Extracardiac Malformations and Their Influence on Surgical Outcomes

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No disclosures

How common are extracardiac malformations in patients with congenital heart disease?

What type of extracardiac malformations are common in patients with congenital heart disease?

What is the effect of extracardiac malformations on outcomes after congenital heart surgery?

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Extracardiac malformations

- Chromosomal abnormalities
  - Trisomies 15, 18, 21
  - Turner syndrome
- Recognized patterns of malformations
  - DiGeorge syndrome
  - VACTERL
  - CHARGE
- Extracardiac malformations (single or multiple) without recognized pattern of malformation

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Table 1
Isolated and associated anomalies in 4005 cases with congenital heart defects ascertained from 1979 to 2004 in 346,831 consecutive pregnancies in Northeastern France.

	N°	%	Prevalence[a]
Associated malformations			
Recognized patterns[b]	99	2.5	2.8
Unrecognized Patterns of MCA[c]	602	15.0	17.4
Sub total	701	17.5	20.2
Chromosomal	354	8.8	10.2
Total Associated	1055	26.3	30.4
Isolated malformation	2950	73.6	85.0
Total	4005	100	115.5

[a] Total prevalence per 10,000 pregnancies.
[b] Includes syndromes, associations, sequences and spectrums.
[c] MCA: multiple congenital anomalies.

Stoll et al. Eur J Med Gen 2015;58:75-85

Table 1 Prevalences of extracardiac malformations in the congenital heart disease (CHD) population

	Cases *n* (%)	Controls *N* (%)	OR (95 % CI)
Total extracardiac malformations	13,213 (13.6)	845,494 (7.0)	2.01 (1.97–2.14)
Genetic syndromes	2,137 (2.2)	36,235 (0.3)	2.52 (2.44–2.61)
Nonsyndromic congenital malformation	11,075 (11.4)	809,258 (6.7)	1.88 (1.73–1.94)
Multiple organ system malformation[a]	2,332 (2.4)	48,314 (0.4)	1.39 (1.14–1.60)

OR odds ratio, *CI* confidence interval

[a] Multiple organ-system malformation is an extracardiac malformation involving ≥2 organ systems

Data from Nationwide Inpatient Sample (NIS)

Births 1998-2008

97,154 pts CHD

12,078,482 controls

Egbe et al. Pediatr Cardiol 2014;35:1239-45.

Class of defect	All CHDs* n (%)	AVSDs‡ n (%)	Ebstein anomaly n (%)
Isolated	5695 (71.3)	109 (24.4)	60 (90.9)
MCAs††	1080 (13.5)	40 (8.9)	4 (6.1)
Syndromes§§	1048 (13.1)	298 (66.7)	2 (3.0)
Trisomy 21	536 (6.7)	258 (57.7)	1 (1.5)
Trisomy 18	134 (1.7)	19 (4.3)	
Trisomy 13	63 (0.8)	7 (1.6)	
22q11 deletion	54 (0.7)		
Laterality defects	161 (2.0)		
Total	7984 (100)	447 (100)	66 (100.0)

Atlanta Congenital
cts Program

stillborn infants and
es with CHD

968-2005

Miller et al. J Pediatr 2011;159:70-8.

Prevalence in Neonates Undergoing CHS (STS)

	NC/GA/S	NC	GA/S	Total
AVSD	212 (59%)	28 (8%)	207 (58%)	357
TOF	417 (44%)	73 (2%)	384 (43%)	1383
Other SV	627 (29%)	151 (7%)	527 (25%)	2147
HLHS	294 (11%)	46 (2%)	272 (11%)	2599
TGA	111 (4%)	15 (1%)	101 (4%)	2778
Total	**2894 (19%)**	**479 (3%)**	**2661 (17%)**	**15376**

NC: Non-cardiac anatomic abnormalities, GA: Genetic abnormalities, S: Syndromes.

Patel et al. Ann Thorac Surg 2016;102:1607-14.

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Prevalence of extracardiac malformations in CHD

- **10-30%** of patients with CHD will have associated extracardiac malformations
- Prevalence varies depending on the particular CHD diagnosis
- The mix between genetic syndromes, recognized patterns, and isolated/multiple congenital anomalies differs among different series

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How common are extracardiac malformations in patients with congenital heart disease?

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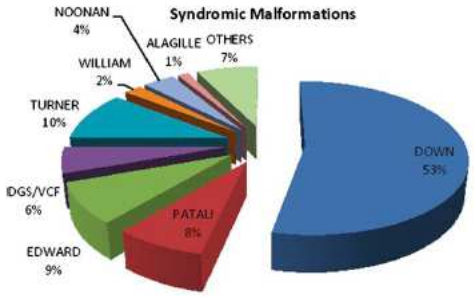
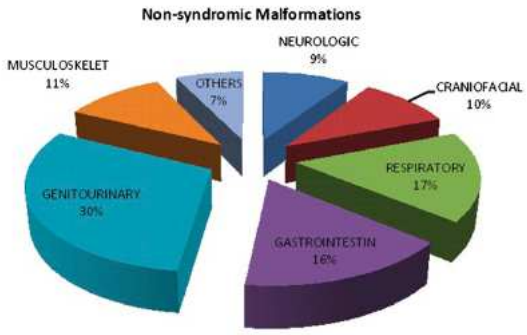
Distribution of extracardiac malformations





Egbe et al. Pediatr Cardiol 2014;35:1239-45.

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Distribution of Non-Syndromic ECM in CHD

	Egbe et al. 2014 (N = 11075)	Stoll et al. 2015 (N = 1197)	Miller et al. 2011 (N = 1080)
Genitourinary	30%	20%	25%
Respiratory	17%	2%	11%
Gastrointestinal	16%	16%	25%
Craniofacial	10%	15%	Not specified
Neurologic	9%	10%	19%
Musculoskeletal	11%	18%	35%

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Distribution of ECM at TCH

Extracardiac malformation	N (%)
Respiratory / airway	246 (24%)
Neurological	120 (12%)
Genitourinary	110 (11%)
Craniofacial	100 (10%)
Gastrointestinal	97 (10%)
Musculoskeletal	83 (8%)
Others	245 (24%)
Total	1001

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STS CHSD Mortality Risk Adjustment Model

Variable	OR (95% CI)	*p* Value
Age in neonates, per week	0.88 (0.81–0.95)	0.0010
Age in infants, per month	1.05 (0.99–1.11)	0.0796
Age in children, per year	1.00 (0.97–1.03)	0.7886
Age in adults, per year	1.04 (1.02–1.05)	<0.0001
STAT Category 2 vs 1	1.75 (1.24–2.46)	0.0013
STAT Category 3 vs 1	2.49 (1.69–3.68)	<0.0001
STAT Category 4 vs 1	5.14 (3.72–7.11)	<0.0001
STAT Category 5 vs 1	11.40 (7.17–18.14)	<0.0001
Weight in neonates, per 1-kg increase	0.58 (0.51–0.65)	<0.0001
Weight in infants, per 1-kg increase	0.71 (0.65–0.78)	<0.0001
Prior cardiothoracic operation	1.50 (1.27–1.78)	<0.0001
Any noncardiac congenital anatomic abnormality	1.35 (1.09–1.66)	0.0056
Any chromosomal abnormality or syndrome	1.57 (1.40–1.77)	<0.0001
Prematurity (in neonates and infants)	1.39 (1.20–1.60)	<0.0001
Preoperative/preprocedural mechanical circulatory support	4.27 (3.03–6.03)	<0.0001
Shock, persistent at time of operation	3.15 (2.46–4.03)	<0.0001
Renal dysfunction or Renal failure requiring dialysis (or both)	2.12 (1.64–2.73)	<0.0001
Mechanical ventilation to treat cardiorespiratory failure	2.11 (1.88–2.37)	<0.0001
Preoperative neurological deficit	1.91 (1.38–2.65)	<0.0001
Any other preoperative factor	1.61 (1.44–1.80)	<0.0001

CI = confidence interval; OR = odds ratio.

O'Brien et al. Ann Thorac Surg 2015;100:1054-62.

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The Effect of Noncardiac and Genetic Abnormalities on Outcomes Following Neonatal Congenital Heart Surgery

Bahaaldin Alsoufi, MD,[*] Scott Gillespie, MS,[†] William T. Mahle, MD,[†] Shriprasad Deshpande, MD,[†] Brian Kogon, MD,[*] Kevin Maher, MD,[†] and Kirk Kanter, MD[*]

- Children's Healthcare of Atlanta
- 1538 neonates (2002-2012)
- 312 (20%) with ECM
  - 263 with genetic anomalies
  - 49 with ECM not associated to GA

Alsoufi B et al. Sem Thorac Cardiovasc Surg. 2016; 28(1):105-13

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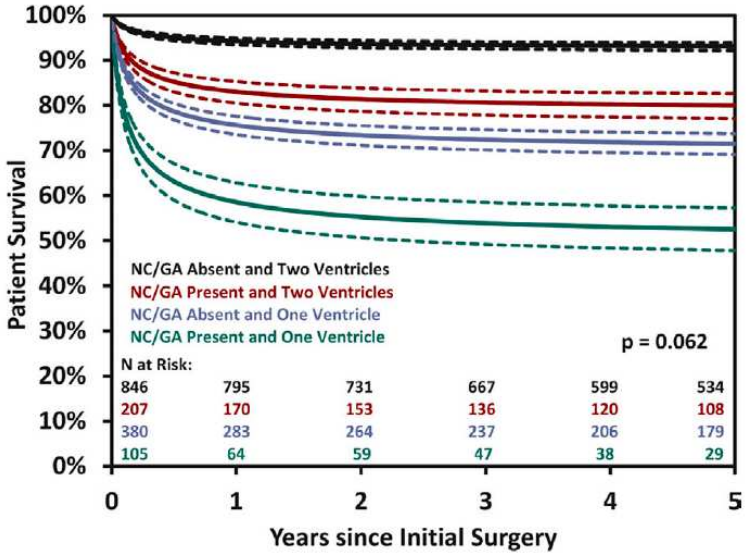

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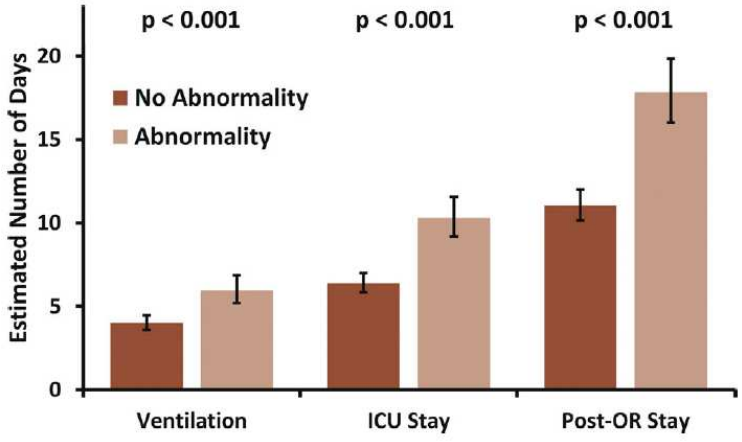

Alsoufi B et al. Sem Thorac Cardiovasc Surg. 2016; 28(1):105-13

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Table 2. Effect of Presence of NC and GA (vs Absence) on Postoperative Survival Among Selected Patient Subgroups. Reported is the HR for Mortality (With 95% Confidence Interval) for NC and GA in Each Patient Subgroup

Patient Subgroup	Effect of NC and GA HR (95% CI)	Effect *P*
NC and GA, Yes	2.38 (1.85-3.07)	<0.001
Weight		
≤2.5 kg	1.91 (1.17-3.12)	0.010
>2.5 kg	2.32 (1.72-3.14)	<0.001
Age at operation		
1-7 d	2.75 (2.03-3.74)	<0.001
8-31 d	2.08 (1.30-3.30)	0.002
Gender		
Male	2.66 (1.93-3.68)	< 0.001
Female	2.12 (1.41-3.21)	< 0.001
Gestation		
Premature	2.14 (1.25-3.65)	0.005
Full term	2.39 (1.78-3.20)	<0.001
STAT category		
1-3	7.86 (3.26-18.97)	< 0.001
4-5	1.86 (1.42-2.43)	< 0.001
Cardiopulmonary bypass use		
Yes	2.34 (1.73-3.17)	<0.001
No	2.68 (1.68-4.26)	<0.001
Underlying cardiac anomaly		
Single ventricle	1.92 (1.37-2.67)	<0.001
2 Ventricles	3.14 (2.11-4.67)	<0.001
Type of cardiac surgery		
Palliation	1.86 (1.38-2.50)	<0.001
Repair	3.09 (1.91-4.99)	<0.001

Alsoufi B et al. Sem Thorac Cardiovasc Surg. 2016; 28(1):105-13

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Effect of Gastrointestinal Malformations

- Retrospective matched cohort study
- All neonates & infants with GI malformations undergoing CHS

Thoracic GI Malformations	Abdominal GI Malformations
Esophageal Atresia	Duodenal stenosis/atresia
Tracheoesophageal Fistula	Imperforate anus
	Hirschprung disease

Mery CM et al. Ann Thorac Surg. 2017; 104:1590-6.

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Gastrointestinal Malformations

- 1:1 or 2:1 variable matching based on:
  - Diagnosis
  - Primary procedure
  - Prematurity (<37 weeks gestation)
  - Presence of a genetic syndrome
- Propensity score including weight and year of surgery

Mery CM et al. Ann Thorac Surg. 2017; 104:1590-6.

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Gastrointestinal Malformations

- 383 Patients
  - Thoracic GI malformations (n=52)
  - Thoracic GI controls (n=98)
  - Abdominal GI malformations (n=80)
  - Abdominal GI controls (n=153)
- Median follow-up: 6 years (16 days – 20 yrs)

Mery CM et al. Ann Thorac Surg. 2017; 104:1590-6.

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Table 4. Outcomes of Patients With Thoracic and Abdominal Gastrointestinal Malformations

Variable[a]	Overall (N = 383)	Thoracic GI Malformations (n = 52)	Thoracic GI Controls (n = 98)	p	Abdominal GI Malformation (n = 80)	Abdominal GI Controls (n = 153)	p
Post-op LOS							
Hospital, d	12 (3–188)	41 (4–188)	13 (3–131)	<0.001[b]	13 (3–88)	10 (3–149)	0.35
ICU, d	5 (1–142)	9 (1–41)	6 (1–117)	0.006[b]	6 (1–88)	4 (1–142)	0.24
Intubation, d	2 (0–179)	5 (0–179)	3 (0–15)	<0.001[b]	2 (0–36)	2 (0–52)	0.56
Peri-op mortality	20 (5)	7 (13)	3 (3)	0.03[b]	2 (3)	8 (5)	0.50

[a] Continuous data are presented as median (range) and categoric data as number (%). [b] Statistically significant ($p < 0.05$).

GI = gastrointestinal; ICU = intensive care unit; LOS = length of stay; peri-op = peri-operative; post-op = post-operative.

Mery CM et al. Ann Thorac Surg. 2017; 104:1590-6.

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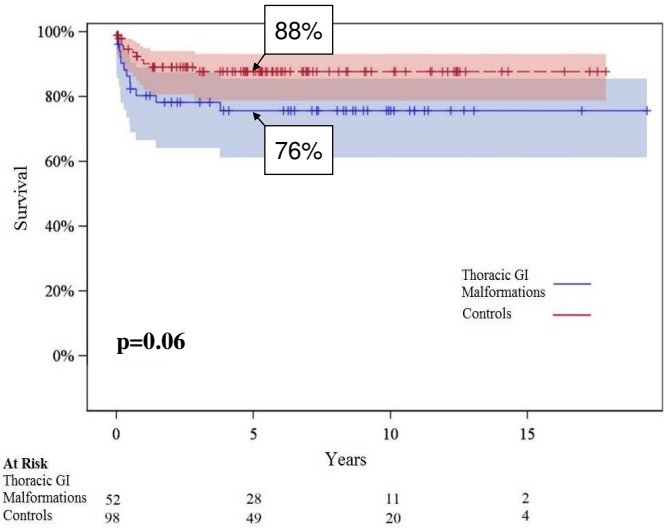
Thoracic GI Malformations



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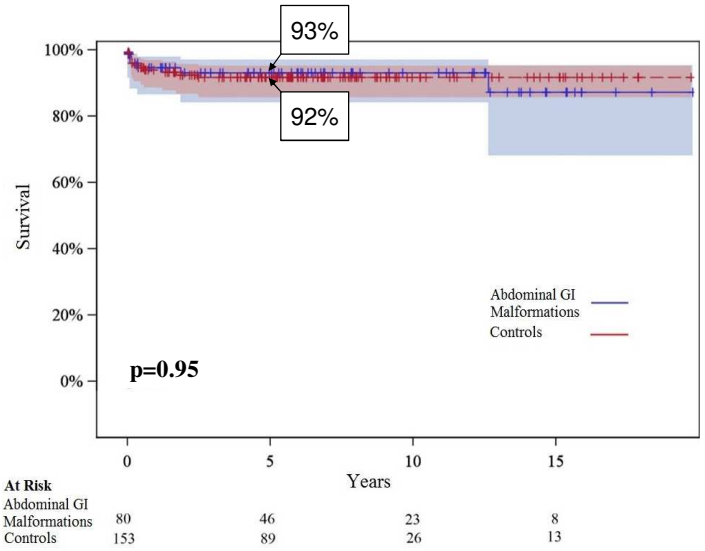
Abdominal GI Malformations



Mery CM et al. Ann Thorac Surg. 2017; 104:1590-6.

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Impact of Noncardiac Congenital and Genetic Abnormalities on Outcomes in Hypoplastic Left Heart Syndrome

Angira Patel, MD, MPH, Edward Hickey, MD, Constantine Mavroudis, MD, Jeffrey P. Jacobs, MD, Marshall L. Jacobs, MD, Carl L. Backer, MD, Melanie Gevitz, BA, and Constantine D. Mavroudis, BA

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STS Database (2002-2006)

- Stage 1 (n=1,236)
- Stage 2 (n=702)
- Stage 3 (n=553)

CHSS Critical LVOTO (1994-2001)

703 infants that underwent stage 1 palliation and were followed

Patel A et al. Ann Thorac Surg. 2010; 89:1805-14

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STS Database

Table 2. Prevalence of Coexisting Noncardiac Congenital Abnormalities and Genetic Syndromes in Infants Enrolled With the STS Congenital Database (2002 to 2006) Who Underwent Staged Univentricular Palliation for HLHS

Variables	Stage 1 (n = 1,236)	Stage 2 (n = 702)	Stage 3 (n = 553)
Noncardiac congenital abnormalities or genetic defects	190	91	63
Prevalence (%)	15%[a]	13%[a]	11%[a]
n			
Trisomy 21	1	0	1
Turner syndrome	9	4	5
DiGeorge	2	2	1
22q11 deletion	0	0	1
Williams-Beuren syndrome	0	0	0
Alagille syndrome	0	0	0
Other chromosomal-syndromic abnormality	27	14	8
Rubella	0	0	0
Marfan syndrome	1	0	0
Asplenia	4	1	1
Polysplenia	2	2	1
Other noncardiac abnormality	126	60	42
Multiple syndromes	18	8	3

[a] $p = 0.06$ between stages 1, 2, and 3.

HLHS = hypoplastic left heart syndrome; STS = Society of Thoracic Surgeons.

Patel A et al. Ann Thorac Surg. 2010; 89:1805-14

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Table 4. Complications Most Frequently Reported to the STS Congenital Database at Each of Stage 1, Stage 2, and Stage 3[a]

	No Noncardiac Anomaly		Noncardiac Anomaly		
Variable	n	%	n	%	*p* Value
Stage 1 (Norwood):					
Delayed sternal closure	346	33	81	43	0.002
Postoperative arrhythmia	131	13	35	18	<0.01
Ventilation > 7 days	97	9	30	16	<0.01
Reintubation	84	8	28	15	<0.01
Stage 2:					
Reoperation (same admission)	10	2	5	6	0.03
Postoperative arrhythmia	34	6	6	7	0.63
Ventilation > 7 days	12	2	5	6	0.06
Reintubation	28	5	9	10	0.04
Phrenic nerve injury	18	3	7	8	0.03
Drainage of pleural effusion	26	4	5	5	0.58
Stage 3 (Fontan):					
Low cardiac output state	17	3	6	10	0.006
Postoperative arrhythmia	46	9	14	22	<0.0001
Permanent pacemaker implantation	6	1	4	6	0.004
Septicemia	10	2	4	6	0.06
Persistent neurologic injury	7	1	4	6	0.03
Drainage of pleural effusion	94	19	22	34	0.008

[a] Prevalence of complications were then compared between children with or without coexisting noncardiac congenital abnormalities or genetic defects using the Fisher exact test.

STS = Society of Thoracic Surgeons.

Patel A et al. Ann Thorac Surg. 2010; 89:1805-14

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STS Database

Variable	In-hospital Mortality N	n	%	p Value	LOS (Days) Mean	p Value
Stage 1 (Norwood):						
No noncardiac abnormality	1,029	204	19.8	0.04	30.6	<0.001
Noncardiac abnormality	187	50	26.7		41.8	
Stage 2:						
No noncardiac abnormality	611	11	1.8	0.68	11.9	0.03
Noncardiac abnormality	91	2	2.2		17.7	
Stage 3 (Fontan):						
No noncardiac abnormality	490	10	2	0.18	13.5	0.89
Noncardiac abnormality	63	3	4.8		13.7	

[a] In-hospital mortality and mean postoperative hospital stay were compared between the two groups at each stage.

Patel A et al. Ann Thorac Surg. 2010; 89:1805-14

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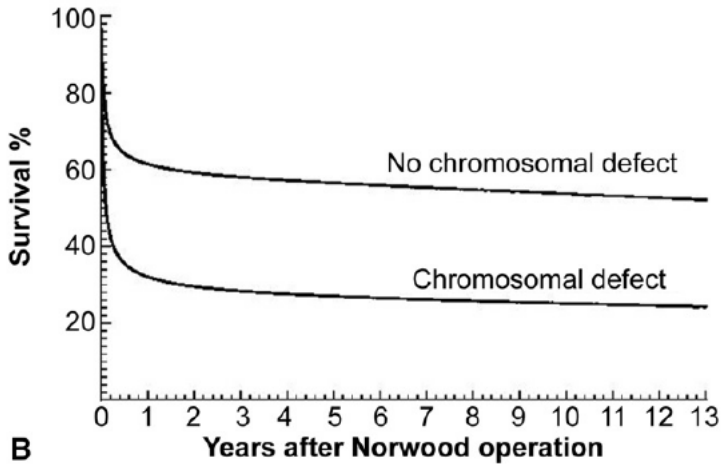
CHSS Database

Table 6. Incremental Risk Factors for Death During the Early Hazard Phase Post-Norwood Operation for HLHS (N = 703) in the CHSS Database

Risk Factor for Death Early Post-Norwood	Parameter Estimate	p Value	Reliability %[a]
Model A[b]			
Aortic atresia versus critical stenosis	+0.43	0.0007	94
Smaller birth weight	+0.43	0.0013	67
Presence of c-existing noncardiac congenital or genetic defect	+0.48	0.0082	51
Model B[c]			
Aortic atresia versus critical stenosis	+0.43	0.0007	94
Smaller birth weight	+0.44	0.0013	65
Presence of a chromosomal abnormality	+0.85	0.0082	53

Patel A et al. Ann Thorac Surg. 2010; 89:1805-14

CHSS Database



Patel A et al. Ann Thorac Surg. 2010; 89:1805-14

Conclusions

- ECM are present in **10-30%** of pts undergoing CHS
- The distribution of types of ECM vary depending on the study (probably related to definition and severity)
- ECM, with or without genetic syndromes, are associated with **worse short-term and long-term prognosis** in patients after CHS

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Conclusions

- The effect on morbidity and mortality likely depends on the type of ECM or genetic syndrome
- More studies are needed to define the impact of **particular malformations and syndromes on particular patients with CHD** to adequate counsel families and direct management

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