



Medical and surgical interventions and outcomes for infants with trisomy 18 (T18) or trisomy 13 (T13) at children's hospitals neonatal intensive care units (NICUs)

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Abstract

Objectives To examine characteristics and outcomes of T18 and T13 infants receiving intensive surgical and medical treatment compared to those receiving non-intensive treatment in NICUs.

Study design Retrospective cohort of infants in the Children's Hospitals National Consortium (CHNC) from 2010 to 2016 categorized into three groups by treatment received: surgical, intensive medical, or non-intensive.

Results Among 467 infants admitted, 62% received intensive medical treatment; 27% received surgical treatment. The most common surgery was a gastrostomy tube. Survival in infants who received surgeries was 51%; intensive medical treatment was 30%, and non-intensive treatment was 72%. Infants receiving surgeries spent more time in the NICU and were more likely to receive oxygen and feeding support at discharge.

Conclusions Infants with T13 or T18 at CHNC NICUs represent a select group for whom parents may have desired more intensive treatment. Survival to NICU discharge was possible, and surviving infants had a longer hospital stay and needed more discharge supports.

Introduction

Recent studies have added to our understanding of the medical care received by infants with trisomy 13 (T13) or trisomy 18 (T18) during and after the neonatal period [1–3]. Some infants with T13 or T18 receive interventions in neonatal intensive care units (NICUs), and their survival to NICU discharge has been reported to be between 20–60% depending on risk factors [2]. The experience of families living with children with these conditions has also been described, and has emphasized the importance of

individualizing counseling to families based on both the specific medical co-morbidities associated with the genetic diagnoses and parental goals for their children [4–8].

After receiving a prenatal diagnosis of T13 or T18, some expectant families choose to carry to term and provide supportive care focused on comfort following delivery. These infants are often cared for in newborn nurseries and avoid NICU admission. Infants with T13 or T18 who are admitted to NICUs may receive interventions for various indications. These include parental desire for providing therapies to infants with confirmed diagnoses, interventions provided in the absence of a confirmatory diagnosis, or inherent medical instability while diagnosis is pending. Both T13 and T18 are associated with anomalies that can be emergently life threatening, but not all infants with T13 or T18 have these anomalies, and this makes caring for these infants in the immediate newborn period complex. Some infants do not require many neonatal interventions and survive, some survive after receiving interventions, and some die despite potentially life-sustaining medical

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or surgical interventions [9]. What is less well-described in the literature is a comparison of the outcomes and predictors of mortality among infants based on the level of medical and/or surgical interventions received.

In a cohort of infants admitted to US children's hospitals NICUs, our objectives were to: (1) categorize infants into groups based on level of NICU interventions received: non-intensive medical interventions, intensive medical interventions alone, and both intensive medical and surgical interventions; (2) assess demographic characteristics, NICU hospital course and discharge outcomes of infants in these groups; and (3) compare the characteristics of infants who die vs. survive to assess predictors of mortality in each of these groups. We hypothesized that infants with T13 or T18 admitted to US children's hospitals NICUs commonly undergo medical and surgical interventions and that these interventions have become more frequent over time.

Materials and methods

The Children's Hospitals Neonatal Database (CHND) captures clinical data for infants admitted to 34 US children's hospitals NICUs (the Children's Hospital Neonatal Consortium, or CHNC) until they either leave the NICU setting or achieve one year of age [10]. Greater than 50% of all infants represented in CHND are ≥ 37 weeks gestation, and a quarter of those have surgical anomalies. The majority of infants in this cohort are out born. The database contains detailed information about medical and surgical interventions, comorbid diagnoses, prenatal and perinatal data, as well as the end of life care practices for infants who die before NICU discharge. Diagnoses of T13 or T18, when entered by a provider in a patient's chart, are uniquely recorded. For both, timing of diagnosis, whether prenatal or postnatal, is recorded. All data points are extracted by trained data coordinators at each CHND site through patient chart review. The CHND does not capture data on infants cared for exclusively in cardiac ICUs. All participating sites in CHND obtained Institutional Review Board approval for participation in the database. The database is approved for use by a central Institutional Review Board (IRB).

For this study, we included all infants with a diagnosis of T13 or T18 admitted to CHNC NICUs between 2010 and 2016. Mosaic T13 or T18 are typically included as a diagnosis of T13 or T18 by the data coordinators and not separately coded as mosaicism. We excluded readmissions as well as open charts, which reflect infants receiving NICU care at the end of the study period.

We first categorized infants into groups based on the level of NICU treatment they received: (1) *surgical treatment* included infants who received one or more major surgical procedures during their NICU stay; these infants

may have received other intensive medical treatment as in (2); (2) *intensive medical treatment* included infants who received one or more of the following medical interventions: delivery room resuscitation requiring positive-pressure ventilation, intubation, cardiac compressions or epinephrine, or in-NICU interventions to include non-invasive positive pressure respiratory support (defined as high flow nasal cannula > 2 liters per minute or nasal CPAP), mechanical ventilation, surfactant, systemic steroids, vasopressors or inotropes, or inhaled nitric oxide (iNO); (3) *non-intensive treatment* included infants who received NICU care and none of these above interventions.

For surgical procedures, we obtained a list of every procedure performed and manually reviewed the list. Commonly performed NICU procedures, such as umbilical catheterizations, intubations, circumcisions, chest tube placement or abdominal paracentesis were not included in the list of surgical procedures. Major surgeries included were typically those that would require a trip to the operating room and/or presence of anesthesiology, such as bronchoscopy for airway evaluation, gastrostomy tube placement, repair of a diaphragmatic hernia, etc. Surgical procedures performed in infants with T13 or T18 and included in this study are listed in Appendix A (online).

Next, we assessed demographic characteristics for infants in each group, such as birth weight, NICU interventions received, details of hospital course, such as length of stay (LOS), and discharge outcomes. We assessed support provided to infants who survived to NICU discharge, including home oxygen or tube feeds. Finally, we compared the characteristics of infants who died vs. survived in each of these treatment groups.

Data analyses were performed using SAS Enterprise Guide 7.1 (Cary, NC). Categorical variables were compared using chi-squared tests of proportions or 2-sided Fisher's exact test as appropriate. Continuous variables were compared using non-parametric Wilcoxon rank-sum test and Kruskal–Wallis test, as distributions departed from normality. Multivariable logistic regression analysis was used to identify predictors of mortality in infants who received intensive medical or surgical treatment.

Results

Table 1 shows demographic characteristics of the cohort by treatment group. 150 infants had a diagnosis of T13 and 317 with T18. The majority of infants in this cohort received some degree of medical and/or surgical interventions (90%). A third of patients in the cohort were prenatally diagnosed, and most were referred in from birth hospitals. Infants in the non-intensive treatment group were more likely to be full-term, delivered vaginally, inborn, and have a 1-min Apgar score of >7 . The proportion of prenatally diagnosed cases

Table 1 Demographic characteristics of infants with T13 or T18 in 3 treatment groups (n = 467).

	Entire cohort 467	Surgical treatment 129	Intensive medical treatment 292	Non-intensive treatment 46	p-value
Gestational age at birth (weeks)	n(%)	n(%)	n(%)	n(%)	0.009
≤27 + 6/7	5 (1%)	2 (2%)	3 (1%)	0(0%)	
28 to 31 + 6/7	41 (9%)	7 (5%)	32 (11%)	2 (4%)	
32 to 36 + 6/7	154 (33%)	53 (41%)	94 (32%)	7 (15%)	
≥37	267 (57%)	67 (52%)	163 (56%)	37 (81%)	
Age at admission (days) median (IQR)	1 [0, 4]	1 [0, 22]	0 [0, 2]	1 [0, 14]	<0.001
Birth weight (g)					
≤ 1500 g	100 (22%)	25 (20%)	69 (24%)	6 (13%)	0.127
1501–2499 g	259 (56%)	81 (64%)	150 (52%)	28 (62%)	
> = 2500 g	101 (22%)	21 (16%)	69 (24%)	11 (25%)	
Small-for-gestational age	305 (65%)	91 (70%)	180 (62%)	34 (74%)	0.091
Male gender	190 (41%)	52 (40%)	123 (42%)	15 (33%)	0.472
Maternal race ^a					
White	241 (52%)	67 (52%)	152 (52%)	22 (48%)	0.244
Black	119 (25%)	35 (27%)	73 (25%)	11 (24%)	
Other	65 (14%)	17 (13%)	41 (14%)	7 (15%)	
Asian	10 (2%)	1 (1%)	9 (3%)	0(0%)	
Hawaiian/Pacific Islander	4 (1%)	0(0%)	2 (1%)	2 (4%)	
Inborn	58 (12%)	11 (8%)	38(13%)	9 (19%)	0.036
Delivery type					
Cesarean	278 (60%)	80 (62%)	182 (62%)	16 (35%)	<0.001
Vaginal	175 (37%)	44 (34%)	106 (36%)	25 (54%)	
Unknown	14 (3%)	5 (4%)	4 (2%)	5 (11%)	
1-minute APGAR score					
< = 2	130 (30%)	38 (31%)	88 (31%)	4 (11%)	<0.001
3 to 6	214 (49%)	59 (49%)	143 (51%)	12 (33%)	
> = 7	92 (21%)	24 (20%)	48 (18%)	20 (56%)	
5-minute APGAR score					
≤ 2	23 (5%)	5 (4%)	16 (6%)	2 (6%)	0.059
3 to 6	143 (33%)	41 (34%)	98 (35%)	4 (11%)	
> = 7	270 (62%)	75 (62%)	165 (59%)	30 (83%)	
Prenatal diagnosis	171 (37%)	55 (43%)	98 (33%)	18 (39%)	0.191
Proportion of prenatally diagnosed cases who were inborn	41 (24%)	9 (16%)	25 (25%)	7 (39%)	0.131
Primary reason for admission					
Anomalies or syndrome	190 (41%)	32 (25%)	136 (47%)	22 (48%)	<0.001
Respiratory	87 (19%)	56 (43%)	29 (10%)	2 (4%)	<0.001
Cardiac	81 (17%)	14 (11%)	57 (20%)	10 (22%)	0.068
Preterm birth	60 (13%)	11 (8%)	45 (15%)	4 (9%)	0.102
Surgical evaluation	34 (7%)	11 (8%)	15 (5%)	8 (17%)	0.010

IQR interquartile range.

Percentages are column percentages.

p values of <0.05 are in bold font.

^aContain missing values and numbers do not add up to 100%.

was not statistically different between groups. Prematurity (<32 weeks) was more common in the group receiving intensive medical treatment.

Appendix B (online) shows the types of medical interventions received by infants in the 3 groups. One third of infants were intubated in the delivery room, but cardiac compressions or epinephrine use was infrequent. Infants who underwent

surgeries were more likely to be mechanically ventilated and required longer duration of mechanical ventilation. The overall proportion of infants who received inotropic support was small.

Appendix C (online) lists the most common surgeries performed in the NICU and outcomes for those patients. For selected surgeries, we also list the total number of patients with associated anomalies in the cohort. For example, for

infants who receive a tracheoesophageal fistula ligation, we list the number of patients in the cohort with a tracheoesophageal fistula. Surgical interventions were performed in 25% of patients. The most frequent surgeries were gastrostomy placement and bronchoscopy, but a small proportion of patients underwent major cardiac, thoracic, or neurological surgeries. When we looked at the number of surgeries per patient, 53 (41%) patients had 1 surgery performed, 48 (37%) had 2–3 surgeries performed, and 28 (22%) patients had >4 surgeries performed.

Table 2 shows discharge outcomes for infants by treatment group. Overall survival to NICU discharge was 40% (when including infants who were transferred in the denominator). When excluding infants who were transferred out from the denominator of total ($n = 419$ infants since 48 were transferred), the survival to NICU discharge was 45%. Infants in the non-intensive treatment group were most likely to survive, while infants in the intensive medical treatment group were least likely to survive. Most infants who died in intensive treatment groups had withdrawal of life-sustaining therapies and/or do not resuscitate (DNR) orders in place at the time of death. All infants in the non-intensive care group had DNR orders in place at the time of death. Among survivors, infants who received surgical interventions had a longer length of stay (LOS), greater duration of mechanical ventilation, and were more likely to be discharged home with feeding and respiratory medical support. More than half of the infants discharged home were referral to palliative care. Infants who received surgical interventions were less likely to be referred to palliative care.

Figure 1 shows temporal trends in admissions of infants with T13 and T18 from 2010 to 2016 separated by treatment group. The total number of infants admitted with T13 or T18 increased over the study period ($p = 0.002$) as did the proportion of total admissions who received surgical interventions ($p = 0.003$), from 15% in 2010 to 33% in 2016. During the same time period, the number of centers contributing to CHNC also increased from 22 centers in 2010 to 30 centers in 2016. The number of infants who received intensive treatment or non-intensive treatment did not statistically increase over time. During the same study period, the proportion of infants who survived overall, or by treatment group did not significantly change.

Figure 2 demonstrates inter-center variability in admissions for infants with T13 or T18 as well as the proportion of infants in the three groups for centers admitting >10 total patients. There was wide variability in both number of admissions and proportion of infants receiving medical and surgical treatment across centers. The proportion of infants receiving intensive medical interventions ranged from 0 to 90%, with a strong positive correlation between center volume and patients who received intensive medical

treatment ($r = 0.89$, $p < 0.001$) as well as those receiving surgical treatment ($r = 0.5$, $p = 0.003$).

Table 3 compares the characteristics of infants who died vs. survived in each of the treatment groups. In both intensive treatment groups, infants who died were more likely to be preterm, of lower birth weight, male, require intubation or mechanical ventilation, and receive systemic steroids for cardiovascular support. In the intensive medical treatment group, the infants who died were more likely to be admitted for a surgical evaluation. In the non-intensive treatment group, the majority of infants who died were admitted for major anomalies. In a multivariable regression model (Appendix D (online)) for both intensive treatment groups, male sex, low birth weight, and need for mechanical ventilation (>1 week) were all significantly associated with mortality. Infants who died in both intensive treatment groups spent twice the amount of time on mechanical ventilation as infants who survived.

Discussion

This is the first study to describe medical and surgical interventions and how they impacted outcomes of infants with T13 or T18 admitted to a large multi-center collaborative of children's hospital NICUs. Our primary conclusions are as follows:

- (1) The majority of infants with T13 or T18 admitted to CHNC NICUs received intensive medical or surgical treatment. This cohort likely represents a selected sample of infants for whom families may have desired at least an initial NICU evaluation and a trial of intensive care, and/or those in whom a confirmatory diagnosis was not achieved prior to NICU admission.
- (2) The most common surgery performed in the NICU was gastrostomy tube placement, but some infants underwent more complex surgeries.
- (3) Overall survival to NICU discharge was 40%; survival was 72% for infants in the non-intensive treatment group; 51% in the intensive surgical treatment group, and 32% in the intensive medical treatment group.
- (4) Infants who died after receiving intensive treatment were more likely male, of low birth weight, and received prolonged mechanical ventilation compared to those who survived. Although numbers were small, certain surgeries were associated with high mortality.
- (5) There was wide inter-center variability in total number of admissions of infants with T13 or T18 as well as the proportion of infants receiving intensive treatment by center.

Table 2 Hospital Outcomes for Infants with T13 or T18 who received surgical, intensive medical or non-intensive treatment (*n* = 467).

	Entire Cohort 467	Surgical treatment 129	Intensive medical treatment 292	Non-intensive treatment 46	<i>p</i> -value
Died before hospital discharge	231 (49)	42 (32)	179 (61)	10 (22)	<0.001
Of those who died,					
DNR Orders	175 (76)	32 (76)	133 (74)	10 (100)	0.182
Medical care withdrawn	164 (71)	34 (81)	129 (72)	1 (10)	<0.001
LOS, median (IQR)	7 [3,17]	17 [9,47]	7 [3,15]	2 [0, 3]	<0.001
Survived to hospital discharge	188 (40)	66 (51)	89 (30)	33 (72)	<0.001
Of those who survived to discharge,					
LOS, median (IQR)	13 [6,25]	27 [16,43]	10 [6,17]	6 [3,12]	<0.001
Total ventilator days, median (IQR)	5 [2,10]	6 [4,18]	3 [1,5]	. [...]	0.003
Therapy at discharge					
Feeding support					
Gastrostomy tube feedings	41 (22)	41 (62)	0(0)	0(0)	<0.001
Respiratory support at discharge					
Tracheostomy	5 (3)	5 (8)	0(0)	0(0)	0.009
Apnea monitor	66 (35)	28 (42)	31 (35)	7 (21)	0.241
Home oxygen	92 (49)	34 (51)	51 (57)	7 (21)	0.002
Mechanical ventilator	5 (3)	4 (6)	1 (1)	0(0)	0.097
Route of feeds at discharge					
Breast	20 (11)	3 (4)	9 (10)	8 (24)	0.026
Bottle	51 (27)	10 (15)	25 (28)	16 (48)	0.005
Tube feedings	157 (83)	62 (94)	75 (84)	20 (61)	0.001
Gastrostomy tube feedings	41 (22)	41 (66)	0(0)	0(0)	
Nasogastric/orogastric tube feedings	113 (60)	18 (27)	75 (84)	19(58)	
Transpyloric feeds	3(1)	2(3)	0(0)	1(3)	
Discharged with a referral to palliative care ^a	97/177(55%)	22/64(34%)	54/83(65%)	21/30(70%)	<0.001
Transferred out ^b	48 (10)	21 (16)	24 (8)	3 (6)	0.029
LOS median (IQR)	17 [6,35]	35 [19,68]	8 [2,19]	2 [0, 7]	<0.001
Of those who transferred out, reasons for transfer,					
Chronic care	1 (2)	1 (5)	0(0)	0(0)	0.041
Growth/discharge planning/ continuing care	17 (35)	7 (33)	8 (33)	2 (67)	
Medical/diagnostic services	1 (2)	1 (5)	0(0)	0(0)	
Palliative care	18 (37)	3 (14)	14 (58)	1 (33)	
Surgery	10 (21)	9 (43)	1 (4)	0(0)	
Unknown	1 (2)	0(0)	1 (4)	0(0)	

DNR do not resuscitate, IQR interquartile range, LOS length of stay.

p values of <0.05 are in bold font.

^aContains 11 missing values.

^bThe number of infants transferred out (*n* = 48) is included in the denominator for percentages.

Overall, this cohort admitted to CHNC NICUs likely represents a select group of infants referred for advanced care. Their families may have had prenatal suspicion for these conditions and desired interventions, or only discovered the diagnosis postnatally. This cohort does not encapsulate infants who were cared for in newborn

nurseries or who died in the delivery room. Prior studies show that fewer than 5% of parents who receive a prenatal diagnosis of T13 or T18 choose to receive intensive medical interventions in the NICU; most choose to terminate the pregnancy or to deliver with a plan for comfort care [9]. We cannot tell from our data the families' goals for NICU

Fig. 1 Time trends in NICU admissions, number of infants receiving intensive vs. non-intensive treatment and percentage of surviving infants from 2010–16 ($n = 467$). X-axis represents year and number of centers contributing data to the CHNC in that year in parenthesis. Y-axis represents number of T13 or T18 admissions in that year.

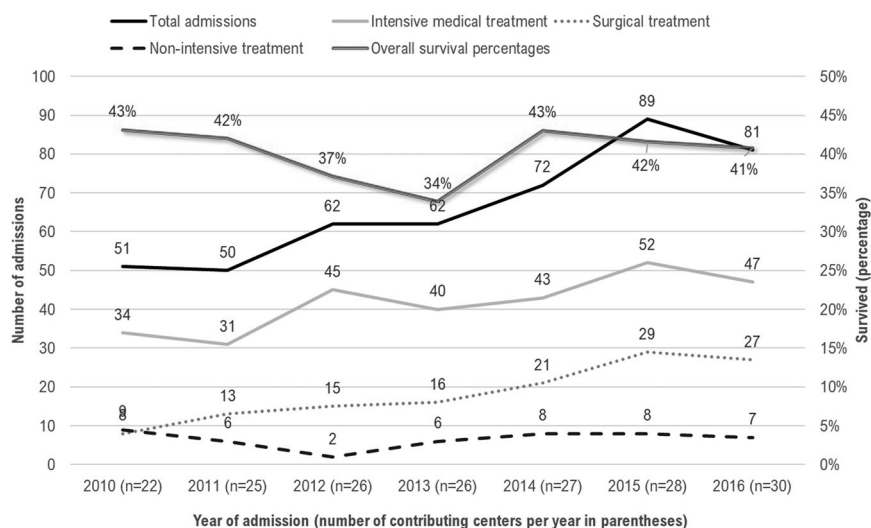
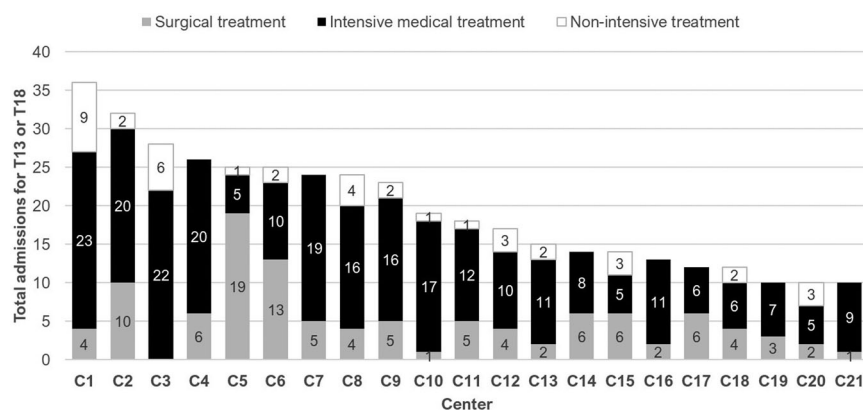


Fig. 2 Center variation in 3 treatment groups for infants with T13 or T18 in centers with >10 patients ($n = 407$). C1 through C21 denote different center locations.



admission; whether for comfort care alone, a trial of interventions, or intensive treatment followed by redirection of care to comfort. It is somewhat surprising in the modern era of prenatal testing that only a third of infants in this cohort had a prenatal diagnosis of T13 or T18. However, when we examined trends in the proportion of prenatally diagnosed cases by year, a significantly higher number of cases (53% in 2016 vs. 17% in 2010, $p < 0.001$) were diagnosed prenatally in later years. Those without confirmatory prenatal diagnosis may have had suspicion based on ultrasound screening or non-invasive screening tests and were either not offered or refused additional prenatal confirmatory genetic testing. As a result, some infants may have received intensive interventions initially followed by realignment of goals of care to comfort after a postnatal genetic diagnosis.

Infants who received non-intensive NICU care may represent a select group whose care focused on comfort or, a physiologically more stable population who did not require many interventions. Fewer in this group were born preterm or admitted for respiratory reasons. Yet among infants in this group who died in the NICU, the majority had

anomalies, perhaps leading to families choosing a plan for comfort care. Infants who received non-intensive treatment were more likely to be discharged home after a short NICU stay, and also more likely to be feeding by bottle or breast. These results support earlier studies that show that some infants with T13 and 18 receive significant NICU interventions, while others infants may not necessarily require a lot of early interventions [2].

The most common surgery performed on infants admitted in our cohort was gastrostomy placement, but some infants did undergo major cardiac, neurologic, and thoracic surgeries. The next most common procedure was a bronchoscopy, presumably for infants with stridor or respiratory distress, which are reportedly common, or in infants with extubation failure [11, 12]. Infants who underwent major cardiac surgeries are likely underrepresented in this study, because the CHND does not capture data on infants cared for exclusively in cardiac ICUs. While surgeries such as diaphragmatic hernia repair were rare, they did occur. In some patients, multiple surgeries were performed. Nelson et al. evaluated types of surgeries performed in a population-

Table 3 Characteristics of Infants who survived vs. died in the 3 treatment groups (*n* = 467).

	Surgical treatment			Intensive medical treatment			Non-intensive treatment		
	Survived ^a	Died	<i>p</i> -value	Survived ^a	Died	<i>p</i> -value	Survived ^a	Died	<i>p</i> -value
	87	42		113	179		36	10	
Gestational age at birth (weeks)									
≤27 + 6/7	1 (1)	1 (2)	0.028	0(0)	3 (2)	<0.001	0 (0)	0(0)	0.054
28 to 31 + 6/7	2 (2)	5 (12)		3 (3)	29 (16)		0(0)	2 (20)	
32 to 36 + 6/7	33 (38)	20 (48)		23 (20)	71 (40)		6 (17)	1 (10)	
≥37	51 (59)	16 (38)		87 (77)	76 (42)		30 (83)	7 (70)	
Birth weight (g)^b									
< = 1500 g	14 (16)	11 (26)	0.023	12 (11)	57 (32)	<0.001	3 (8)	3 (30)	0.247
1501–2499 g	52 (61)	29 (69)		67 (60)	83 (47)		23 (66)	5 (50)	
> = 2500 g	19 (22)	2 (5)		33 (29)	36 (20)		9 (26)	2 (20)	
Male gender									
	26 (30)	26 (62)	0.001	33 (29)	90 (50)	<0.001	9 (25)	6 (60)	0.057
Maternal race^b									
Asian	1 (1)	0(0)	0.954	2 (2)	7 (4)	0.113			0.736
Black	24 (28)	11 (26)		23 (20)	50 (28)		9 (25)	2 (20)	
Native Hawaiian/Pacific Islander	0 (0)	0(0)		2 (2)	0(0)		2 (5)	0(0)	
Other	11 (13)	6 (14)		13 (11)	28 (16)		6 (17)	1 (10)	
White	44 (51)	23 (55)		68 (60)	84 (47)		15 (42)	7 (70)	
Primary reason for admission									
Anomalies or Syndrome	20 (23)	12 (29)	0.519	52 (46)	84 (47)	0.905	13 (36)	9 (90)	0.004
Cardiac	11 (13)	3 (7)	0.547	25 (22)	32 (18)	0.449	9 (25)	1 (10)	0.420
Preterm birth	4 (5)	1 (2)	1.000	0(0)	10 (6)	NA	0 (0)	0(0)	NA
Respiratory	9 (10)	2 (5)	0.502	23 (20)	22 (12)	0.069	4 (11)	0(0)	NA
Surgical evaluation	33 (38)	23 (55)	0.089	6 (5)	23 (13)	0.044	2 (5)	0(0)	NA
Other	10 (11)	1 (2)	0.102	7 (6)	8 (4)	0.590	8 (22)	0(0)	NA
NICU interventions^c									
Delivery room interventions									
PPV	43 (57)	26 (67)	0.322	82 (74)	133 (78)	0.566	0(0)	0(0)	NA
Intubation	17 (21)	22 (56)	<0.001	25 (23)	95 (55)	<0.001	0(0)	0(0)	NA
Chest compressions	4 (5)	3 (7)	0.686	7 (6)	22 (13)	0.109	0(0)	0(0)	NA
Epinephrine	1 (1)	1 (2)	1.000	0(0)	5 (3)	NA	0(0)	0(0)	NA
None of the above	43 (49)	11 (26)	0.014	27 (24)	37 (21)	0.562	36(100)	10(100)	0.171
Respiratory support during admission									
Conventional ventilation	67 (82)	41 (98)	0.011	40 (37)	140 (78)	<0.001	0(0)	0(0)	NA
HFJV or HFOV	3 (4)	11 (26)	<0.001	3 (3)	40 (22)	<0.001	0(0)	0(0)	NA
NIMV	21 (26)	5 (12)	0.103	12 (11)	23 (13)	0.714	0(0)	0(0)	NA
NCPAP	32 (39)	7 (17)	0.014	36 (34)	40 (22)	0.039	0(0)	0(0)	NA
High flow nasal cannula	45 (55)	17 (40)	0.184	65 (61)	56 (31)	<0.001	0(0)	0(0)	NA
iNO	1 (1)	3 (7)	0.112	1 (1)	23 (13)	<0.001	0(0)	0(0)	NA
None of the above	8 (9)	0(0)	NA	18 (16)	0(0)	NA	36(100)	10(100)	0.171
Ventilator days in those receiving invasive mechanical ventilation, median (IQR) days	8 [4,21]	19 [8,48]	0.064	3 [1,5]	6 [3,11]	0.001	[...]	[...]	NA
Cardiovascular interventions									
Vasopressors/Inotropic support	0(0)	1 (4)	NA	2 (5)	20 (16)	0.107	0(0)	0(0)	NA
Surfactant	7 (8)	6 (15)	0.348	15 (13)	38 (22)	0.086	0(0)	0(0)	NA
Systemic steroids	3 (13)	7 (50)	0.023	0(0)	27 (75)	NA	0(0)	0(0)	NA
None of the above	77 (88)	29 (69)	0.013	98 (87)	118 (66)	<0.001	36(100)	10(100)	0.171

HFJV high frequency jet ventilation, HFOV high frequency oscillatory ventilation, NIMV non-invasive mechanical ventilation, NCPAP nasal continuous positive airway pressure, iNO inhaled nitric oxide, IQR interquartile range.

p-values of <0.05 are in bold font.

^aThe survived group includes infants who were transferred.

^bContains missing values and totals do not add up to 100%.

^cSome infants may have received more than one intervention and totals may add up to >100%.

based study in Canada and found that ear-nose-throat surgeries followed by feeding ostomies were the most common procedures in these children [3]. Many ear-nose-throat procedures, such as cleft palate repair, are not typically performed in the neonatal period, which may be why gastrostomy was more common in our cohort. In addition, a gastrostomy tube can provide feeding stability for an infant with T13 or T18 and facilitate discharge home. Our finding that infants undergoing surgical procedures will spend more time ventilated and have a longer NICU length of stay can be used to counsel families providing more accurate expectations of their child's hospital course.

Survival to NICU discharge was 40%, similar to what has been reported previously in the NICU population [2]. Survival in the group that received surgical treatment was higher than in the group that received intensive medical treatment alone. This may be because the most common surgeries performed were ones not necessarily associated with high mortality (such as gastrostomy tubes). It is also possible that some infants in the intensive medical treatment group had major surgical anomalies but did not undergo surgery because they were too sick, or surgery did not align with parental goals. Infants in the non-intensive treatment group were most likely to survive and were discharged earlier than other groups. This could be due to one of two reasons; the infants were physiologically more stable and did not require a lot of interventions, or families chose to take infants home sooner with the goals of comfort care and hospice support. This information may be useful for families considering varying levels of intervention for their child: survival after medical and surgical interventions is possible, but these infants will have a longer hospital stay and will need more support to discharge home. On the other hand, there are infants who do not necessarily require a lot of interventions, and families who choose to limit intensive interventions may still be able to achieve the goal of taking their baby home depending on the child's physiologic stability.

We found that the majority of infants who died in the intensive treatment groups had withdrawal of life-sustaining therapies; this may have been due to realignment of goals of care to comfort after interventions 'failed' or after confirmatory postnatal testing. We are not able to tell from this data what conversations were had with families when interventions were started or when the decision was made to stop. It is notable that the frequency of death due to withdrawal of life-sustaining therapies in this cohort (71%) is similar to the rate reported in the entire population of infants who die in CHNC NICUs [13].

Our results additionally show that there is wide variability in the numbers of infants admitted to US children's hospitals with T13 or T18, as well as the proportion of those infants who received intensive vs. non-intensive treatment. Differences in intensive treatment rates may to some degree represent differences between what individual centers offer to families. For families whose children may need intensive

interventions and who desire such interventions, especially surgical, it will be important to determine which children will benefit from surgical interventions and in whom the interventions may cause harm. Many recent studies, including ours, focus on short-term outcomes, and we do not know the impact of interventions on long-term survival or other developmental outcomes. Indeed, ethical arguments have been made both for and against why these children should or should not be offered certain surgeries [14].

Previous studies have shown that male sex, lower birth weight, and need for mechanical ventilation are predictors of mortality [2]. Our data extend these findings for children receiving both medical and surgical interventions. Even among infants who received minimal interventions, male infants were at higher risk of dying. The number of infants undergoing more complex surgeries such as diaphragmatic hernia repair was small, but these surgeries did occur, and mortality was high. Before offering or recommending an intervention, it is important to understand parents' goals and how they expect the intervention would benefit their child. For example, some families may desire tube placement for long-term nutrition but would not want major cardiac surgeries. Families may be given the option of taking their baby home with a nasogastric tube for the short term, with the option of a gastrostomy tube later if the family desires. Other families may demand all interventions that a child without T13 or T18 would be offered, even if likelihood of long-term survival is low.

We do not have information on long-term survival or developmental outcomes for our cohort. While ethical arguments regarding what interventions should and should not be offered to families is beyond the scope of this paper, we urge providers to engage with families in open and honest discussion about the risks and benefits of interventions and the limits of our current knowledge. Decision-making should continue to be personalized, through a process of partnership with families. The significant mortality observed in the small number of these infants undergoing complex surgeries calls for caution in wider prescription of these procedures and continued discussion of the burdens and potential benefits of such procedures.

Limitations

This was a large multi-center study reporting the outcome of infants with T13 or T18 in the CHNC consortium. For individual patients in our database, we do not know what the goals of care were at the time of birth, or when in the course of care decisions regarding DNR or withdrawal were made. Treatment group does not necessarily imply intention behind the treatment, especially for cases of postnatal diagnosis. We cannot ascertain nuanced details of prenatal or postnatal counseling that families received nor if families perceived that interventions may have benefited their children regardless of survival.

Surgical treatment encompassed a wide range of interventions with varying morbidity and mortality risks; overall survival numbers may not apply to more complex surgeries. Cardiac surgeries are underrepresented in this cohort. Additionally, we were not able to assess long-term outcomes in this cohort.

Conclusions

Infants with T13 or T18 admitted to CHNC NICUs underwent a variety of interventions during their initial hospital course. Survival to NICU discharge was possible after medical and surgical interventions, but surviving infants had a longer hospital stay and needed more discharge supports. This study provides a better understanding of the spectrum of NICU care T13 and T18 infants receive and can be used to improve future counseling to families that desire interventions.

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