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Diagnostic delay and socio-demographic predictors of stage at diagnosis and mortality in unilateral and bilateral retinoblastoma

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Abstract

Background—More invasive retinoblastoma (Rb), characterized by increased morbidity and mortality, with lower rates of eye salvage and higher rates of extraocular dissemination, appears more prevalent in resource-poor countries. The relationship of diagnostic delay (lag time) and socio-demographic factors on the extent of disease at diagnosis has not been examined separately for unilateral and bilateral Rb.

Methods—At diagnosis, consenting parents of 179 Mexican children with Rb were interviewed about initial symptoms and household demographic characteristics. Clinical presentation was classified using St. Jude's, International Staging System (ISS), and International Intraocular Retinoblastoma Classification (IIRC) criteria. Lag time (delay between noting symptoms and diagnosis), and socio-demographic factors were examined as predictors for higher stage at diagnosis and overall survival (OS).

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Results—In bilateral disease, lag time predicts stage at diagnosis using St. Jude's, and ISS criteria ($p<0.005$ in multivariate regression), and OS ($p<.05$,CoxHazards), but not extent of intraocular disease (by IIRC). In unilateral disease, lag time predicts neither extent of disease (using ISS, St Jude's and IIRC), nor OS. Indicators of prenatal poverty, including lower maternal education and the presence of dirt flooring in the home, predict more advanced disease by IIRC for bilateral Rb, and for unilateral by ISS, and St Jude's ($p<0.001$) as well as OS ($p<0.05$).

Conclusion—These results suggest unilateral and bilateral retinoblastoma differ in factors governing progression and extra-retinal extension, possibly reflecting underlying biological heterogeneity.

Impact—This demonstrates differing effect of social factors on extent of intra- and extraocular disease depending on laterality with implications for screening strategies.

Keywords

Retinoblastoma; Diagnostic delay; Survival; Prenatal environment; Socio-demographic predictors

Introduction

In resource-poor settings, the majority of retinoblastoma (Rb) cases have significant retinal involvement at the time of diagnosis, rendering eye salvage difficult. Evidence of extraocular dissemination at time of diagnosis is documented in a larger proportion of cases in resource-poor populations than in those with greater resources(1, 2). Because success rates for conservative therapies are greater when therapy is administered in earlier stage disease(3–5), leading to improved survival(5), there has been longstanding interest in decreasing the incidence of more invasive retinal and extraocular Rb.

Clinical presentation of Rb varies widely. Unilateral Rb typically has a later median age at diagnosis than bilateral disease(6). While some younger patients may present with clinically aggressive Rb, others may present at older ages without clinical or histopathologic evidence of extraocular disease(7, 8). Socio-demographic factors may contribute to prolonged delays in obtaining access to care and therefore diagnosis, particularly in resource-poor settings(1, 2, 5, 9). Several centers have reported that a large proportion of the delay in diagnosis for Rb is attributable to delayed referral to specialists(5, 6, 10–12). Two South American centers found that longer intervals between noting symptoms and diagnosis (lag time) were associated with increased likelihood of extraocular disease at diagnosis(1, 2, 13). Swiss researchers found that lag time predicted extent of intraocular disease using International Intraocular Retinoblastoma Classification (IIRC) criteria(14, 15). Screening and public media education campaigns have begun in some populations with the goal of decreasing diagnostic delay in order to reduce the frequency of advanced disease(16).

Our objective here is to examine the relationship between socio-demographic factors, diagnostic delay and the extent of disease at diagnosis in patients with unilateral and bilateral Rb treated in a tertiary care hospital in an Upper Middle Income country (UMIC) (17). No published studies have examined unilateral and bilateral Rb separately in order to assess the differential impact of diagnostic delay on the degree of disease spread, or

mortality, nor to examine the association between the degree of intra and extraocular spread and socio-demographic factors.

Materials and Methods

Inclusion Criteria

Parents of children diagnosed with retinoblastoma between January 2000 and July 2010 and treated at the Hospital Infantil de México (HIM) in Mexico City were invited to participate in a study examining environmental contributors to sporadic (non-familial) Rb(18).

Exclusion criteria

Parents of children with a known family history of Rb were not eligible to participate. Parents of 180 children agreed (2 declined) to participate and were enrolled after giving written consent. The study was approved by the Institutional Review Boards of HIM and Columbia University.

Staging

All patients underwent an extent of disease evaluation including head imaging (MRI or CT), bone marrow, and lumbar puncture. Intraocular staging was done by one observer. Intra and extraocular staging was categorized according to those systems routinely used at HIM: IIRC grouping for predicting eye salvage(14), and the St. Jude's staging system, which predicts child survival(19). St. Jude's classification, which typically has stages 1 through 4, was modified by subdividing stage 2 into "2" and "2N". The modified stage (2N) included optic nerve involvement that was either pre or post lamina-cribrosa, but not at the surgical margin. For statistical analyses, stage 2N was considered intermediate between stage 2 disease, not involving the optic nerve (with either vitreous seeds, or isolated choroidal or emissary involvement), and stage 3 disease (extraocular spread without metastases). It was reasoned that in comparison to non-optic nerve stage 2 (originally St Jude's 2a and 2c), involvement of the optic nerve (2N) suggested a greater degree of spread, which has been associated with inferior survival(20). Our classification thus included stage 1 (retinal), stage 2 (ocular without optic nerve infiltration), stage 2N (ocular with optic nerve infiltration), stage 3 (localized extraocular dissemination including optic nerve involvement at the surgical margin), and stage 4 (distant metastases including central nervous system and/ or bone marrow).

Because of evolving standards in clinical classification, we also reclassified the extent of disease in our study population using the newer International Staging System (ISS), which although similar to St Jude's staging, contains several differences designed to better reflect current treatment algorithms and understanding of predictors of survival(21). The ISS contains an "N" sub-category used to more fully categorize ISS stage 1 and 2 disease, in which a stage of N=0 represents microscopic residual but no optic nerve involvement. ISS is used by several Latin American referral centers treating retinoblastoma and in the Children's Oncology Group(21).

For each child, classification by IIRC Group (from A to E, sequentially predicting lesser eye salvage) was determined for each affected eye by the ophthalmologist using an indirect ophthalmoscope or a direct Retcam examination under anesthesia(14). St. Jude's stage was assigned by an oncologist in conjunction with a pathologist (if enucleation occurred), who reviewed multiple histologic slides per case. All pathology slides were reviewed by one pathologist. The IIRC group utilized in our analyses for children with bilateral disease was that of the eye with more advanced disease.

Data Collection

Parents were interviewed during initial consultation at the HIM ophthalmology service using a questionnaire designed specifically for this population(18, 22). Parents were queried about the date at which symptoms were first noted, as well as socio-demographic characteristics; such as the number of hours of transit time between home and hospital, parental education level (number of years of school completed), number of siblings currently living with the patient, combined total monthly income, and characteristics of the home in which the mother resided during her pregnancy with the patient. The prenatal rather than current residence was utilized for analysis because families from more distant areas frequently move temporarily while their child undergoes initial evaluation and treatment.

Survival and follow up were documented by the treating oncologist (AMS) and ophthalmologist (MARO). Off therapy follow up for patients included ophthalmologic exams under anesthesia every 4 months until age 60 months for bilateral Rb, and until age 36 months for unilateral Rb and physical exams (without anesthesia) every 8 months. Patients underwent monthly exams by the oncology team (months 0–6 off therapy), every 2 months (months 6–24), every 3 months (months 25–36), every 6 months (months 37–60) and then annually.

Variable definition

Using a case series design, predictors of higher St Jude stage and higher IIRC group Rb were examined in 179 children with unilateral (109) and bilateral (70) Rb. Laterality was not available for one child who was then excluded from further analysis.

Lag time was calculated as the number of months elapsing between the time at which parents reported that they (or another family member) had first noted symptoms and the date of diagnosis. The date of diagnosis was confirmed by review of the medical record. Clinical descriptors and demographic characteristics for the study population are shown in Table 1.

Statistical Analysis

Spearman correlation coefficients were calculated and unadjusted logistic regressions were used to examine the bivariate associations between outcome variables (IIRC grouping and St. Jude's and ISS staging) and demographic predictors, as previously mentioned (See Supplementary: Table 1). Variation in mean scores for the staging outcome variables were examined with Wilcoxon rank sum tests (See Supplementary: Table 2).

Summary statistics were derived to describe sample characteristics separately for each laterality. Chi-square test was used to detect differences between unilateral and bilateral Rb for categorical variables of demographic characteristics and symptoms, and Wilcoxon rank sum test was used for quantitative variables, including staging variables. In the bivariate analysis for each laterality, the Wilcoxon test was used to detect differences between two categories of a quantitative variable. Student's t-tests and Wilcoxon rank sum test were used to compare unilateral and bilateral cases for continuous variables such as lag time, maternal age at child's birth, level of parental education and household income. Spearman correlation coefficient was calculated to assess bivariate associations between quantitative variables including staging score variables, lag time and socio-demographic variables. Multiple linear regression models for predicting staging scores as outcomes were run for each laterality to assess the associations between a staging score and predictors including lag time as well as the socio-economic variables that showed significant association with a staging variable in the bivariate analysis. Lag time and income had skewed distributions and thus had square root and logarithmic transformation applied respectively to improve model fit.

Survival analysis was performed to examine the effect of lag time and socio-demographic factors, along with staging variables, on the time from diagnosis to death. The log rank test was used to examine the effect of each of the predictors on the survival time. Cox proportional hazards models were used to assess the simultaneous effect on overall survival (OS) of lag time and socio-demographic predictors, with and without controlling for a staging score variable. Analyses were performed separately for the two lateralities using SAS 9.3.1 and SPSS 18.

Results

The study population was comprised of 179 children (109 unilateral, 70 bilateral). Unilateral Rb represented 60.9% of the patients, consistent with the distributions seen in other reports (1, 6, 23). Paternal information was not available for 10 unilateral and 7 bilateral children while information on prenatal housing was missing for 4 unilateral and 4 bilateral children. Children with unilateral and bilateral disease did not differ significantly in any socio-demographic characteristics or in their clinical presentation, except that unilateral Rb cases were older at diagnosis (Table 1). Mean lag time for children with unilateral disease was 6.73 months (range 0.25 to 66 months), seemingly shorter than for children with bilateral disease (mean: 7.54 months; range: 0.25–24 months; $p=0.09$, by Wilcoxon rank sum). St Jude's staging was missing for two children (one unilateral and one bilateral), while IIRC grouping was missing for one child with unilateral disease enucleated prior to initial consultation. There were no significant differences in the distribution of IIRC groups between children with unilateral and bilateral Rb though unilateral Rb cases appeared to have overall higher stage disease by St. Jude's ($p=0.06$) and ISS criteria ($p=0.09$) (using Wilcoxon rank sum test). Specifically, a higher proportion of children with unilateral Rb had stage 3 or 4 ($p<0.05$).

Because we considered that neo-adjuvant chemotherapy might affect histologic stage assigned at enucleation, we examined the associations between predictors and outcomes with and without 7 children (3 bilateral, 4 unilateral), who received chemotherapy prior to

enucleation, and whose post-enucleation staging was St Jude's stage 2 or 3 disease. Excluding these children from analysis did not change the direction or the strength of the associations, thus they were kept in the final analyses. Neither lag time nor distribution of staging varied significantly over the course of the study period.

Supplemental Table 1 shows the bivariate associations between lag time and socio-demographic predictors, and the three clinical classification systems (ISS, St Jude, and IIRC). Among cases with bilateral disease, lag time appeared associated with St. Jude, ISS and IIRC grouping; however, only the associations with St. Jude's and ISS staging were significant ($p<0.01$) (Supplemental Table 1). Lag time was not associated with either IIRC grouping or St Jude's staging in unilateral cases.

Longer lag time was associated with dirt flooring during pregnancy for unilateral (p 0.046, Wilcoxon Rank Sum test), but not bilateral disease. None of the other markers of socioeconomic status or housing conditions appeared to be associated with lag time in bivariate analyses. Supplemental Table 2 shows how IIRC classification, St Jude's and ISS staging at time of diagnosis varied with household conditions during pregnancy. Poor living condition categories had higher staging scores.

The predictors that were related to any outcome (IIRC, ISS or St Jude's) in the bivariate analysis included lag time, maternal education, paternal education, number of live-in siblings, monthly household income, age at diagnosis and dirt flooring during pregnancy. Linear models were used to examine the simultaneous effect of lag time and the socio-demographic predictors of Rb staging classification systems.

Using multivariate regression analysis, linear regression models were built using maternal education, income, number of siblings, lag time, housing conditions, presence of dirt flooring, and lack of a toilet as main predictors. Monthly household income (natural log transformed) was included in the final model for unilateral disease (St. Jude's) even though it did not remain significant in the final model because its inclusion affected the estimates of association parameters for the significant predictors. Maternal education was used in the final models predicting St. Jude's and ISS staging, recognizing that for unilateral disease, the effect of paternal education may be similar to that of maternal education. For IIRC grouping, the effect of maternal education was more predictive than paternal education in univariate analysis, particularly for unilateral disease. The year of diagnosis was initially included in the models predicting grouping or stage outcomes because referral patterns and buying power of an income figure might vary during the time period examined, and because IIRC grouping might differ over time, however, its inclusion did not change the direction or strength of the main associations.

Table 2 shows the final models by laterality for each staging outcome with the final predictors: lag time, maternal education and dirt flooring during pregnancy. Monthly income was included in the final models predicting St. Jude's and ISS staging. We show the final model including lag time plus any socio-demographic predictors significant in univariate analysis that remained significant at $p<0.05$ or whose inclusion modified the beta of the significant predictors by >10%. Results for St. Jude's and ISS staging were very similar for

unilateral Rb, in which lower maternal education and the presence of dirt floors in the home independently predicted higher stage, while neither lag time nor other socio-demographic factors were significant predictors. For bilateral Rb, the regression models showed that longer lag time was significantly associated with higher St. Jude's staging, with and without including maternal education as a predictor. Dirt flooring was not a significant predictor. In contrast, regression models for predicting IIRC grouping demonstrated that lag time does not predict intraocular spread in either laterality. In bilateral Rb, after accounting for maternal education, which is strongly predictive for IIRC grouping, the presence of dirt flooring in the home appeared to predict IIRC group.

Survival and follow up data were available for 103 unilateral and 66 bilateral cases. Twelve unilateral and 8 bilateral cases died during follow up. The length of follow up time did not differ by laterality (median of 4.96 years for unilateral Rb, and 4.90 years for bilateral Rb). Both children with unilateral disease who were missing lag time data were alive at last follow up, while one of three bilateral children missing lag time died.

The log rank test suggested no significant difference in survival curves between unilateral and bilateral cases, while higher scores for ISS and St Jude's criteria predicted shorter OS time in both unilateral ($p<0.0001$) and bilateral ($p<0.01$) cases. Higher score for IIRC grouping predicted lower OS for unilateral (but not bilateral) disease. Among unilateral cases, those whose mothers had fewer years of schooling, or had dirt flooring during pregnancy were at higher risk of death or had shorter OS ($p<0.005$). Maternal education and dirt flooring were not related to the OS of bilateral cases.

In unilateral cases, lag time was not associated with survival time (log rank test, $p=.17$), or mother's education (Spearman correlation $r = -0.10$, $p=0.29$), nor staging variables: St Jude's ($r=0.07$, $p=0.45$), ISS ($r=0.08$, $p = 0.42$), IIRC ($r=-0.10$, $p=0.21$). Cox proportional hazard models (Table 3) suggested that lag time was unrelated to survival time, while lower maternal education and/or higher score on any of the staging variables were associated with higher hazards of death. When including maternal education in the models, dirt flooring was not significant.

In bilateral cases, shorter length of survival was significantly associated with longer lag time (log rank test, $p=.03$) and with St Jude's and ISS (log rank test, $p<0.001$) but not with IIRC classification. Survival was not predicted by the level of maternal education nor by presence of dirt floors. The Cox proportional hazard models (Table 4), with the same variables used for unilateral Rb, suggested that the association between longer lag time and hazard of death or shorter survival time in children with bilateral disease became attenuated after controlling for either St Jude's or ISS staging scores and appeared to mediate the effect of lag time on survival in bilateral disease.

Discussion

Our data from Mexico, suggest that delay in diagnosis (lag time), predicts degree of extraocular spread as well as mortality for bilateral disease. We did not find evidence of lag time predicting degree of intra-ocular invasion (using IIRC grouping) for either laterality,

nor extraocular spread (St. Jude's or ISS staging) or mortality for unilateral Rb. Instead, socio-demographic characteristics such as maternal education and housing conditions were significant predictors for St. Jude's and ISS staging and survival for unilateral disease, and for IIRC grouping in bilateral Rb.

Using multivariate models, we found that lower maternal education, as well as dirt flooring were significantly predictive of more advanced St. Jude's and ISS stage and overall survival in unilateral disease, while lower maternal education predicted more advanced IIRC grouping in bilateral disease. Overall, the significant predictors for the final models for unilateral St. Jude's and ISS staging were very similar to those predicting IIRC grouping for bilateral disease. Because most of our unilateral cases presented with disease too advanced to consider eye salvage, the utility of predicting IIRC grouping for unilateral disease is less meaningful, while being of high clinical relevance for bilateral disease. Indicators of perinatal poverty including presence of a dirt floor, in addition to lower maternal education, are strongly indicative of higher stage disease, independent of diagnostic delay.

The major implication of our results derives from the clear difference in predictors of disease severity between the two main clinical manifestations of the disease. Our data suggests that higher IIRC grouping and St. Jude's (or ISS) staging, is not determined solely by delays in diagnosis. In unilateral disease, which represents the majority of Rb, lag time does not predict extra-retinal disease by IIRC, St. Jude's or ISS criteria. In bilateral disease, lag time is associated with extraocular spread but is less useful for predicting eye salvage (predicted by IIRC Grouping). The implication is that the two lateralities may differ biologically in the factors governing spread to the optic nerve and extraocular tissues. Understanding the laterality-specific association between more advanced disease and socio-demographic predictors, which may themselves be proxies for environmental exposures, may improve our approach towards decreasing morbidity.

Our results show that for bilateral disease, predictors of more advanced IIRC grouping differ from those predicting more advanced St. Jude's staging. One goal in initial treatment of bilateral Rb is to maximize the likelihood of eye salvage, as well as OS. Therefore, our findings may be relevant for designing future strategies for improving outcome for bilateral patients, since they suggest that shortening lag time may be less helpful for improving eye salvage.

In our data, higher stage disease (by St Jude's and ISS criteria) is associated with both lower maternal education and poor prenatal housing conditions. The significant role of maternal education in predicting both OS and higher stage disease is novel. Although we have not taken into account such critical factors as therapeutic schema, maternal education is significantly predictive of mortality even after accounting for clinical stage, suggesting that maternal contribution to survival has effects beyond those attributable to caretaking. There may be etiologic differences associated with maternal education and perinatal poverty, which contribute to development of more aggressive disease(24). Although having a dirt floor could be a marker of extreme perinatal poverty or remote rural location, it is notable that we did not have the same effect from similar characteristics, such lack of running water. Because toddlers spend a significant amount of time on the floor, we consider that a dirt

floor might serve as a source of a direct exposure to potential genotoxins present in soil (including agrochemical residues, particulate matter and metals) that might predict more aggressive disease(25–28).

Rates of metastatic Rb and mortality are highest in poorer countries(1, 2). Our data suggest that the higher incidence of metastatic disease may not be secondary to lesser access to healthcare or diagnostic delay. Rather, our results may be consistent with biochemical research demonstrating underlying biological differences between localized and metastatic disease(29–31). Future efforts to understand risk factors for more invasive disease may also need to consider new histo-pathologic criteria for assigning risk of progression(17, 20, 32).

In our population of uninsured patients, we examined other variables that might be considered as deterrents to bringing a child to a specialist such as travel time from home to hospital, or the number of siblings residing in the home (requiring care in the mother's absence). Although the number of siblings was predictive of St. Jude's stage for unilateral disease on univariate analysis, it did not remain predictive in multivariate analysis, presumably because it was closely and inversely correlated with maternal education.

The majority of reports on the incidence of retinoblastoma do not take into account the clinical stage of disease because cancer registries do not generally collect this information(23, 33). Moreover, the prevalence of more invasive or metastatic disease is limited to the reports of clinical treatment centers and not population-based data. The proportion of cases with metastatic disease varies considerably among centers (reports range from 9.9%(34) to 20.95%(35)). The proportion of Rb presenting with extra-ocular disease increases as economic indices decrease (2). Over time, disease at diagnosis has had lesser intraocular involvement (using IIRC grouping) as well as shorter time intervals between symptom presentation and diagnosis(15). Centers in Argentina and Brazil have noted that children with greater delay in diagnosis have more advanced disease at time of diagnosis(1, 36). These findings suggest that it is beneficial to diagnose the disease as close as possible to the time in which symptoms are first noticed, implying that there is a direct relationship between delay in diagnosis and disease progression. However, these studies have not evaluated the two disease lateralities separately, nor have they accounted for both IIRC and St Jude or ISS classification systems.

There has been an interest in increasing public awareness and screening for leukocoria in order to diminish diagnostic delay with the intent of decreasing morbidity and mortality(37). While one public education campaign, which alerted families to the symptoms of Rb, was associated with a decrease in the incidence of extraocular disease, there was no accompanying decrease in the duration of lag time between noting symptoms and diagnosis, suggesting an alternate etiology for the decrease in extraocular disease(16, 37). Detecting retinoblastoma once either leukocoria or strabismus are present may not result in decreased ocular morbidity or improve ocular salvage(38). Given the low incidence of Rb, resource investment in screening or early detection needs to consider the impact of these measures on Rb morbidity or mortality.

Other investigators have noted that increased diagnostic delay was associated with invasion of the choroid or of the optic nerve(39, 40) with metastatic disease at presentation(35) and with strabismus(10, 13, 39). Some of the discrepancy between our results and prior findings may be the result of the more contemporary nature of our study population, reflecting relatively newer therapeutic and diagnostic alternatives, including newer imaging modalities and the RetCam.

One limitation in our study design is that we did not document the time elapsed between initial attempts at seeking medical care and actual diagnosis and are unable to differentiate between lag time due to parental factors and health care system delays(5). Because HIM is a referral center for those without private insurance we were unable to examine the impact of differing types of insurance(1). An inherent limitation to studying Rb is the rarity of the disease. We thus report the results of data collected prospectively from newly diagnosed patients consulting to one hospital over a large number of years.

Our findings may be particularly relevant to other countries classified as UMIC and even to sub-populations within wealthier countries. Our finding of the association between survival and maternal education is generally consistent with Canturk et al.'s finding that higher country level indicators of literacy may predict improved survival from Rb(2). However, our work suggests that socioeconomic factors also contribute to survival at an individual level, and that within a heterogeneous society, such factors may be proxies for environmental exposures contributing to biological differences.

Some groups have advocated for screening campaigns in order to diagnose Rb at earlier stages with the goal of decreasing morbidity and mortality. Our results showing lack of association between diagnostic delay and both mortality and extraocular disease in unilateral disease, and lack of association with likelihood of eye salvage for bilateral disease suggest the need for consideration of laterality specific policies when implementing population wide strategies aimed at decreasing morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic characteristics, presenting symptoms, and stage at diagnosis for children with unilateral and bilateral retinoblastoma

Variables	Unilateral (N=109)	Bilateral (N=70)
	% (n/N)	% (n/N)
Gender		
Females	56 (61/109)	52.9 (37/70)
Living condition during pregnancy		
Toilet available	65.1 (69/106)	68.7 (46/67)
Running water available	86.9 (93/107)	88.1 (59/67)
Dirt floor	17.3 (18/104)	10.4 (7/67)
Presenting symptom		
Strabismus	50.5 (54/107)	49.3 (33/67)
Leukocoria	80.4 (86/107)	77.6 (52/67)
Parental impression that child's vision was impaired	25.2 (27/107)	22.4 (15/67)
Deceased during follow up	11.6 (12/103)	12.1 (8/66)
Lost to follow up	3.7 (4/109)	4.3 (3/70)
IIRC group	N = 108 % (n)	N = 70 % (n)
Group A	0 (0)	0 (0)
Group B	0 (0)	1.4 (1)
Group C	2.8 (3)	2.9 (2)
Group D	39.8 (43)	40.0 (28)
Group E	57.4 (62)	55.7 (39)
St. Jude	N=108	N=69
O	1.9 (2)	0 (0)
I	1.9 (2)	1.4 (1)
II	42.6 (46)	55.1 (38)
IIN	26.9 (29)	34.8 (24)
III	21.3 (23)	5.8 (4)
IV	5.6 (6)	2.9 (2)
International staging system (ISS)	N = 108	N = 69
0	1.9 (2)	0 (0)
1	44.4 (48)	55.1 (38)
1N>0	27.8 (30)	36.2 (25)
2	4.6 (5)	0 (0)
3	15.7 (17)	5.8 (4)
4	5.6 (6)	2.9 (2)
	Mean ± SD (N)	Mean ± SD (N)
Age at diagnosis (months)[a]	27.70 ± 19.56 (107)	14.57 ± 9.62 (67)

Variables	Unilateral (N=109)	Bilateral (N=70)
	% (n/N)	% (n/N)
Lag time (months)	6.73 ± 9.21 (107)	7.54 ± 6.38 (67)
Maternal education (yrs of schooling)	8.39 ± 3.59 (107)	8.34 ± 4.45 (67)
Paternal education (yrs of schooling)	8.46 ± 3.53 (97)	8.88 ± 4.00 (60)
Monthly Income (pesos)	3796.40 ± 8224.49 (100)	2870.63 ± 2327.08 (57)
Maternal age at delivery (years)	26.13 ± 6.50 (107)	26.48 ± 6.96 (67)
Length of commute from child's home to hospital (hours)	4.73 ± 3.32 (97)	4.98 ± 3.31 (62)
Follow up time	4.96 ± 3.41 (105)	5.02 ± 3.10 (69)

[a] p=0.001 from t-test for difference in natural log transformed variable between lateralities

Table 2

Estimated linear regression coefficient (95% CI) with predictors of IIRC groups, St Jude's Staging, and International Staging System (ISS) by laterality

	IIRC staging		St. Jude's Staging		ISS	
	Unilateral (N=102)	**Bilateral (N=66)**	**Unilateral (N=108)**	**Bilateral (N=69)**	**Unilateral (N=108)**	**Bilateral (N=69)**
	B (95%CI)	**B (95%CI)**	**B (95%CI)**	**B (95%CI)**	**B (95%CI)**	**B (95%CI)**
Lag time (months)^†	0.040 (−0.049, 0.130)	0.062 (−0.059, 0.182)	0.004 (−0.159, 0.167)	0.237[d] (0.089,0.384)	0.038 (−0.170, 0.247)	0.330[d] (0.146, 0.514)
Maternal education	−0.023 (−0.054, 0.008)	−0.052[d] (−0.085, −0.019)	−0.093 [d] (−0.152, −0.033)	−0.022 (−0.064, 0.019)	−0.100[c] (−0.176, −0.024)	−0.017 (−0.069, 0.035)
Dirt floor during pregnancy	0.168 (−0.137, 0.473)	0.426[a] (−0.042, 0.894)	0.912 [d] (0.327, 1.498)	0.504[a] (−0.067, 1.075)	1.097[d] (0.348, 1.846)	0.879[a] (0.166, 1.592)
Monthly household Income^			0.247[a] (−0.037, 0.531)		0.137 (−0.226, 0.501)	
R^2	0.057	0.230	0.208	0.214	0.189	0.253

[a] p<0.09;

[b] p<0.05;

[c] p<0.01;

[d] p<0.005.

^ natural log transformed.

† square root transformed for bilateral Rb

Table 3

Hazard ratio (95% CI) derived from Cox proportional hazard models for predictors of mortality for **unilateral** cases[a]

	Unadjusted	Model 1	Model 2	Model 3	Model 4
Predictor	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**
Lag time^ (month)	1.372 (0.846, 2.227)	1.332 (0.856, 2.071)	1.356 (0.857, 2.146)	1.348 (0.840, 2.162)	1.338 (0.862, 2.078)
Maternal education		0.765[c] (0.633, 0.925)	0.782[b] (0.637, 0.960)	0.738[b] (0.569, 0.957)	0.732[b] (0.567, 0.944)
IIRC			@ *d*		
St. Jude				6.77[d] (2.75, 16.66)	
ISS					3.88[d] (2.10, 7.18)

@All 12 deaths occurred in children with IIRC classification of “E”, resulting in an extremely large coefficient.

[a]Of 107 children with unilateral disease with lag time data, 103 were followed, 12 of these died; 88.35% censored.

[b]p<0.05;

[c]p<0.01;

[d]p<0.0001.

^natural log transformed

Table 4

Hazard ratios (with 95% CI) derived from Cox proportional hazard models for predictors of mortality **bilateral** cases. [a]

	Unadjusted	Model 1	Model 2	Model 3	Model 4
Predictor	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**	**Hazards ratio (95% CI)**
lag time^	1.85[c] (1.00, 3.41)	1.73 [c] (0.92, 3.26)	1.73 [c] (0.887, 3.167)	1.39 (0.715, 2.699)	1.380 (0.714, 2.668)
Maternal education		0.955 (0.817, 1.117)			
IIRC			2.089 (0.469, 9.302)		
St Jude				2.61[c] (1.175, 5.797)	
ISS					1.985 [c] (1.134, 3.475)

[a] Of the 69 children with bilateral disease, 66 had follow up information, and 8 of them died; 87.88% censored.

[b] p<0.09;

[c] p≤0.05; c p<0.01;

^ square root transformed