ORIGINAL ARTICLES

Actuarial Survival Based on Gestational Age in Days at Birth for Infants Born at <26 Weeks of Gestation

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Objective To provide comprehensive, contemporary information on the actuarial survival of infants born at 22-25 weeks of gestation in Canada.

Study design In a retrospective cohort study, we included data from preterm infants of 22-25 weeks of gestation admitted to neonatal intensive care units participating in the Canadian Neonatal Network between 2010 and 2017. Infants with major congenital anomalies were excluded. We calculated gestational age using in vitro fertilization date, antenatal ultrasound dating, last menstrual period, obstetrical estimate, or neonatal estimate (in that order). Infants were followed until either discharge or death. Each day of gestational age was considered a category except for births at 22 weeks, where the first 4 days were grouped into one category and the last 3 days were grouped into another category. For each day of life, an actuarial survival rate was obtained by calculating how many infants survived to discharge out of those who had survived up to that day.

Results Of 4335 included infants, 85, 679, 1504, and 2067 were born at 22, 23, 24, and 25 weeks of gestation, respectively. Survival increased from 32% at 22 weeks to 83% at $25^{4-6/7}$ weeks. Graphs of actuarial survival developed for the first 6 weeks after birth in male and female children indicated a steep increase in survival during the first 7-10 days postnatally.

Conclusions Survival increased steadily with postnatal survival and was dependent on gestational age in days and sex of the child. *(J Pediatr 2020;225:97-102)*.

Survival of extremely preterm infants has been increasing, as reported by several investigators.[1-3] Most of those studies depict survival as a static measure, calculated as a function of gestational age at birth or birth weight stratum. This approach does not take into account the progression of an infant as he or she survives and matures. The median age at death for infants born at <29 weeks of gestation was identified as 8 days, indicating that the likelihood of neonatal death reduces after the first week of survival.[2] Life table analyses based on gestational age at birth fail to provide such information.

Actuarial survival takes into consideration the child survival on each day and adjusts the capability of prognostication to provide for the actual likelihood of survival at each given postnatal age to which the infant survives. This approach has the advantage of providing specific information regarding survival as an infant matures and facilitates counseling of the parents. Previous studies have attempted to delineate actuarial survival. Cooper et al reported data from 3 hospitals in Texas,[4] Abdel-Latif et al reported data from 2 regions in Australia,[5] and Jones et al reported actuarial survival data from Canada.[6] All these reports lumped data from completed weeks of gestation in to a single category. It is now known that, for instance, an infant born at 23 weeks and 1 day of gestational age has a different prognosis than an infant born at 23 weeks and 6 days.[7] Thus, to provide parents and caregivers with comprehensive information, there is a need to create actuarial survival charts based on each individual day of gestation at birth that follow the progress of these infants before discharge to home. In this study, we aimed to provide such comprehensive, contemporary information using data from the Canadian Neonatal Network (CNN), a population-based

CNN	Canadian Neonatal Network
NICU	Neonatal intensive care unit

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database of preterm infants in Canada for infants born at 22-25 weeks gestational age.

Methods

The CNN is a multidisciplinary collaborative research program involving all 30 tertiary-level neonatal intensive care units (NICUs) in Canada. Our retrospective cohort study included data from preterm infants born at 22-25 weeks of gestation and admitted between January 1, 2010, and December 31, 2017, to CNN NICUs. Infants who had a major congenital anomaly or were moribund on admission (ie, no resuscitation was offered at birth) were excluded from the analysis.

Abstract at each of the tertiary-level NICUs across Canada collected data as part of the standard collection for benchmarking purposes for the CNN database. Data were collected using methods prescribed in a standardized manual across the NICUs[8,9] and were then transmitted to the CNN Coordinating Centre. Data collection at each site was approved by a local Research Ethics Board or Quality Improvement Committee. The database has been shown to have very high reliability and internal consistency.[9] This study was approved by the Executive Committee of the CNN and by the Research Ethics Board at Mount Sinai Hospital, Toronto.

In the CNN database, gestational age was calculated using in vitro fertilization date, antenatal ultrasound dating (if done before 16 weeks), last menstrual period, obstetrical estimate, or neonatal estimate, in that hierarchical order. We used the best estimate of gestational age from this hierarchy at the individual day of gestation level. Our outcome of interest was survival. Infants were followed until either discharge to a step-down unit or home or death. Owing to the centralized perinatal care in Canada, when neonates do not need intensive care they are transferred to level 2 units in the community, near the parents' home. We counted such infants as having survived beyond the date of transfer to level 2 hospitals. In our previous follow-up study, we identified extremely low mortality even extending to 2 years of follow up,[10] so this assumption was unlikely to introduce bias. We evaluated data for both sexes separately.

Analyses

From $22^{0/7}$ weeks to 25 $\text{weeks}^{6/7}$, each day of gestational age was considered a category. The only exception was for infants born during 22 weeks of gestation, for which the first 4 days were grouped into one category and the last 3 days were grouped into another category owing to the small number of infants. For each category of gestational age in days, the total number of infants and the total number of survivors to discharge were counted. On each day of life, an actuarial survival rate was obtained by determining how many infants survived to discharge out of those who had survived up to that given day. In other words, the actuarial survival rate on each day indicated how likely an infant was to survive to discharge, given that the infant had already survived up to that day. The data were graphically displayed until 6 weeks of postnatal age, because the graphs for each gestational age plateaued beyond 6 weeks.

Results

During the study period, a total of 4681 infants born at <26 weeks of gestational age were admitted to participating NICUs. Of these, 4335 infants were eligible for inclusion in this study. Among these, 161 infants were excluded due to major congenital anomaly and 183 were excluded who were moribund on admission. Two outborn infants with no birthdate record were also excluded. The baseline characteristics of the included infants are reported in Table I.

Among the included infants, 85, 679, 1504, and 2067 were of 22, 23, 24, and 25 weeks of completed gestational age at birth, respectively. Graphs of actuarial survival for the first 6 weeks of postnatal age are shown in Figure 1. We truncated the graphs in Figure 1 to 42 days postnatally. In infants who survived until 42 days, the rate of late death beyond 42 days was 12.9% (4 of 31) at 22 weeks of gestation, 7.3% (26 of 354) at 23 weeks, 4.2% (46 of 1085) at 24 weeks, and 3.2% (55 of 1734) at 25 weeks. Table II reports the median age at death for individual gestational age categories (each divided into 2 groups representing the first 4 days of the week and the last 3 days of the week). The data show that median age at death increased as gestational age at birth increased.

The most important variable affecting mortality in these extremely preterm infants was sex. Figure 2 (available at www.jpeds.com) shows similar actuarial survival curves for males and females, respectively. Figure 3 and Table II show at which postnatal ages an infant reached 80% survival (∼25 weeks of postmenstrual age), 85% survival (∼26 weeks), 90% survival (∼28 weeks), and 95% survival (∼30 weeks). The fitted line for these milestones is nonlinear, and owing to the small numbers of patients at each individual gestational age, the postmenstrual age to reach 95% survival was variable.

Table I. Baseline patient characteristics (N = 4335)

Characteristics	Values
Gestational age, wk, mean (SD)	24.3 (0.8)
Birth weight, g, mean (SD)	715 (146)
Male sex, n (%)	2269 (52)
Antenatal steroid use, n (%)	3622 (86)
Maternal hypertension, n (%)	406 (10)
Maternal diabetes, n (%)	235 (6)
Outborn, n (%)	731 (17)
Cesarean delivery, n (%)	2102 (49)
Apgar score at 5 min <7, n (%)	2467 (72)
Score for Neonatal Acute Physiology II score >20, n (%)	2071 (50)

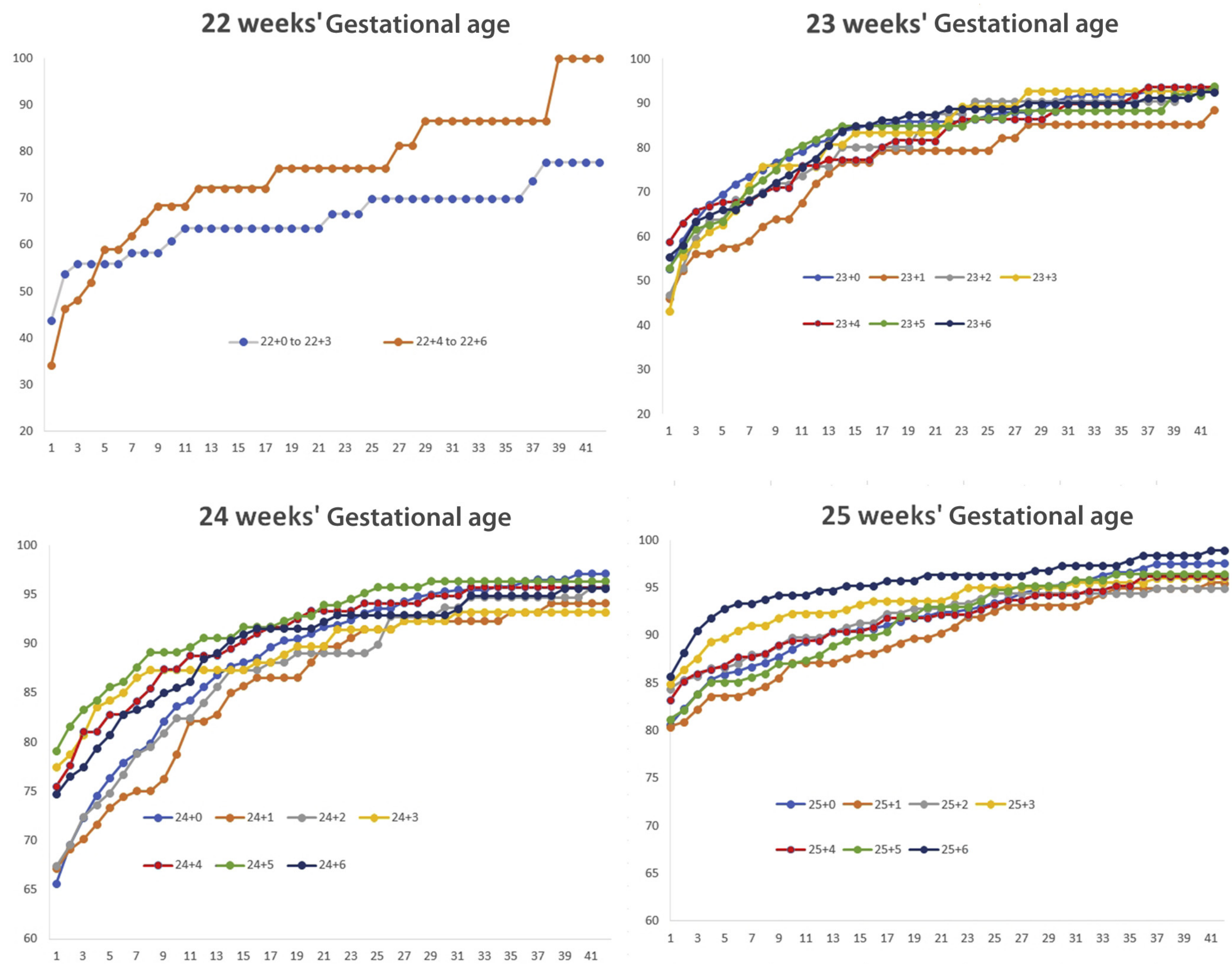

Figure 1. Actuarial survival curves by gestational age. The *x*-axes represent postnatal age in days; the *y*-axes, percentages. Late deaths beyond 42 days were 12.9% (4 of 31) at 22 weeks of gestation, 7.3% (26 of 354) at 23 weeks, 4.2% (46 of 1085) at 24 weeks, and 3.2% (55 of 1734) at 25 weeks among those who survived until 42 days.

Discussion

In this national population-based cohort study, we identified that survival increased steadily and rapidly with increasing postnatal age in all gestational age groups. Survival was 80% by 4-5 weeks for infants born at 22 weeks, by 2-3 weeks for those born at 23 weeks, by 0-10 days for those born at 24 weeks, and at birth for those born at 25 weeks. The survival rates differed between the start of the week after completed gestational age in weeks and the end of the week for all gestational age groups. Moreover, actuarial survival curves differed between boys and girls. Our results are applicable only to those infants who received active care at birth, as those who were not resuscitated were excluded.

Cooper et al reported actuarial survival data for infants born at 23-29 weeks of gestation admitted to Baylor College of Medicine-affiliated nurseries in Texas between 1986 and 1994.[4] They provided graphs for each individual gestational age in weeks and at 100-g birth weight intervals. They reported that survival increased significantly during the first few postnatal days; however, there was a significant incidence of late mortality in their cohort. Jones et al also reported actuarial survival data on infants born at 22-30 weeks of gestation admitted between 1996 and 1997 to 17 NICUs in Canada that were part of the CNN at that time.[6] Their graphs reported gestational age in weeks. Our current data represent a more contemporary cohort, with data collected during a recent 8-year period that better reflects the current situation. Jones et al also reported the predicted probability of increasing survival with advancing postnatal age, with the greatest risk of death during the first 6 days. Similar results were reported by Abdel-Latif et al, from 2 territories in Australia, for infants born at 22-32 weeks of gestation between 1997 and 2006.[5]

Table II. Survival, median age at death, and postnatal age when survival reaches preset milestones by gestational age category

Gestational age groups, wk	Survival, n/N (%)	Age at death, d, median (IQR)	Postnatal age when survival ≥80%, wk	Postnatal age when survival ≥85%, wk	Postnatal age when survival ≥90%, wk	Postnatal age when survival ≥95%, wk
22^{0-3}	14/41 (34)	2 (1-25)	33^{0}	38^{1}	39^{6}	48^{3}
22^{4-6}	13/44 (30)	2 (2-8)	26^{3}	26^{5}	28^{1}	28^{1}
23^{0}	102/204 (50)	4 (2-12)	24^{5}	25^{2}	27^{2}	29^{6}
23^{1}	23/53 (43)	8 (2-14)	26^{6}	27^{1}	31^{2}	32^{5}
23^{2}	28/66 (42)	3.5 (2-12)	25^{2}	26^{1}	26^{5}	35^{0}
23^{3}	25/64 (39)	3 (2-8)	25^{2}	26^{4}	27^{3}	36^{1}
23^{4}	54/82 (66)	8.5 (2-22)	26^{0}	26^{6}	28^{5}	30^{3}
23^{5}	45/96 (47)	6 (2-10)	25^{2}	27^{1}	29^{2}	29^{6}
23^{6}	62/114 (54)	9 (3-14)	25^{5}	26^{2}	29^{1}	30^{5}
24^{0}	363/570 (64)	6 (3-14)	25^{2}	25^{5}	26^{4}	28^{1}
24^{1}	96/144 (67)	11 (5-21)	25^{5}	26^{1}	27^{3}	31^{0}
24^{2}	89/134 (66)	9 (4-19)	25^{4}	26^{1}	28^{0}	30^{1}
24^{3}	96/131 (73)	6 (2-27)	24^{6}	25^{2}	27^{4}	32^{6}
24^{4}	111/152 (73)	8 (3-17)	25^{0}	25^{5}	26^{5}	29^{1}
24^{5}	155/199 (78)	7.5 (3-21)	25^{0}	25^{3}	26^{3}	28^{1}
24^{6}	130/174 (75)	10.5 (5-21.5)	25^{4}	26^{1}	26^{6}	30^{3}
25^{0}	656/826 (79)	10.5 (3-27)	25^{1}	25^{4}	26^{6}	29^{1}
25^{1}	148/188 (79)	15 (4-32)	25^{2}	26^{3}	28^{1}	31^{0}
25^{2}	168/200 (84)	16 (7-47.5)	25^{3}	25^{4}	27^{1}	31^{6}
25^{3}	191/226 (85)	9 (4-37)	25^{4}	25^{5}	26^{2}	28^{5}
25^{4}	178/216 (82)	14.5 (4-34)	25^{5}	25^{6}	27^{3}	30^{3}
25^{5}	160/199 (80)	14 (4-25)	25^{6}	26^{2}	28	29^{4}
25^{6}	180/212 (85)	5 (3-20)	26^{0}	26^{0}	26^{2}	27^{6}

Late deaths were included in this calculation.

They also noted that infants who survived the first few days after birth had a very high probability of survival before discharge, with specifically notable improvements in infants born at <26 weeks of gestation. Hornik et al reported data on infants born at 22-29 weeks of gestation between 1997 and 2013 from 362 NICUs of the Pediatrix Medical Group in the US.[11] Similar to previous studies, these authors also reported increasing survival with advancing

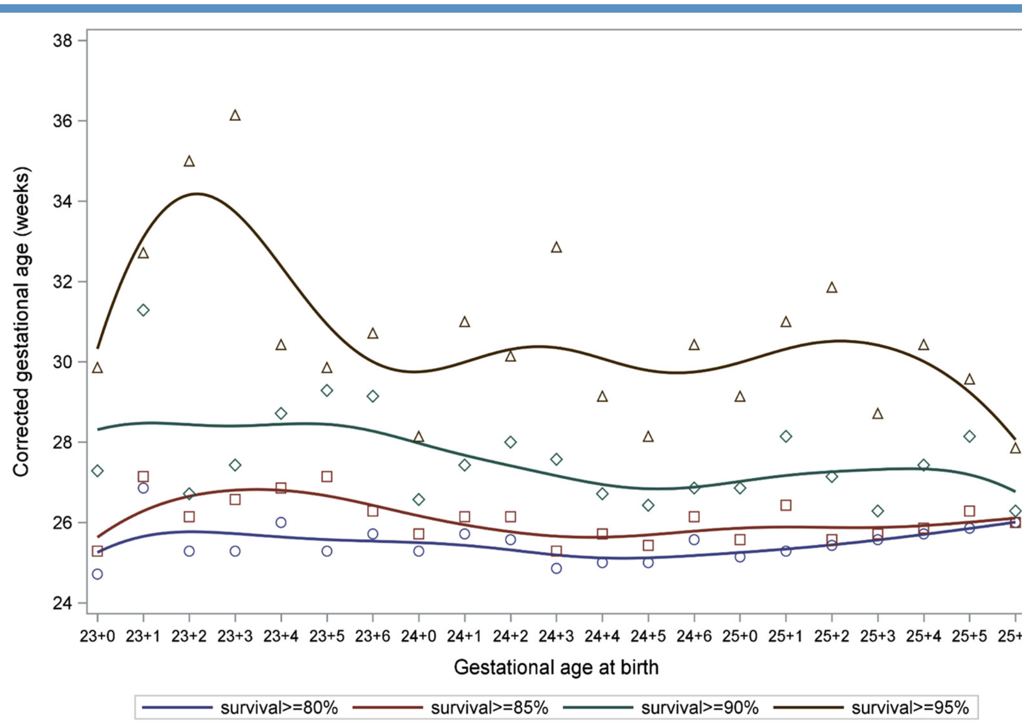

Figure 3. Survival as a function of gestational age and corrected gestational age. Late deaths were included in the calculation. Owing to smaller numbers of neonates at lower gestational ages, the fitted lines are not smooth.

gestational age and postnatal age. They found that survival increased steeply for the first 7 days, then increased steadily for the next 3 weeks, and finally either plateaued or declined.

Our results are similar to the findings reported by the foregoing studies, but extend beyond them. First, we concentrated on infants born at <26 weeks of gestation, as survival has improved significantly for infants born at higher gestational age, with an approximate survival rate of 90% for those born at 26 weeks even at birth. Second, because we used a large, multicenter database, we were able to generate graphs for individual days of each gestational age between 23 and 26 weeks. For individual weeks of gestation at birth, we identified that survival was higher in the latter part of the week compared with the earlier part. We acknowledge that gestational age measurement, irrespective of the criteria used (except for in vitro fertilization date) is prone to error. Our comprehensive, hierarchical structure for estimation of gestational age was implemented in the CNN database based on then-current recommendations form the Society of Obstetricians and Gynecologists of Canada. All measures may have variations of 3-7 days from the estimate, and this should be kept in mind when interpreting our results. Nonetheless, we do not feel that such differences could introduce bias in the application of our results, given that the same estimates are currently used when counseling parents based on completed weeks of gestational age.

There are several potential uses of our graphs. They can be used in counseling parents regarding the potential for survival as their infant matures in the NICU. For parents willing to receive such information, access to such information may provide welcome ongoing prognostic information about their infant. Predicted survival by postnatal age provides more updated information for counseling then the currently used methods based on gestational age at birth or intuition-based estimates. Meadow et al found that a significantly high proportion of infants predicted to die by at least one health care provider ultimately survived.[12] Our graphs provide actual data stratified by gestational age in days and could be very useful for such a purpose. This information can also be used for resource planning by administrators, as infants may need acute and intense resources for the first 1-2 weeks after birth and then, once classified as stable or surviving, plans can be made for a longer length of stay.

Our study has some limitations. First, we only included infants who were admitted to a NICU. Thus, those who were stillborn or who died in the delivery room were not included. This must be kept in mind when the charts are used, because they are only applicable for admitted infants. Second, gestational age estimates still involve inaccuracies that we need to understand, as is evident from the data showing more infants with gestational age reported as completed weeks of gestation rather than incomplete weeks. Refinement of the assessment of gestational age using early ultrasound whenever possible will be helpful in future studies. We also postulate that some of the variation in mortality may be due to treatment decisions or thresholds applied before and after birth (eg, antenatal steroids, cesarean delivery, resuscitation); however, we do not have data on such decision making in this study and so cannot evaluate its impact. Third, we did not directly compare survival between male and female infants, because identifying statistically significant differences between the sexes was not a focus of this study. Rather, the purpose was to provide graphs that can be of use in parent counseling.

In conclusion, for infants born at <26 weeks of gestation, postnatal survival increases steeply in the first few postnatal days and varies by gestational age in days, even within a category of completed gestational age in weeks. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Revisiting a Diagnostic Dilemma 50 Years Later: Partially Treated Bacterial Meningitis

Winkelstein JA. The Influence of Partial Treatment with Penicillin in the Diagnosis of Bacterial Meningitis. J Pediatr 1970;77:619-24.

Cerebrospinal fluid (CSF) analysis and culture remain the gold standard diagnostic evaluation for bacterial meningitis. However, early initiation of antibiotics may complicate the interpretation of subsequently obtained CSF, rendering it difficult to distinguish viral from bacterial meningitis. A landmark study in 1970 challenged this presumption. Winkelstein tested whether procaine penicillin, the drug most commonly prescribed for febrile children in a community in Alaska, would modify CSF findings and obfuscate the diagnosis. The records of 21 children who had received penicillin were compared with 16 who had not received penicillin before their diagnostic lumbar puncture. There was no significant effect of antibiotic pretreatment on clinical presentation, CSF variables, or ability to differentiate bacterial from viral meningitis. However, the predominant bacterial etiology in that study was *Haemophilus influenza.*

Today, however, the epidemiology of pediatric bacterial meningitis has changed, reflecting the success of vaccines for *H influenza*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Although *H influenzae* has been eradicated, pneumococcal and meningococcal disease persist owing to incomplete vaccine protection against all serotypes. This in turn, has led to the emergence of nonvaccine serotypes as causative pathogens. Furthermore, there are no vaccines for group B streptococcus, staphylococcus, or *Escherichia coli*, which have increasingly become more important causes of meningitis, particularly in infants.

Additionally, newer antimicrobials such as third-generation cephalosporins and carbapenems have supplanted penicillins, which has important implications for CSF interpretation. For example, ceftriaxone achieves higher central nervous system concentrations and has been shown to rapidly sterilize CSF, even after 1 dose for *N meningitidis*. These newer antibiotics may also cause a more rapid shift from a neutrophilic-to a monocytic-predominant CSF profile, although there is persistence of pleocytosis and elevated protein levels.

The clinical imperative or temptation to initiate antibiotics has become more "common practice," particularly in settings where a lumbar puncture is difficult to perform or unsuccessful. The lack of microbiological CSF data poses a diagnostic challenge hindering opportunities for appropriate antibiotic stewardship. This issue has been especially evident in managing infants treated for *E coli* urosepsis where interpretation of pretreated CSF is limited. Newer molecular diagnostic tools including broad-range polymerase chain reaction targeting the 16S ribosomal RNA gene of bacteria are promising, but more research is required. Despite great advances, the challenge of partially treated bacterial meningitis endures.

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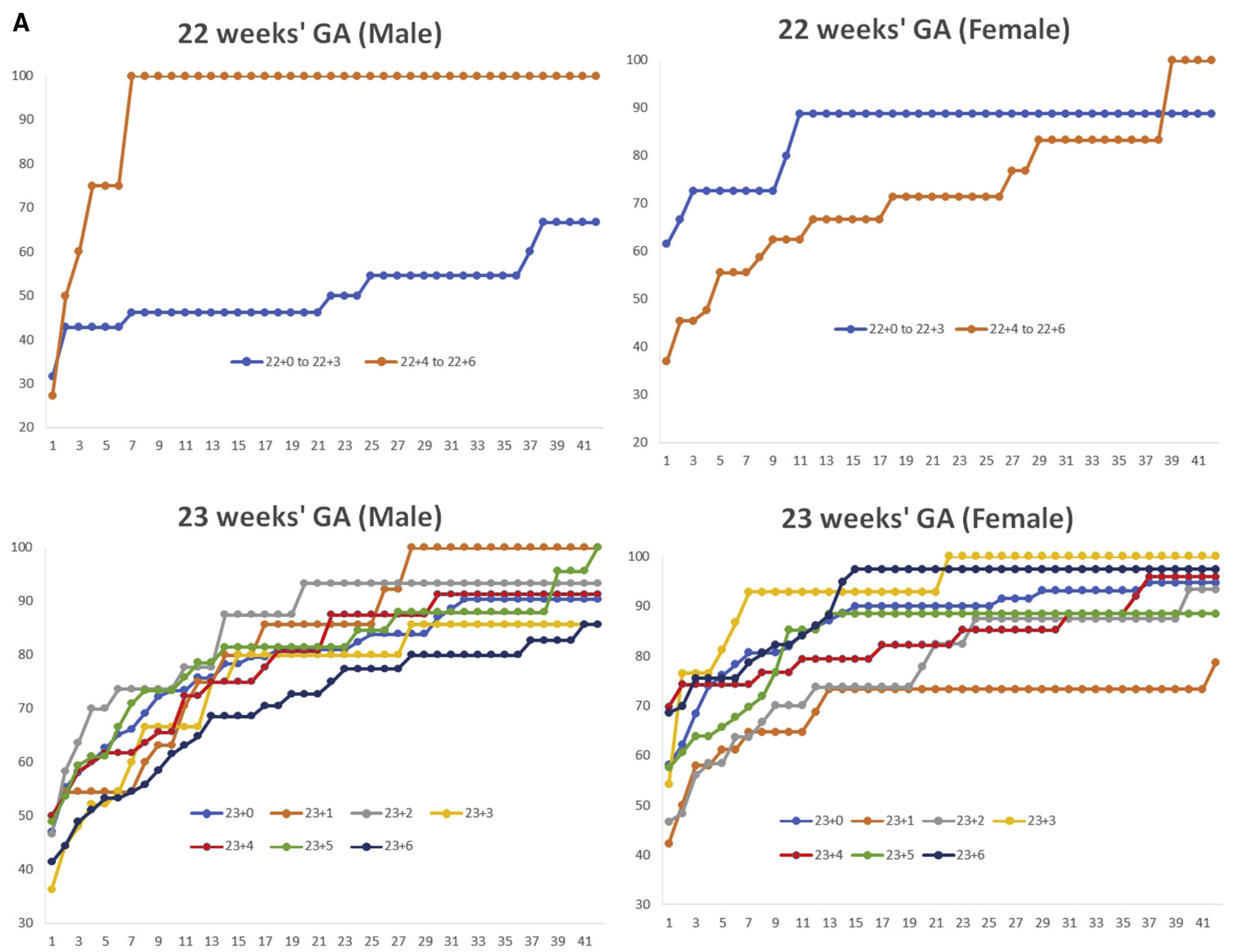

Figure 2. Actuarial survival curves by gestational age and sex. The *x*-axes represent postnatal age in days; the *y*-axes, percentages. *(Continues)*

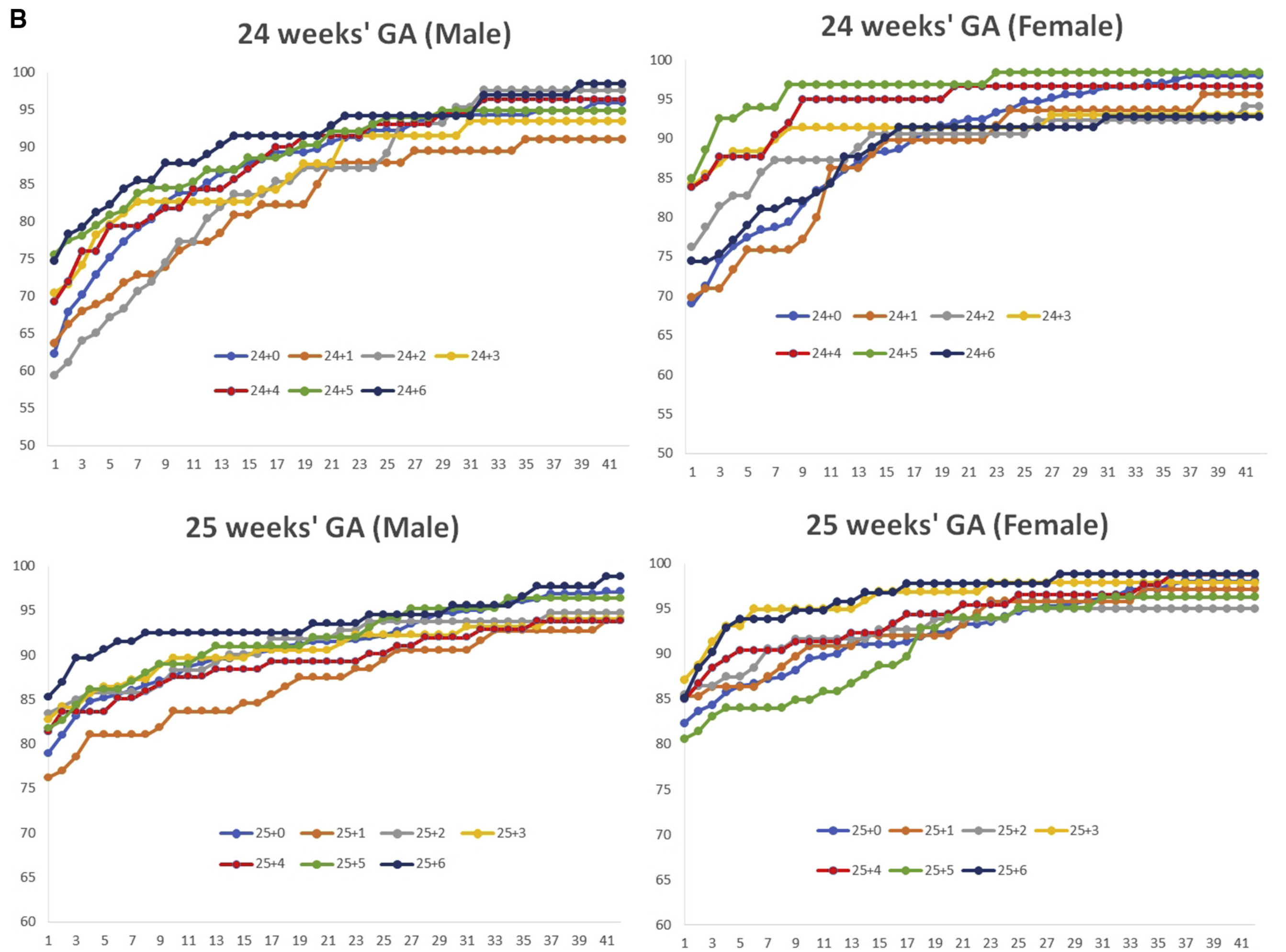

Figure 2. Continues