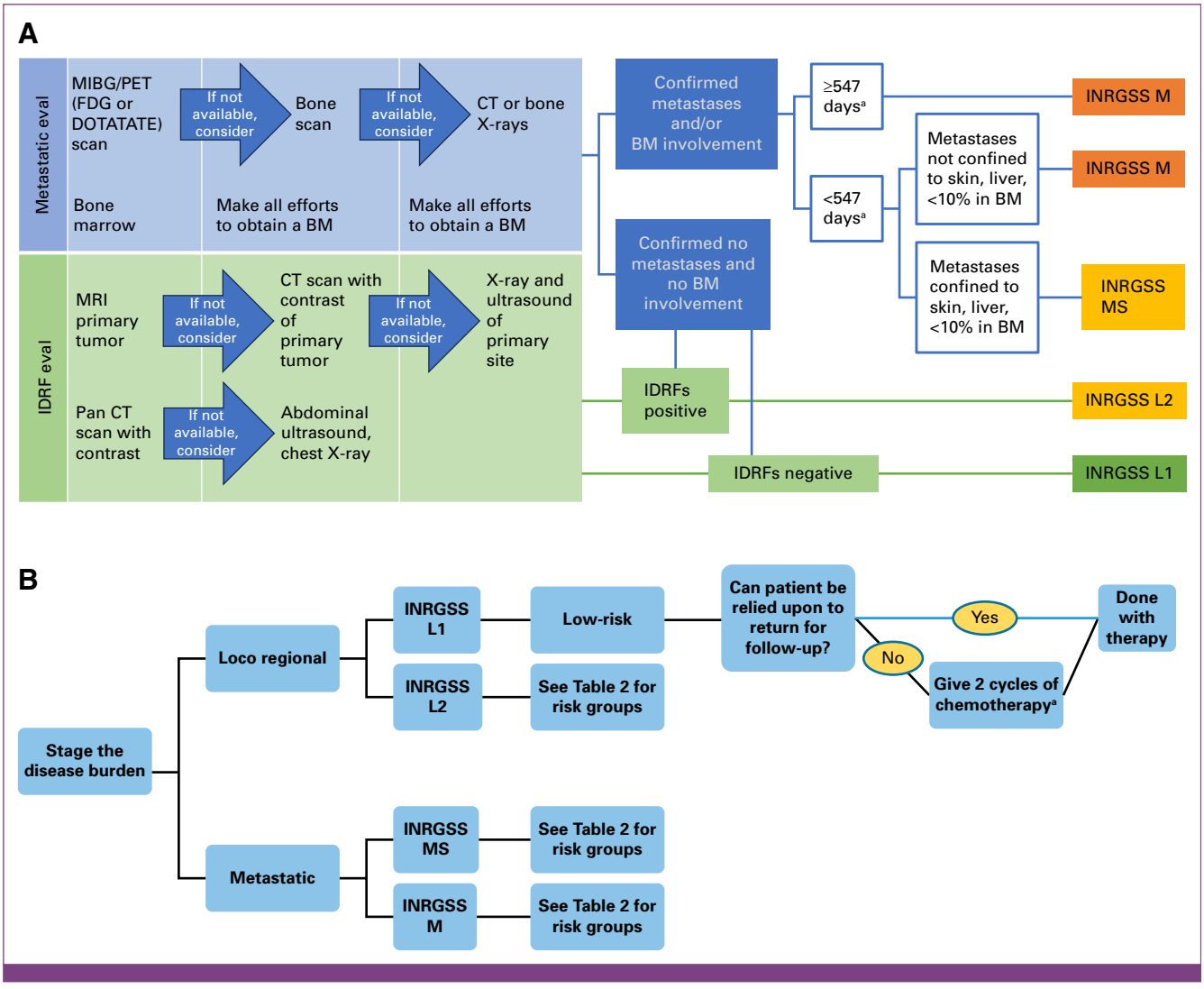


**FIG 1.** (A) Flow diagram of adaptive determination of INRGSS after histologic confirmation of neuroblastoma. [a]Age at diagnosis. (B) Decision tree to determine initial treatment intensity for children with neuroblastoma in low- and middle-income countries (for INRGSS 4S, metastases are limited to skin, liver, and <10% of bone marrow). [a]At the physician's discretion, it may be preferable to give additional frontline therapy since salvage options are scarce in LMIC. BM, bone marrow; CT, computed tomography; FDG, fluorodeoxyglucose; IDRF, image-defined risk factor; INRGSS, International Neuroblastoma Risk Groups Staging System; LMIC, low- and middle-income countries; MIBG, [$^{125}$I]meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography.

tree's first level consisted of INSS subgroups (1/2A, 2B/3, 4, 4S). Within a given stage, age, LDH, and ferritin were tested; of the statistically significant ($P < .05$) factors, the one with the largest hazard ratio (HR) was selected to create two subgroups. The remaining factors were tested within each subgroup, and partitioning was repeated until n < 10 or no significant factors remained.[18] *MYCN* oncogene status testing is limited in many LMIC; because *MYCN* status is so highly prognostic,[7,8] supplementary analyses included *MYCN* status.

The overall cohort was randomly divided into test (n = 7,251) and validation (n = 7,250) sets. After analyses in the test set, if the validation survival trees were found conceptually identical, the test and validation sets would be combined for the primary analysis to increase statistical power. *P* values <.05 were considered statistically significant. Analyses were conducted using SAS Version 9.4 (SAS Institute Inc, Cary, NC).

Fixed EFS cutoffs were not applied to define risk groups. Within each terminal node, the proportion of patients by initial treatment *assignment* was calculated; INRGDC does not include data about treatment *received*. Risk group assignment (ACNRG low-, intermediate-, or high-risk) was made subjectively, accounting for the assigned treatment that enabled patients to achieve a particular level of outcome. For example, 70% 5-year EFS may seem intermediate-risk; however, if most of those patients were assigned to high-risk therapy, then we elected to continue to classify them as high-risk.

In addition to statistical evidence, the practical needs of treating physicians in LMIC were considered in decision trees to determine INRGSS and risk group (Figs 1A and 1B). After histologic confirmation of NB, treating physicians may consider the disease burden (locoregional [INRGSS L1, L2] or metastatic [INRGSS MS, M]), and whether the patient will return for follow-up after frontline therapy. For descriptive validation, the ACNRG and INRG classifications were compared, calculating concordance and discordance. With no gold standard for risk classification in NB, sensitivity and specificity were not calculated.

## RESULTS

The results in the validation set were conceptually identical to the test set (Data Supplement, Figs S1 and S2, Tables S1 and S2). The test and validation sets were combined for the definitive analysis.

### Univariate Analyses

The overall 5-year EFS and OS were 67.8% ± 0.4% and 74.9% ± 0.4%, respectively. In univariate analyses, age, stage, LDH, and serum ferritin were highly statistically significantly prognostic of EFS and OS (Table 1, Data Supplement, Figs S3A and S3D). Of these factors, the greatest disparity in outcome occurred for INSS 4 versus 1, 2, 3, 4S (38.8% ± 0.7% *v* 85.6% ± 0.4%, respectively; HR, 5.5). The HRs for age ≥547 days, LDH ≥ 1,400 IU/L, and ferritin ≥30 ng/mL were 3.2, 3.4, and 2.1, respectively, compared with reference subgroups.

### Survival Tree Recursive Partitioning: Age, INSS, LDH, and Ferritin

There were no violations of the proportional hazards assumption. Combining the prognostic strength of INSS with the physician's desire to differentiate locoregional from metastatic disease, the first splits in the survival regression tree were INSS (1, 2A) versus (2B, 3) versus 4S versus 4 (Fig 2A). The 5-year EFS of these stages were 92% ± 0.5% (n = 3,891), 78% ± 0.8% (n = 2,932), 81% ± 1.2% (n = 1,140), and 39% ± 1% (n = 5,092), respectively (Data Supplement,

**TABLE 1.** Clinical Characteristics and Outcome of the INRGDC Analytic Cohort (N = 14,501)

| | Patients | | EFS | | EFS | | OS | |
|---|---|---|---|---|---|---|---|---|
| Factor | No. | % | HR | 95% CI on HR | 5-Year EFS ± SE, % | Log-Rank *P* | 5-Year OS ± SE, % | Log-Rank *P* |
| Age at diagnosis, days | | | | | | | | |
| <547 | 7,853 | 54.2 | 3.2 | 3 to 3.4 | 82.5 ± 0.4 | <.0001 | 89.8 ± 0.4 | <.0001 |
| ≥547 | 6,648 | 45.8 | | | 50.6 ± 0.7 | | 57.6 ± 0.7 | |
| INSS | | | | | | | | |
| 1, 2, 3, 4S | 8,929 | 63.7 | 5.5 | 5.2 to 5.9 | 85.6 ± 0.4 | <.0001 | 92.7 ± 0.3 | <.0001 |
| 4 | 5,092 | 36.3 | | | 38.8 ± 0.7 | | 46.4 ± 0.7 | |
| LDH, IU/L | | | | | | | | |
| <1,400 | 5,992 | 83.1 | 3.4 | 3.1 to 3.7 | 72.5 ± 0.6 | <.0001 | 80.3 ± 0.6 | <.0001 |
| ≥1,400 | 1,216 | 16.9 | | | 34.1 ± 1.4 | | 37.8 ± 1.5 | |
| Ferritin, ng/mL | | | | | | | | |
| <30 | 3,007 | 42.1 | 2.1 | 1.9 to 2.3 | 78.4 ± 0.8 | <.0001 | 85.7 ± 0.7 | <.0001 |
| ≥30 | 4,130 | 57.9 | | | 60 ± 0.8 | | 66.9 ± 0.8 | |

Abbreviations: EFS, event-free survival; HR, hazard ratio; INRGDC, International Neuroblastoma Risk Group Data Commons; INSS, International Neuroblastoma Staging System; LDH, serum lactate dehydrogenase; OS, overall survival; SE, standard error.

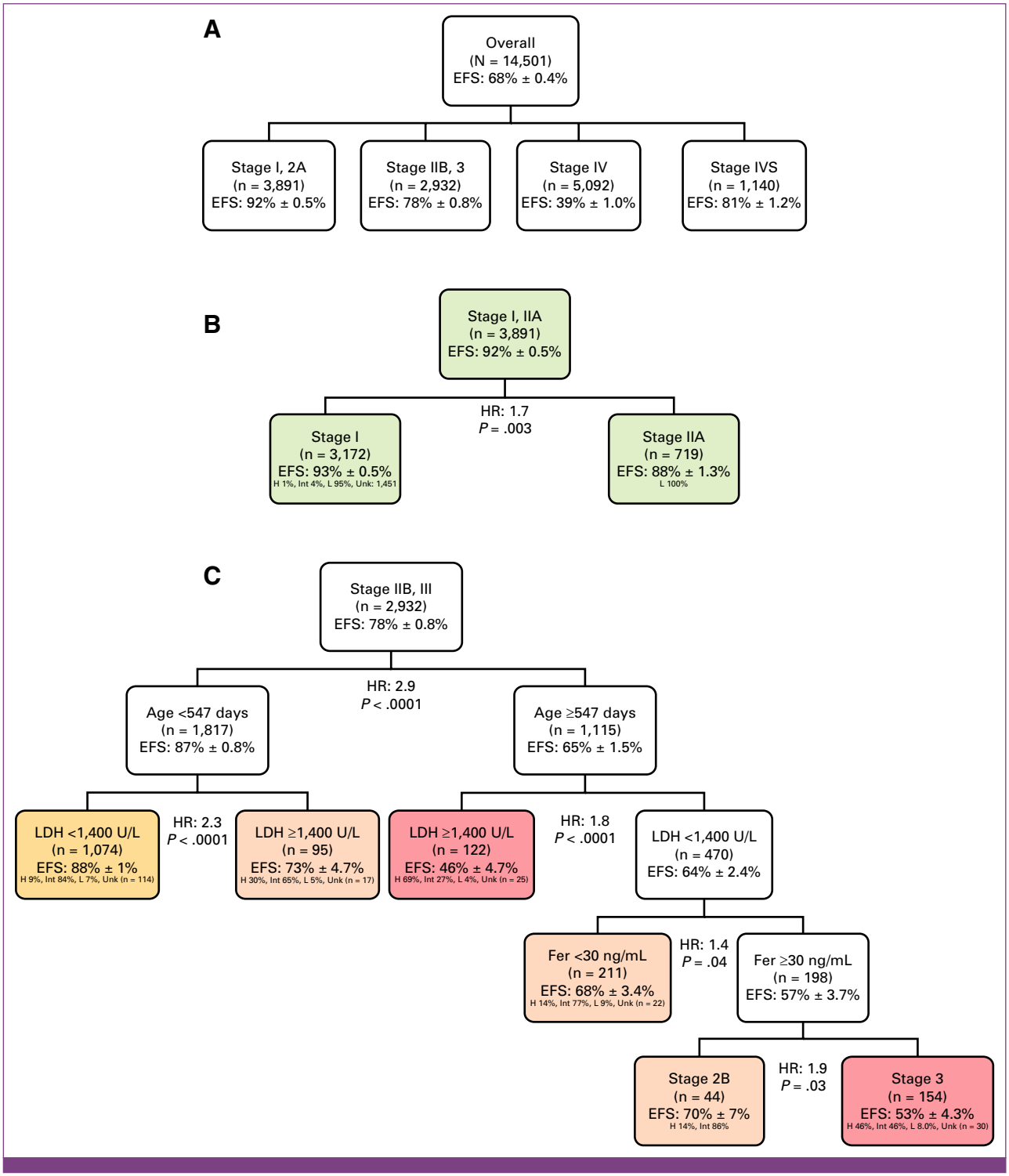


**FIG 2.** Survival tree regression of ACNRG, using age, INSS, LDH, and serum ferritin. (A) Overall, by INSS; (B) INSS 1 and 2A; (C) INSS 2B and 3; (D) INSS 4; (E) INSS 4S (green = ACNRG low-risk; tan = ACNRG intermediate-risk; gold = ACNRG intermediate-/high-risk; red = ACNRG high-risk). ACNRG, Adaptive Clinical Neuroblastoma Risk Groups; EFS, 5-year event-free survival; HR, hazard ratio; INSS, International Neuroblastoma Staging System; LDH, serum lactate dehydrogenase. (continued on following page)

Fig S3B). Hereafter, we provide justification for classifying terminal nodes as either ACNRG low-, intermediate-, high-risk, or at the physician's discretion (only 3.7% of patients; MYCN status, if available, could discriminate between intermediate- and high-risk; Data Supplement, Table S3).

### INSS 1, 2A

Within INSS 1, 2A (n = 3,891), the most highly prognostic factor was INSS, with worse EFS for stage 2A compared with stage 1 (HR, 1.7; $P$ = .003; Fig 2B). INSS 1 and INSS 2A were

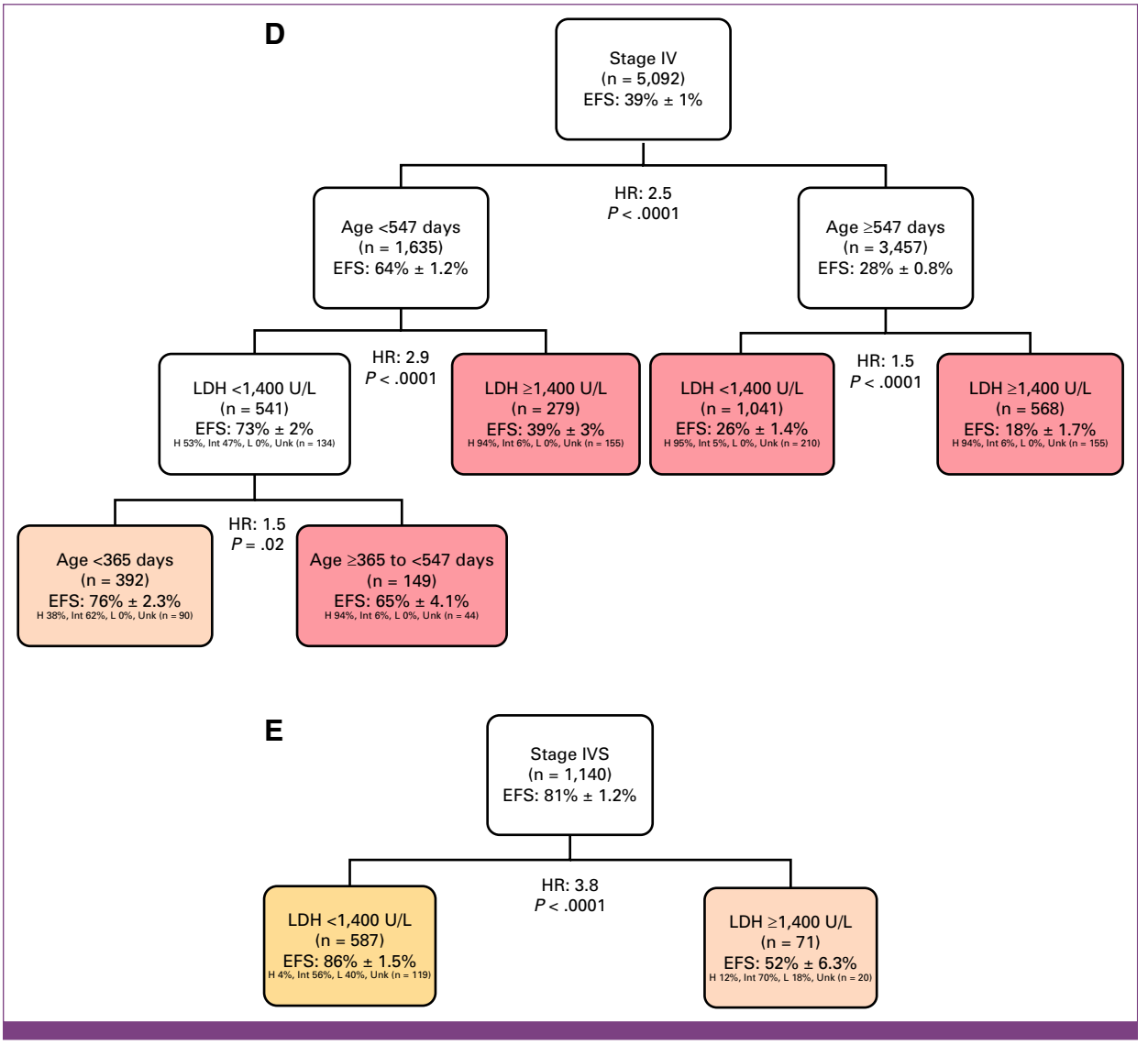


**FIG 2.** (Continued).



terminal nodes (no further significant factors), and subjectively classified as ACNRG low-risk. 95% of INSS 1 patients were assigned to initial treatment with surgery, resulting in EFS = 93%; 100% of INSS 2A patients were assigned to initial treatment with surgery, resulting in EFS = 88% (Table 2).

### INSS 2B, 3

Within INSS 2B, 3 (n = 2,932), the most highly prognostic factor was age, with worse EFS for age ≥547 days versus <547 days (HR, 2.9; $P$ < .0001; Fig 2C). Within age <547 days, the strongest prognostic factor was LDH, with worse EFS for LDH ≥ 1,400 IU/L versus <1,400 IU/L (HR, 2.3; $P$ = .0001). LDH ≥ 1,400 IU/L and LDH < 1,400 IU/L were terminal nodes. Patients with INSS 2B, 3, age <547 days, and LDH < 1,400 IU/L were classified as ACNRG intermediate-risk: 84% were assigned to initial treatment with conventional-dose chemotherapy plus surgery, resulting in EFS = 88% (Table 2). Patients with INSS 2B, 3, age <547 days, and LDH ≥ 1,400 IU/L (n = 95; 0.8% of patients) are classified at the physician's discretion: 65% were assigned to conventional-dose chemotherapy plus surgery and 30% to intensive multimodality therapy, resulting in EFS = 73%.

Within stage 2B, 3 patients age ≥547 days, the most highly prognostic factor was LDH, with worse EFS for LDH ≥ 1,400 IU/L versus LDH < 1,400 IU/L (HR, 1.8; $P$ < .0001; Fig 2C). Within the terminal node INSS 2B, 3, age ≥547 days, and LDH ≥ 1,400 IU/L, 69% were assigned to intensive multimodality therapy, resulting in EFS = 46%, and classified as ACNRG high-risk (Table 2). Within LDH < 1,400 IU/L, the most prognostic factor was ferritin; ferritin ≥30 ng/mL had worse EFS than <30 ng/mL (HR, 1.4; $P$ = .04). Within the terminal node INSS 2B, 3, age ≥547 days, LDH < 1,400 IU/L, and ferritin <30 ng/mL node, 77% were assigned to conventional-dose chemotherapy plus surgery, resulting in EFS = 68%; these patients (n = 211; 1.9% of

**TABLE 2.** ACNRG Classification: One Row for Each Terminal Node of the Survival Tree (n = 11,341)

| | | | | | | | | Assigned Treatment[c] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| INRGSS[a] | INSS | Age | Serum LDH, IU/L | Serum Ferritin, ng/mL | ACNRG | No.[b] | 5-Year EFS ± SE, % | H% | I% | L% | #U |
| L1 | 1 or 2A | Any | Any | Any | Low | 3,891 | 91.6 ± 0.5 | 0.7 | 2.8 | 96.6 | 1,451 |
| L2 | 2B, 3 | <547 days | <1,400 | Any | Int | 1,074 | 87.5 ± 1 | 8.5 | 84.1 | 7.4 | 114 |
| | | | ≥1,400 | Any | Int or high[d] | 95 | 73.1 ± 4.7 | 29.5 | 65.4 | 5.1 | 17 |
| | | ≥547 days | <1,400 | <30 | Int or high[d] | 211 | 68.1 ± 3.4 | 14.3 | 77.2 | 8.5 | 22 |
| | | ≥547 days | <1,400 | ≥30 | Int or high[d] | 198 | 56.9 ± 3.7 | 37.5 | 56.6 | 6 | 30 |
| | | ≥547 days | ≥1,400 | Any | High | 122 | 46 ± 4.7 | 69.1 | 26.8 | 4.1 | 25 |
| MS | 4s | Any | <1,400 | Any | Int[e] | 587 | 85.8 ± 1.5 | 4.5 | 56.2 | 39.3 | 119 |
| | | | ≥1,400 | Any | Int or high[d] | 71 | 52.4 ± 6.3 | 11.8 | 70.6 | 17.6 | 20 |
| M | 4 | <365 days | <1,400 | Any | Int | 392 | 75.7 ± 2.3 | 38.1 | 61.6 | 0.3 | 90 |
| | | ≥356 to <547 days | <1,400 | Any | High | 149 | 64.7 ± 4.1 | 94.3 | 5.7 | 0 | 44 |
| | | <547 days | ≥1,400 or Unk | Any | High | 1,094 | 60 ± 1.6 | 38 | 57.7 | 4.3 | 539 |
| | | ≥547 days | Any | Any | High | 3,457 | 27.7 ± 0.8 | 82 | 15.8 | 2.2 | 1,296 |

Abbreviations: ACNRG, Adaptive Clinical Neuroblastoma Risk Groups; EFS, event-free survival; INRGSS, International Neuroblastoma Risk Groups Staging System; INSS, International Neuroblastoma Staging System; LDH, serum lactate dehydrogenase; SE, standard error.
[a]INRGSS was mapped to INSS after data analysis was performed using INSS stage.
[b]A terminal node is a subgroup in the survival tree that has no further splits. The sample size of a terminal node is the number of patients with known data for that factor, that is, excluding patients with unknown data. Therefore, the sample size column of this table adds up to less than the total for the overall analytic cohort (n = 14,501).
[c]L = low-risk assigned treatment; I = intermediate-risk assigned treatment; H = high-risk assigned treatment; #U = number with unknown assigned treatment (not reported).
[d]At the physician's discretion. This represents 3.7% of the overall cohort.
[e]Low-risk if asymptomatic; intermediate-risk if symptomatic.



patients) may be classified at the physician's discretion. For those with ferritin ≥30 ng/mL, the differentiation of INSS 2B versus 3 was the most prognostic (HR, 1.9; $P$ = .033), with stage 3 having worse EFS than stage 2. INSS 3, age ≥547 days, LDH < 1,400 IU/L, and ferritin ≥30 ng/mL was a terminal node: 46% were assigned to intensive multimodality therapy, resulting in EFS = 53%, and classification as ACNRG high-risk. Within the INSS 2B, age ≥547 days, LDH < 1,400 IU/L, and ferritin ≥30 ng/mL terminal node, 86% were assigned to conventional-dose chemotherapy plus surgery, resulting in EFS = 70% (Table 2). These patients (n = 44; 0.4% of patients) may be classified at the physician's discretion.

## INSS 4

For stage 4 (n = 5,092), the most prognostic factor was age, with age ≥547 days having worse EFS than age <547 days (HR, 2.5; $P$ < .0001; Fig 2D). LDH was the most prognostic factor within age ≥547 days as well as within age <547 days, with LDH ≥ 1,400 IU/L having worse EFS versus LDH < 1,400 IU/L (HR, 1.5; $P$ < .0001, HR, 2.9; $P$ < .0001, respectively). Within age <547 days, LDH < 1,400 IU/L: age ≥365-<547 days (94% assigned to intensive multimodality therapy, resulting in EFS = 65%; classified as ACNRG high-risk) had worse EFS than age <365 days (62% assigned to conventional-dose chemotherapy plus surgery, resulting in EFS = 76%; classified as ACNRG intermediate-risk; HR, 1.5; $P$ = .02). The other LDH nodes had no significant factors, that is, all three were terminal nodes and classified as ACNRG high-risk: 38% of patients INSS 4, age <547 days with LDH ≥ 1,400 IU/L or unknown were assigned to intensive multimodality therapy and had EFS = 60%; and 82% of patients INSS 4, age ≥547 days and any LDH were assigned to intensive multimodality therapy and had EFS = 28% (Table 2).

## INSS 4S

For stage 4S (n = 1,140), the most highly prognostic factor was LDH, with LDH ≥ 1,400 IU/L having worse EFS than LDH < 1,400 IU/L (HR, 3.8; $P$ < .0001; Fig 2E). LDH ≥ 1,400 IU/L and LDH < 1,400 IU/L were terminal nodes. Within the LDH < 1,400 IU/L node, 40% were assigned to surgery and observation, and 56% to conventional-dose chemotherapy plus surgery, and had EFS = 86%; these patients were assigned to ACNRG intermediate-risk (Table 2). However, per COG guidelines, intermediate-risk therapy is needed only if the patient is symptomatic[5,11–17]; therefore, asymptomatic patients may be classified as low-risk at the physician's discretion. Within LDH ≥ 1,400 IU/L, 70% were assigned to conventional-dose chemotherapy plus surgery, resulting in EFS = 52%. These patients (n = 71; 0.6% of patients) may be classified at the physician's discretion.

To simplify presentation and application of the ACNRG, terminal nodes of the same risk group were combined into a single table row (Table 2). A small proportion of patients (3.7% in this study) benefit if *MYCN* status can be determined,

whereby further discrimination between ACNRG intermediate- and high-risk patients is possible (shaded columns of the Data Supplement, Table S3). For the subset of n = 8,152 patients with sufficient data to determine both ACNRG and INRG, risk group assignment was 86.6% concordant and 13.4% discordant (Fig 3). For ACNRG, 45%, 20%, and 34% were assigned to high-, intermediate-, and low-risk, while INRG was 45%, 7%, and 48%, respectively. The EFS curves for the low- and high-risk groups are similar for the two classification systems, although the intermediate-risk curve for ACNRG is somewhat higher (77% ± 3% at 5 years) than INRG (66% ± 3% at 5 years; Figs 4C and 4D, respectively; Fig 3; Figs 4A and 4B). To determine the ACNRG classification for a given patient, physicians in LMIC may apply an adaptive staging flow diagram (Fig 1) and a decision tree (Fig 1B; and Table 2), leading to a recommendation of initial treatment intensity for a child with NB.

If age and stage are known, but only one additional known factor (LDH, serum ferritin, or *MYCN* status), it may still be possible to estimate the patient's risk group (Data Supplement, Table S4).

## DISCUSSION

We have developed the ACNRG risk classification using easily obtained clinical factors for use in LMIC to guide treatment stratification for children with NB. Our approach was more data-driven than the approaches used for the SIOP-PODC[23] or the ARIA Guide Neuroblastoma Adapted Management Guide (Version 1.2; 2025) (unpublished data). ACNRG first requires a confirmed diagnosis of NB. Age is the most easily determined of the ACRNG factors, although it is possible the exact birthdate could be unknown. LDH and serum ferritin can be determined from standard blood tests performed in hospitals in LMIC. To determine INRGSS, a flow diagram was developed of the optimal and minimum essential imaging modalities (Fig 1A). Access to more advanced imaging techniques is not always feasible in LMIC; efforts to obtain them may delay or disrupt patient treatments. To improve the accuracy of risk assessment, travel to obtain optimal imaging is strongly recommended. Additionally, it is crucial to maintain continuity of imaging with the same technique throughout treatment. Despite variability across LMIC, most institutions have access to computed tomography scans with contrast and can perform a bone marrow

| | | INRG (n = 9,233 known)<br>Age, INRGSS, histologic category, grade, *MYCN* status, 11q status, ploidy | | | | |
|---|---|---|---|---|---|---|
| | | High | Int | Low | Unk | Total |
| ACNRG<br>(n = 11,341 known)<br><br>Age, INRGSS, LDH, ferritin | High | (n = 3,904)<br>(96.9% of INRG high-risk)<br>5-year EFS: 28 ± 1%<br>5-year OS: 36 ± 1% | (n = 180)<br>(54.7% of INRG int-risk)<br>5-year EFS: 65 ± 4%<br>5-year OS: 78 ± 3% | (n = 359)<br>(9.5% of INRG low-risk)<br>5-year EFS: 89 ± 2%<br>5-year OS: 93 ± 1% | 692 | 5,135<br>(45%) |
| | Int | (n = 68)<br>(1.7% of INRG high-risk)<br>5-year EFS: 45 ± 6%<br>5-year OS: 56 ± 6% | (n = 83)<br>(25.2% of INRG int-risk)<br>5-year EFS: 59 ± 6%<br>5-year OS: 76 ± 5% | (n = 358)<br>(9.4% of INRG low-risk)<br>5-year EFS: 87 ± 2%<br>5-year OS: 96 ± 1% | 1,806 | 2,315<br>(20%) |
| | Low | (n = 58)<br>(1.4% of INRG high-risk)<br>5-year EFS: 52 ± 7%<br>5-year OS: 77 ± 6% | (n = 66)<br>(20.1% of INRG int-risk)<br>5-year EFS: 77 ± 5%<br>5-year OS: 87 ± 4% | (n = 3,076)<br>(81.1% of INRG low-risk)<br>5-year EFS: 93 ± 1%<br>5-year OS: 98 ± 0.3% | 691 | 3,891<br>(34%) |
| | Unk | 122 | 282 | 677 | 2,079 | 3,160 |
| | Total | 4,152 (45%) | 611 (7%) | 4,470 (48%) | 5,268 | 14,501 |

**FIG 3.** Concordance of ACNRG with INRGs (n = 8,152 patients with known prognostic factors for determination of both ACNRG and INRG classification). Concordant 86.6% (blue), discordant 13.4% (yellow). ACNRG, Adaptive Clinical Neuroblastoma Risk Groups; EFS, event-free survival; INRG, International Neuroblastoma Risk Group; INRGSS, INRGs Staging System; LDH, serum lactate dehydrogenase; OS, overall survival.

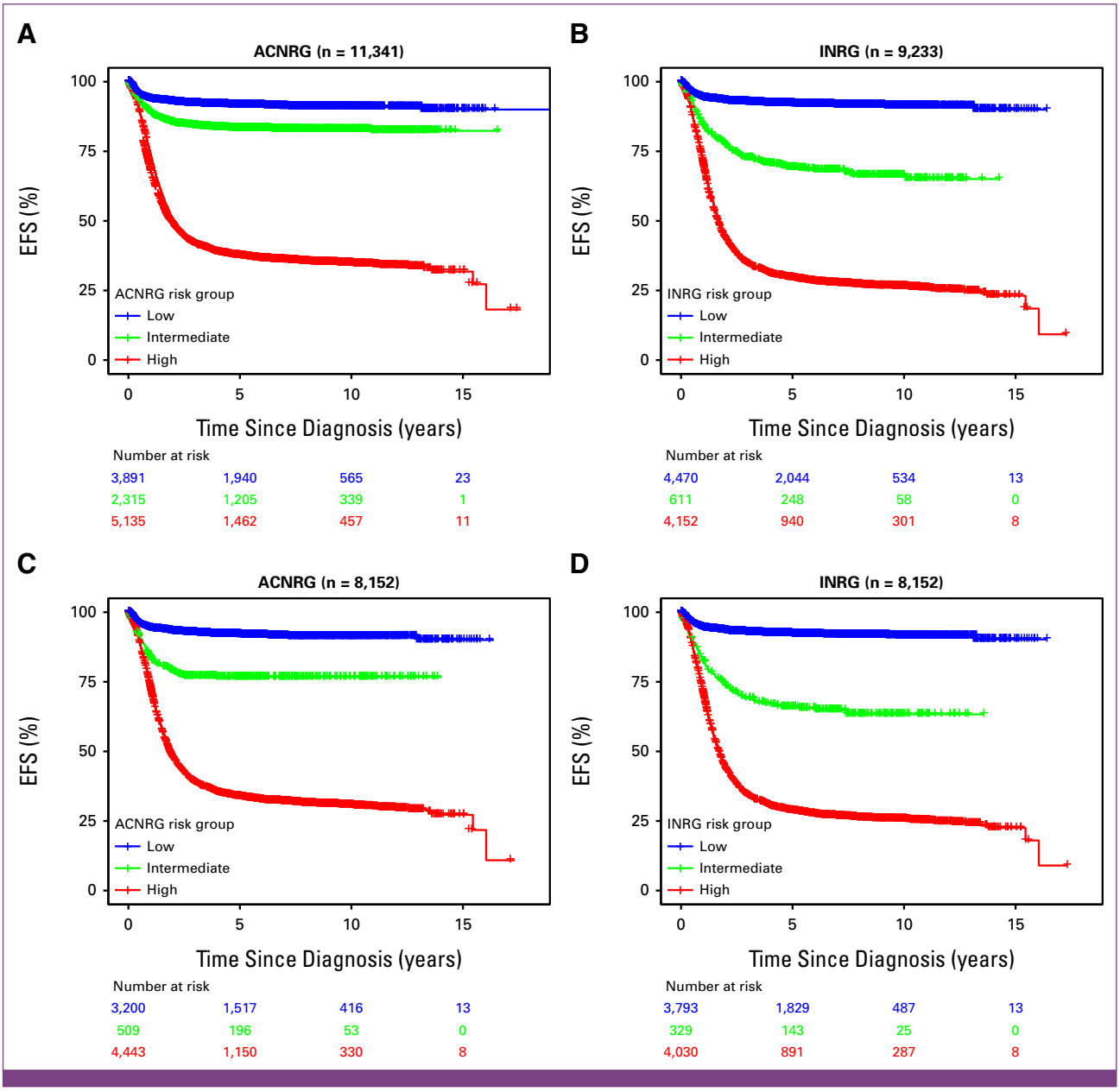


**FIG 4.** Kaplan-Meier curves of EFS for ACNRG and INRG. (A) ACNRG (n = 11,341 for whom there were sufficient data to determine ACNRG). 5-Year EFS: high—37% ± 0.7% (n = 5,135); intermediate—83% ± 0.8% (n = 2,315); low—92% ± 0.5% (n = 3,891). (B) INRG (n = 9,233 for whom there were sufficient data to determine INRG). 5-Year EFS: high—29% ± 0.7% (n = 4,152); intermediate—69% ± 2% (n = 611); low—92% ± 0.4% (n = 4,470). (C) ACNRG (n = 8,152—the intersection of patients for whom there were sufficient data to determine both ACNRG and INRG). 5-Year EFS: high—36% ± 1% (n = 4,696); intermediate—77% ± 3% (n = 256); low—92% ± 1% (n = 3,200). (D) INRG (n = 8,152—the intersection of patients for whom there were sufficient data to determine both ACNRG and INRG). 5-Year EFS: high—29% ± 1% (n = 4,030); intermediate—66% ± 3% (n = 329); low—92% ± 0.5% (n = 3,793). ACNRG, Adaptive Clinical Neuroblastoma Risk Groups; EFS, event-free survival; INRG, International Neuroblastoma Risk Group.

biopsy/aspirate; however, metastatic assessments such as [$^{125}$I] metaiodobenzylguanidine (MIBG) or positron emission tomography (PET) scans (fluorodeoxyglucose [FDG], DOTATATE) are often available only in middle-income countries or not done until after treatment initiation.

NB is heterogeneous and rich in strong prognostic factors, with many correct/useful ways to stratify patients into clinically distinct risk groups with statistically significantly differing outcome. Noted statistician George Box reminds us that, "All models are wrong but some are useful."[44] ACNRG and INRG were 13.4% discordant, which is not surprising given there is no gold standard for NB risk stratification. Both ACNRG and INRG assign 45% of patients to high-risk; the apparent upstaging of 9.5% of INRG low-risk patients to ACNRG high-risk is, in part, a result of cross-tabulating a

subgroup for which both INRG and ACNRG can be determined.

Our analysis has several limitations. Admittedly, the outcome achieved by patients in the INRGDC (Europe, Japan, North America, and Australia) will not be representative of outcome in LMIC. LDH and ferritin data were unknown for half the patients in the INRGDC; however, characteristics of patients with unknown LDH/ferritin were similar to those with known LDH/ferritin (data not shown), so the bias should be minimal. Ferritin, an inflammatory marker of infection, should be interpreted with caution when upstaging patients who have high infection burden. The survival trees from the test and validation sets differ, but conceptually are the same (Data Supplement, Figs S1 and S2). Furthermore, there was subjectivity in deciding the risk classification, using initial treatment assignment and outcome as determining factors; when EFS was suboptimal despite multimodal intensive therapy, the subgroup was assigned to high-risk, and *MYCN* status was irrelevant. From INRGDC, only the *assigned* treatment is known, not the actual treatment. Some LMIC hospitals will be unable to perform MIBG, FDG-PET, or bone scan, limiting ability to discriminate between INRGSS M versus MS. The biases introduced by these limitations might lead to undertreatment/overtreatment of some patients, but for most patients, the ACNRG should lead to improved accuracy of risk classification and treatment intensity.

The ACNRG and our approach have several strengths. We addressed the challenge of missing data by using factors that are easily obtained and more likely to be nonmissing. A higher proportion of patients were able to be risk classified using ACNRG (78%) than INRG (64%). Of 11,341 patients assigned by ACNRG, 96.3% were stratified using only age, INRGSS stage, LDH, and ferritin; the remaining 3.7% could be stratified by including *MYCN* status. The ACNRG classification makes adjustment for confounding of initial treatment assignment with prognostic factors; risk classification was subjectively determined on the basis of objective evidence: the proportion of patients' assigned treatment by risk group and their ultimate outcome inform the classification. In the approach by Cohn et al,[18] INRG terminal nodes were categorized for descriptive purposes, without accounting for treatment assignment, by applying fixed cutoffs (5-year EFS > 85%—very-low-risk; >75%-85%—low-risk; 50%-75%—intermediate-risk; <50%—high-risk). For intermediate-risk EFS curves (Fig 4), ACNRG (5-year EFS = 83%) appears similar to COG (5-year EFS approximately 85%)[5]; ACNRG and COG intermediate-risk EFS curves appear higher than INRG (5-year EFS = 69%). A strength of ACNRG is the ability to identify which patients are high-risk; many hospitals in LMIC are unable to provide intensive multimodality therapy and may instead choose to provide palliative care for high-risk disease. A feasibility/pilot trial is in development to implement the ACNRG classification at hospitals in Southeast Asia and Africa, including prospective data collection of treatment administered and outcome.

Using just age, INRGSS, LDH, and ferritin at diagnosis, physicians in LMIC can apply the ACNRG classification to make informed decisions about an appropriate level of initial treatment intensity for children who are newly diagnosed with NB. We propose the ACNRG as an alternative that might work better than existing algorithms in some LMIC. The ACNRG overcomes practical challenges and allows physicians to focus resources on low- and intermediate-risk patients for whom cure is possible with little or no therapy.



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## DATA SHARING STATEMENT

The data that support the findings of this study are openly available in International Neuroblastoma Risk Group (INRG) Data Commons at https://inrgdb.org/.
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