Variation in Pre- and Intra-Operative Care for First Stage Palliation for Single Ventricle Heart Disease: Report from the National Quality Improvement Collaborative

(Brief title: Intraop Variation for Single V Heart Disease)

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Abstract

Background and Methods. As the first multi-center quality improvement collaborative in pediatric cardiology, the NPCQIC national registry collects information on the clinical care and outcomes of infants discharged home after first stage palliation of single ventricle heart disease, the Norwood operation and variants. We sought to describe the pre- and intra-operative characteristics of the first 100 patients enrolled in the NPC-QIC registry.

Results. From 21 contributing centers, fifty-nine percent of infants were male, with median birth weight 3.1 kg (1.9-5.0 kg); the majority had hypoplastic left heart syndrome (71%). A prenatal diagnosis of congenital heart disease was made in 75%; only 1 had fetal cardiac intervention. Chromosomal anomalies were present in 8%, and major non-cardiac organ system anomalies in 9%. Pre-operative risk factors were common (55%), but less frequent in those with prenatal diagnosis (p=0.001). Four patients underwent pre-operative transcatheter intervention.

Substantial variation across participating sites was demonstrated for choice of initial palliation for the 93 patients requiring a full first stage approach, with 50% of sites performing Stage I with right ventricle to pulmonary artery conduit as the preferred operation; 89% of hybrid procedures were performed at a single center. Significant intra-operative variation by site was noted for the 83 patients who underwent traditional surgical Stage I palliation, particularly with use of regional perfusion and depth of hypothermia.

Conclusions. In summary, there is substantial variation across surgical centers in the successful initial palliation of infants with single ventricle heart disease, particularly with regard to choice of palliation strategy, and intra-operative techniques including use of regional perfusion and depth of hypothermia. Further exploration of the relationship of such variables to subsequent outcomes after hospital discharge may help reduce variability and improve long-term outcomes.

Abbreviations

CHD, congenital heart disease

HLHS, hypoplastic left heart syndrome

JCCHD, joint council on congenital heart disease

NPCQIC, national pediatric cardiac quality improvement collaborative

RVPA, right ventricle to pulmonary artery

Key words

Congenital Heart Disease, Pediatric, Cardiac, Quality Improvement

Introduction

Among congenital cardiac defects, those resulting in univentricular physiology remain the most complex and have the highest rates of associated morbidity and mortality. Approximately 4000 infants with univentricular congenital heart disease (CHD) are born in the United States each year (1, 2), and most require staged surgical palliation beginning in the newborn period (e.g., Stage I Norwood operation, Blalock-Taussig shunt, or pulmonary artery band), followed by bidirectional Glenn shunt at 4-6 months of age, and Fontan procedure at 2-4 years of age (3). Children with hypoplastic left heart syndrome (HLHS) and other forms of left heart hypoplasia face the highest mortality rates, up to 30-45% in their first four years of life, with typical mortality rates of 15-20% occurring around the first stage palliation, and "inter-stage" mortality rates of 10-15% before the time of Glenn procedure (4, 5). Associated morbidities include poor growth and feeding difficulties, vocal cord paralysis, phrenic nerve injury, renal dysfunction, seizures and developmental delay, and frequent and often prolonged hospitalizations (6). Concomitantly, due to the small numbers of such patients followed at any one clinical center and marked institutional variability, evidence-based guidelines for the inpatient or outpatient care of such infants are sorely lacking, leaving physicians little guidance with managing a disease with high morbidity and mortality.

To help address this need, national leaders in the medical and surgical care of patients with CHD (the Joint Council on Congenital Heart Disease, JCCHD) established the National Pediatric Cardiology Quality Improvement Collaborative (NPCQIC) in 2008. Modeled after other successful quality improvement networks such as the Vermont Oxford Neonatal Network (7) and the Northern New England Cardiovascular Disease Study Group (8), the goal of the NPCQIC was to reduce mortality and improve the quality of life of infants with HLHS during the interstage period between discharge from the Stage I palliation and admission for the bi-directional Glenn procedure (9). The NPCQIC aims include 1) developing, maintaining and expanding a multicenter national registry of patients with HLHS or similar univentricular CHD to gather clinical process and outcomes data for the interstage period between the initial surgical palliation and Glenn operation, and 2) improve clinical outcomes by effectively implementing tools and strategies that reduce variation and facilitate systematic care coordination, interstage cardiovascular and nutritional monitoring into every day practice. By documenting variation in care across cardiac centers, and promoting standardization of best practices of care among these institutions, the collaborative could

effectively improve the quality of care and patient outcomes such as mortality rates, weight gain, readmission and serious adverse event rates. The NPCQIC has been expanded into a nation-wide data collection network of over 30 pediatric cardiovascular care centers in North America.

The specific aim of the current investigation is to describe the pre- and intra-operative characteristics and center-specific variation in surgical practice of the first 100 patients enrolled in the NPCQIC registry.

Methods

Inclusion criteria for entry into the NPCQIC registry consists of 1) univentricular heart disease such as HLHS requiring Stage I Norwood operation or similar variant, and 2) survival to and discharge from the hospital prior to bi-directional Glenn operation. At participating centers, all infants meeting these criteria were identified for potential enrollment. As some registry data includes patient-specific identifiers, all data collection was performed after obtaining IRB approval at each participating institution.. The first 100 patients entered into the database include those born between June 2008 and January 2010. The NPCQIC registry database was developed by JCCHD Task Force members using Vanderbilt University's REDCap software to manage the data.

Eligible infants were followed from birth to the time of bidirectional Glenn operation. Multiple data elements were collected including patient demographics and care processes during their initial neonatal hospitalization, subsequent discharge, interstage clinic visits and readmissions as well as the hospitalization for their bidirectional Glenn procedure. For the purposes of the current study, data elements evaluated included the presence of prenatal diagnosis, patient demographic and anatomic factors including chromosomal anomalies and other associated organ system abnormalities, the presence of pre-operative risk factors, and intra-operative surgical factors such as choice of initial palliation, use of regional perfusion, times of cardiopulmonary bypass, aortic cross-clamp, and circulatory arrest. Some limited post-operative factors such as re-operations were included in the current study, although the variation in inpatient post-operative care and variation in interstage outpatient care are the subject of other current investigations.

Data for the first 100 patients entered into the database was collected and analyzed using simple descriptive statistics. Fisher's exact test was used for evaluating the relationship of prenatal diagnosis

with pre-operative morbidity measures. For the purposes of comparing center-specific variation, we chose an arbitrary cut-off for "Sites" as those centers entering ≥4 patients in the NPCQIC registry over the 18-month time period of the study.

This study was performed according to a protocol approved by the internal review boards of all participating institutions, including the Committee for Clinical Investigation at Children's Hospital Boston. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patients

From July 2008-February 2010, 100 patients from 21 participating cardiovascular centers across the United States survived to hospital discharge following Norwood-type palliation and were enrolled in the JCCHD NPC-QIC database registry. Eleven centers met our criteria as "sites" for comparison of center-specific variation. Patient demographic data is shown in Table 1; of note, fifty-nine percent of infants were male, median birth weight was 3.1 kg (range 1.9 – 5.0 kg), and the majority had variants of HLHS (71%). A prenatal diagnosis of congenital heart disease was made in 75%; only 1 had undergone a fetal cardiac intervention. Chromosomal anomalies were present in 8% and major non-cardiac organ system anomalies in 9%.

Pre-operative risk factors were present in the majority (57%), mechanical ventilatory support being the most common. Patients with a prenatal diagnosis were less likely to have pre-operative morbidity (45% versus 84%, p=0.001). After excluding pre-operative mechanical ventilation, patients with a prenatal diagnosis were still less likely to have pre-operative morbidity (29% versus 64%, p=0.004). While most individual morbidity components did not differ significantly between patients with and without prenatal diagnosis, those with a prenatal diagnosis were less likely to have acidosis (13% versus 56%, p<0.001), ventilatory support (27% versus 68%, p<0.001), and renal insufficiency (3% versus 16%, p=.03).

Surgical Approach

Median age at Stage I palliation was 5 days, although the range was broad (2-78 days, Table 2). Choice of initial palliation strategy is demonstrated in Table 2 and Figure 1A; the most common strategy

was Stage I with right ventricle to pulmonary artery (RVPA) conduit (55%). Among participating surgical centers (defined as ≥4 patients in the database), there was significant site-specific variation in strategy (Figure IB). Several centers used exclusively RVPA conduits with Stage I palliation, and one center performed almost exclusively hybrid Stage I procedures, which represented 89% of hybrid operations in the whole registry cohort.

Intraoperative Management

Intraoperative management varied significantly across the cohort. Median total cardiopulmonary bypass time (excluding hybrid Stage I operations) was 137 minutes (38-403 minutes, Table 2), with most sites in the 100-200 minute range although there was significant center-specific variation (Figure 2). Aortic cross clamp was utilized in 90% patients (excluding those with hybrid Stage I operations), with median time for those in whom it was utilized 48 minutes (0-145 min); there was more pronounced center-specific variation than with cardiopulmonary bypass time (Figure 3). Circulatory arrest was utilized in 77% of patients (excluding hybrid Stage I operations), with median 10 minutes (0-79 minutes), and by site had the greatest degree of site-specific variation (Figure 4).

There was also significant variation with regards to the depth of hypothermia in the OR, with the median lowest temperature in the OR being 18°C (range 14-35.1°C, Table 2); among participating sites, most had median lowest temperatures under 20°C, although the range was broad and one site had a median lowest temperature in the mid-20s (Figure 5). Use of regional perfusion techniques was 70% for the whole cohort, although there was marked variation across sites (Figure 6); three sites utilized regional perfusion for all cases in the registry, while at least two sites used no regional perfusion.

Immediate Post-operative Course

Three patients (3%) required the use of extra-corporeal membrane oxygenator (ECMO) in the immediate post-operative period. Median ventilator days to final extubation was 9 days (0-83 days), with 21% requiring at least one reintubation (Table 2). Re-operations were performed on 19 patients, although 6 of these were chest re-explorations for recurrent bleeding (Table 3).

Discussion

In this observational study of the first 100 infants entered into the NPCQIC registry, we found significant site-specific variation in the surgical management of infants with univentricular CHD, perhaps most strikingly in terms of surgical approach to initial palliation. As clearly evident in Figure 1B, several centers performed exclusively one type of Stage I palliation (most commonly with RVPA conduit), and 9 of 11 centers had a preferred approach making up >2/3 of enrolled cases. Interestingly, only one center utilized all 3 approaches (RVPA conduit, Norwood with Blalock-Taussig shunt, hybrid). Center-specific variation in approach might in reality be more pronounced than demonstrated by this dataset, as some of the NPCQIC sites enrolling patients were also participating in a multi-center randomized trial of Stage 1 Norwood versus Stage I RVPA conduit (10), which may have resulted in a more even distribution of approach at those sites than otherwise would be the case. The superiority of one particular approach has not yet been conclusively demonstrated; while several retrospective single center studies suggested reduced mortality with the Stage I RVPA conduit versus Stage I Norwood (5, 11, 12), a recently completed multicenter prospective trial found no significant difference in transplant-free survival after 12 months between the two approaches (10). Hybrid Stage I palliation has been adopted by some centers as the initial palliation of choice (as demonstrated by Site H in Figure IB in the present study) while other centers have reserved hybrid palliation for higher-risk patients (13, 14) including those with the HLHS subtype with mitral stenosis and aortic atresia (15, 16). More research, including longer-term follow-up data from the previously mentioned randomized trial, is clearly needed to help determine which approach will achieve the best outcome for a given patient.

We also found significant variation across participating centers in intraoperative factors including duration of cardiopulmonary bypass, duration of aortic cross-clamp, duration of circulatory arrest, depth of hypothermia, and use of regional perfusion techniques for patients who had non-hybrid Stage I operations. The most marked center-specific differences were noted with circulatory arrest time, a factor that has been identified as a risk factor for subsequent worse neurocognitive outcomes (17, 18). Several centers in our cohort utilized less than 20 minutes of circulatory arrest time for the majority of their enrolled cases, but others had median times above 40 minutes, a threshold time under which at least one study has shown to be relatively safe in infant heart surgery (19). The use of regional perfusion techniques have been advocated by some as an alternative to long periods of deep hypothermic

circulatory arrest, although most studies to date (20) including one randomized trial in patients undergoing Stage I palliation (21) have failed to demonstrate improved subsequent neurodevelopmental outcomes with its use. Nevertheless regional perfusion techniques were widely used in our cohort, although center-specific variation is clearly evident as some sites used no regional perfusion. The variation in depth of hypothermia across higher-volume sites, in some respects, may be explained by the variable use of regional perfusion techniques between centers. With such wide variation in intraoperative practices demonstrated across centers in the US, further study is necessary to identify and disseminate best practices for infants with HLHS.

We also found that co-morbidities and pre-operative risk factors were quite common in this population of survivors after initial palliation of univentricular CHD. Chromosomal anomalies were present in a significant portion of patients (8%), similar to that reported in another contemporary large single ventricle cohort (25), and major extracardiac organ system anomalies were present in another 9%. Genetic syndromes have been established as a risk factor for death in patients with HLHS (26), and patients with major extracardiac anomalies were found in one recent large multicenter study to have a 10-fold increase in odds for pre-operative mortality (24); while the present study was limited to survivors of surgical palliation only, clearly genetic syndromes and other congenital malformations pose significant additional risk for poor outcome for these patients.

In addition, acquired pre-operative risk factors were present in the majority of our registry cohort, most commonly the use of mechanical ventilation, although other factors including acidosis, renal dysfunction, and sepsis were present in a significant proportion. While few such factors (such as pre-operative shock (27)) have been clearly associated with increased mortality after Stage I palliation, there is evidence that pre-operative mechanical ventilatory support for infants with HLHS has been associated with some measures of morbidity, including worse neurodevelopmental outcomes later in childhood (28). There was a relatively high rate of prenatal diagnosis of univentricular CHD (75%), in agreement with that reported in other recent studies (22-24). While no conclusions regarding the effect of prenatal diagnosis on mortality can be drawn from this study, we did find that prenatal diagnosis was associated with reduced pre-operative morbidity overall, as well as specific measures including need for ventilatory support, acidosis, and renal insufficiency. While more studies are necessary to confirm this data, the

current study clearly demonstrates that despite improved rates of prenatal diagnosis of univentricular CHD and improvements in pre-operative intensive care, acquired pre-operative risk factors are common even in this cohort of survivors.

Limitations of the study

There are several limitations to this study. First, as only survivors to hospital discharge were eligible for inclusion in the registry, no information regarding non-survivors or those who remained inpatient until bidirectional Glenn procedure is included, precluding an analysis of pre-operative or intra-operative factors that might influence this major source of morbidity and mortality. Additionally, as informed consent was required for inclusion, some families may have declined participation, which would result in further inclusion bias. As currently the registry population has a defined end-point at bidirectional Glenn, no information regarding the relationship of such pre-operative and intra-operative variables to long-term patient outcomes can be evaluated. Nevertheless, this is a large registry that includes patients from multiple centers across the United States, and begins to document some of the variation in pre-operative co-morbidities and intra-operative strategies utilized across centers.

Conclusion

In summary, there is substantial variation across surgical centers in the successful initial palliation of infants with single ventricle heart disease, particularly with regard to choice of palliation strategy, and intra-operative techniques including use of regional perfusion and depth of hypothermia. Further exploration of the relationship of such variables to subsequent outcomes after hospital discharge may help reduce variability and improve long-term outcomes.

Funding Sources

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Disclosures

There are no disclosures to report.

Table 1. Demographic and diagnostic data of 100 infants surviving to hospital discharge after first stage Norwood-type palliation for single ventricle heart disease. Data expressed as median (range) or number (percent).

Gender	Male	59 (59)
	Female	41 (41)
Race	White	68 (68)
	Black/African American	14 (14)
	American Indian/Alaska Native	1 (1)
	Other	12 (12)
	Unknown	5 (5)
Prenatal Diagnosis of CHD		75 (75)
Gestational Age (wks)		39 (33-40)
Birth Weight (kg)		3.1 (1.92-5.04)
Chromosomal Anomaly[1]		8 (8)
Major Non-Cardiac Organ Anomaly[2]		9 (9)
Pre-Operative Risk Factor (any)		55 (55)
	Mechanical Ventilatory Support	37 (37)
	Arterial pH <7.2	15 (15)
	Renal Insufficiency	6 (6)
	Arrhythmia	5 (5)
	Shock	6 (6)
	Necrotizing Enterocolitis	2 (2)
	Sepsis	1 (1)
	Seizures	1 (1)
Preoperative Interventional Catheterization[3]		4 (4)
Primary Cardiac Diagnosis		
	Hypoplastic Left Heart Syndrome	71 (71)
	HLHS Mitral and Aortic Atresia	35 (35)
	HLHS Mitral and Aortic Hypoplasia	19 (19)

HLHS Mitral Stenosis, Aortic Atresia	12 (12)
HLHS Mitral Atresia, Aortic Stenosis	4 (4)
Double Outlet Right Ventricle/LV Hypoplasia	7 (7)
Unbalanced Complete Atrioventricular Canal	6 (6)
Tricuspid Atresia with Aortic Arch Hypoplasia	5 (5)
Severe Left Ventricular Outflow Tract Obstruction	5 (5)
Double Inlet Left Ventricle	4 (4)
Other[4]	3 (3)

[1]Heterotaxy syndrome (n=3), Trisomy 21 (n=2), gain chromosome 13 (n=1), partial deletion chromosome 16 (n=1), hemoglobin SS (n=1), partial deletion chromosome 1 (n=1)
[2]Central nervous system (n=3), renal/genitourinary (n=3), gastrointestinal (n=1), ear/nose/throat (n=1), endocrine (n=2).
[3]Interventions included atrial septostomy (n=1), balloon dilation aortic valve (n=1), other (n=2).
4Hypoplastic left heart syndrome with unknown mitral valve severity (1), double-inlet right ventricle (1), congenitally corrected transposition of the great arteries (1).
CHD: congenital heart disease; HLHS: hypoplastic left heart syndrome; LV: left ventricle.

Table 2. Surgical data for infants surviving to hospital discharge after first stage palliation for single ventricle heart disease, Norwood operation and variants (n=100). Data expressed as median (range) or number (percent).

Age at Initial Pallliation (days)	5 (2-78)
Weight at Time of Surgery (kg)	3.2 (2.4-5.0)
Choice of Initial Palliation Operation	
Stage I Norwood/Blalock-Taussig Shunt	28 (28)
Stage I RV-PA Conduit	55 (55)
Hybrid Stage I	10 (10)
DKS and Blalock-Taussig Shunt	7 (7)
Stage I Surgical Data[1]	
Cardiopulmonary Bypass Time (min)	137 (38-403)
Aortic Cross Clamp Time (min)	48 (0-145)
Circulatory Arrest Time (min)	10 (0-79)
Lowest Temperature in OR (degrees Celsius)	18 (14-35.1)
Use Regional Perfusion (percent cases)	63 (70%)
Out of OR on ECMO	3 (3%)
More Than One Extubation Prior to Discharge	21 (21%)
Ventilator Days to Final Extubation	9 (0-83)

[1]N=90 for those who underwent Stage I palliation; excludes patients who underwent hybrid Stage I.
RV-PA: right ventricle to pulmonary artery; DKS: Damus-Kaye-Stansel procedure; OR: operating room; ECMO: extra-corporeal membrane oxygenator.

Table 3. Surgical re-operation data for infants surviving to hospital discharge after first stage palliation for single ventricle heart disease, Norwood operation and variants (n=100). Data expressed as median (range) or number (percent).

Reoperations[1]	19 (19%)
Exploration for Rebleeding	6 (6%)
Sternal or Mediastinal Debridement	2 (2%)
ECMO Decannulation	3 (3%)
Aortic Arch Repair	2 (2%)
Blalock-Taussig Shunt Revision	2 (2%)
Aortopexy	1 (1%)
Peritoneal Dialysis Catheter Placement	1 (1%)
RV-PA Conduit Revision	1 (1%)
Shunt Exploration	1 (1%)
Tricuspid Valve Repair	1 (1%)
Thoracic Duct Ligation	1 (1%)

[1]Excludes routine delayed sternal closure.
ECMO: extra-corporeal membrane oxygenator; RV-PA, right ventricle to pulmonary artery

FIGURE LEGENDS

Figure 1. **Choice of Initial Surgical Palliation**. A) Choice of initial palliation for whole cohort (n=100) surviving to hospital discharge after palliation of single ventricle heart disease with Norwood operation and variants. B) Choice of initial palliation by type among participating surgical sites (data shown only for those centers enrolling ≥4 patients). RVPA: right ventricle to pulmonary artery conduit.

Figure 2. **Cardiopulmonary Bypass Time**. Total cardiopulmonary bypass time (min) for those undergoing surgical Stage I Norwood or variants among participating surgical sites (data shown only for those centers enrolling ≥ 4 patients, n=80 patients); data excludes those who underwent hybrid Stage I. Straight and dashed lines represent the median and 25th and 75th percentiles for the whole cohort.

Figure 3. **Aortic Cross Clamp Time.** Total aortic cross clamp time (min) for those undergoing Stage I Norwood or variants at participating surgical sites (data shown only for those centers enrolling ≥ 4 patients, n=80 patients); data excludes those who underwent hybrid Stage I. Straight and dashed lines represent the median and 25th and 75th percentiles for the whole cohort.

Figure 4. **Circulatory Arrest Time**. Total circulatory arrest time (min) for those undergoing Stage I Norwood or variants among participating surgical sites (data shown only for those enrolling ≥ 4 patients, n=80 patients); data excludes those who underwent hybrid Stage I. Straight and dashed lines represent the median and 25th and 75th percentiles for the whole cohort.

Figure 5. **Lowest Intraoperative Temperature**. Lowest recorded patient temperature in the operating room (degrees Celsius) at participating surgical sites (data shown only for those centers enrolling ≥ 4 patients, n=80 patients); data excludes those who underwent hybrid Stage I. Straight and dashed lines represent the median and 25th and 75th percentiles for the whole cohort.

***Figure 6*. Use Regional Perfusion**. Use of intraoperative regional perfusion techniques, by percent of cases, for those undergoing Stage I Norwood or variants at participating surgical sites (data shown only for those centers enrolling ≥ 4 patients, n=80 patients); data excludes those who underwent hybrid Stage I.

FIGURE 1A

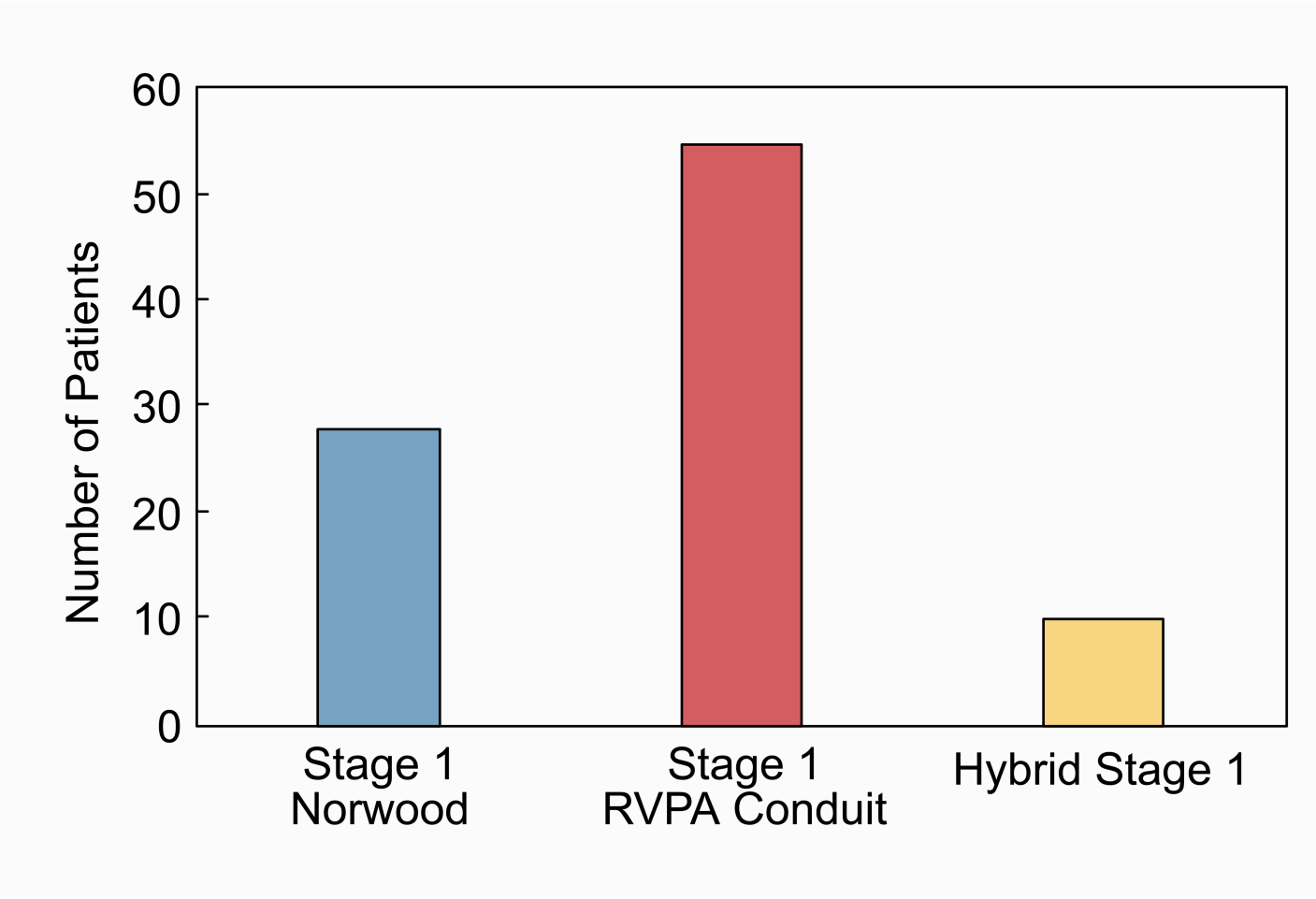

60
50
40
30
20
10
0
Number of Patients
Stage 1
Norwood
Stage 1
RVPA Conduit
Hybrid Stage 1

FIGURE 1B

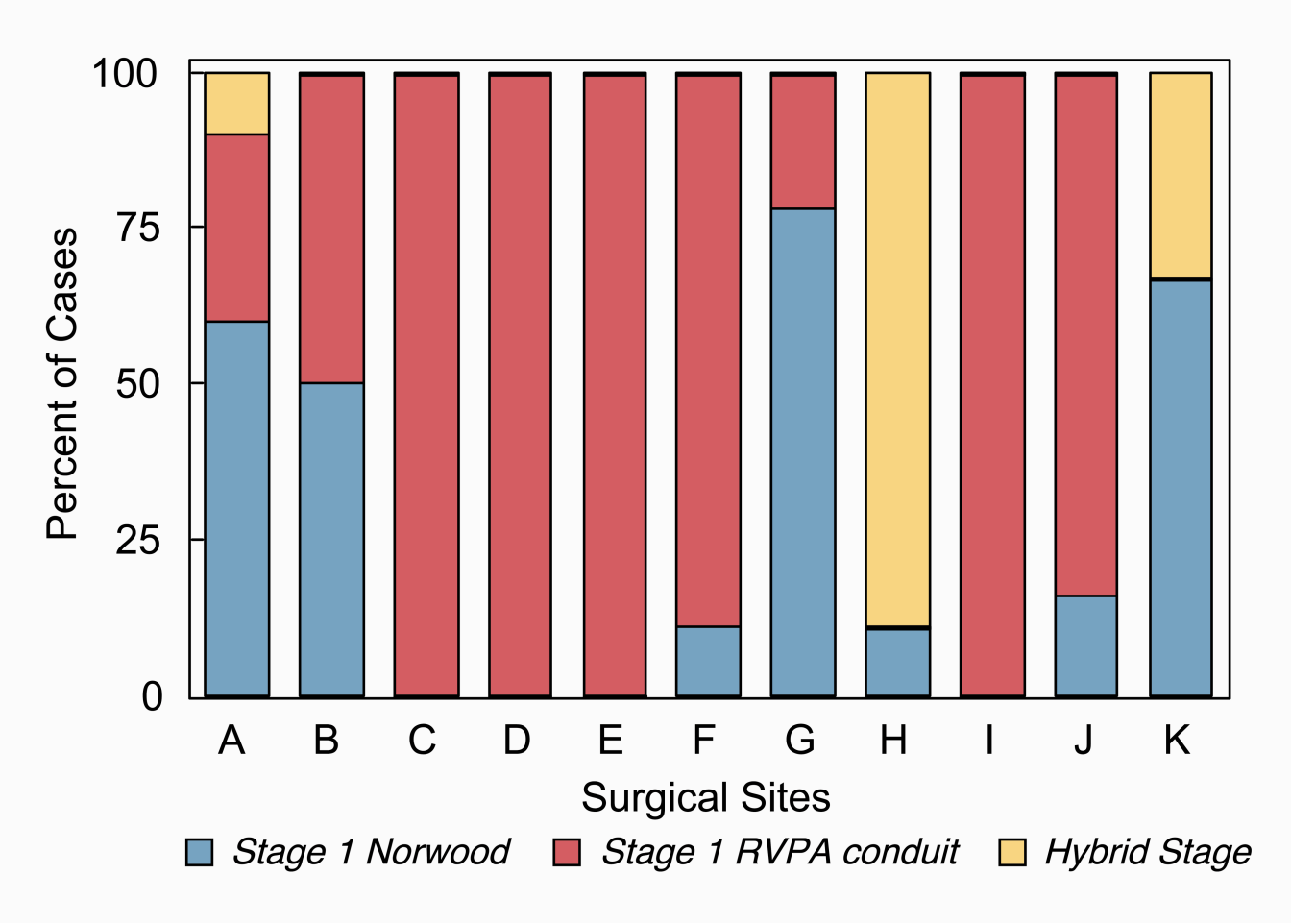

100
75
50
25
0
Percent of Cases
A
B
C
D
E
F
G
H
I
J
K
Surgical Sites
Stage 1 Norwood
Stage 1 RVPA conduit
Hybrid Stage

FIGURE 2

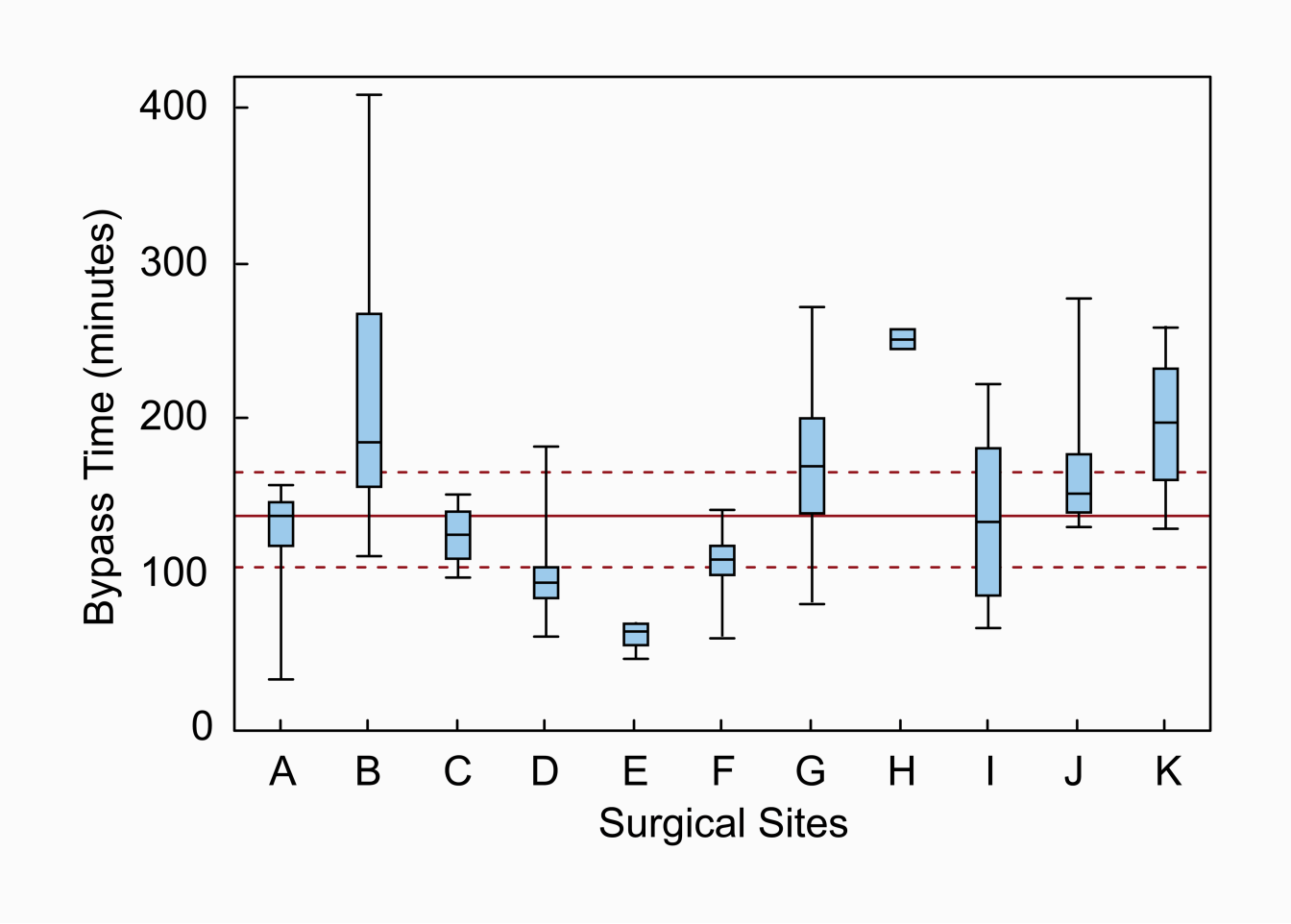

Bypass Time (minutes)
400
300
200
100
0
A
B
C
D
E
F
G
H
I
J
K
Surgical Sites

FIGURE 3

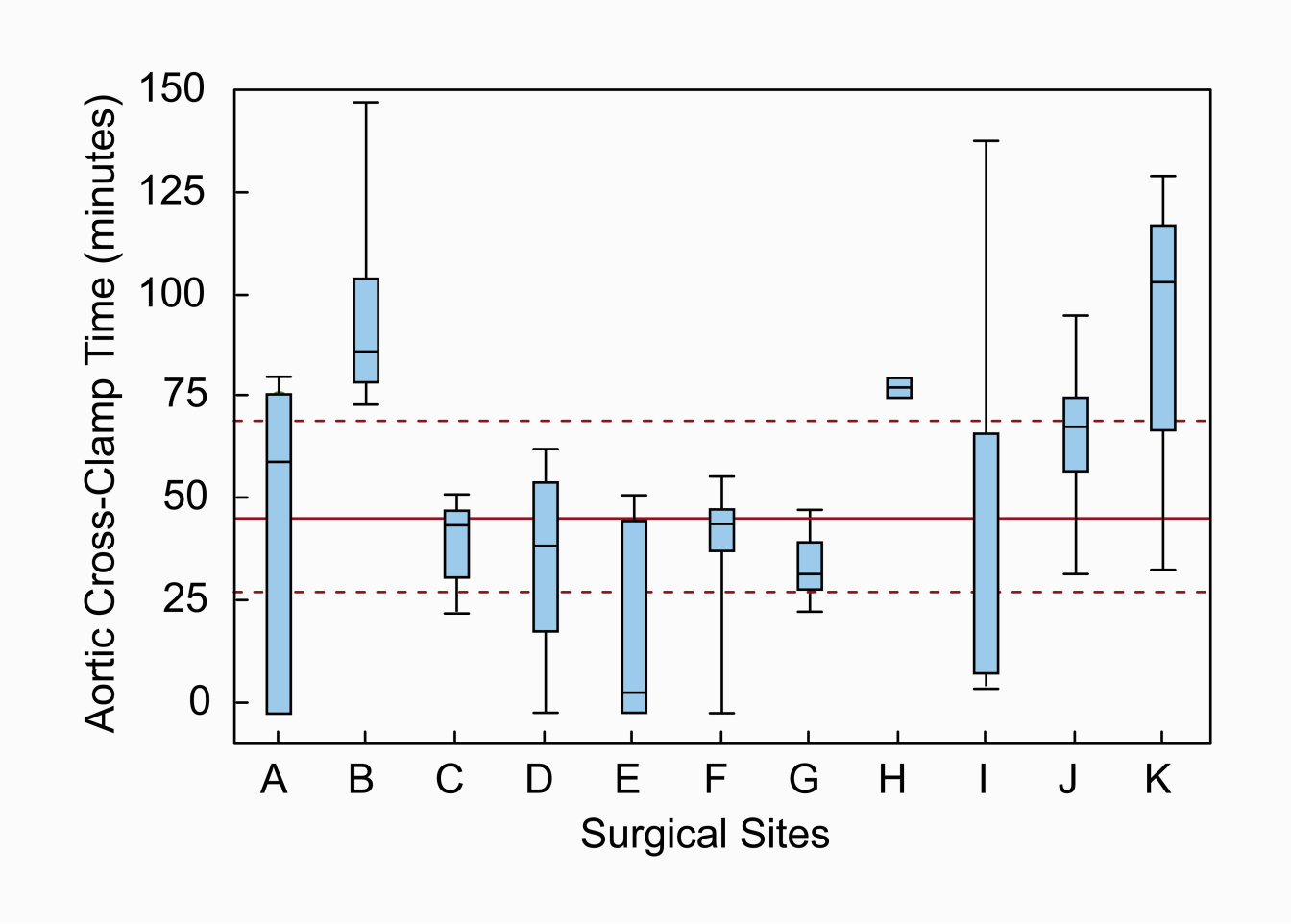

Aortic Cross-Clamp Time (minutes)
150
125
100
75
50
25
0
A
B
C
D
E
F
G
H
I
J
K
Surgical Sites

FIGURE 4

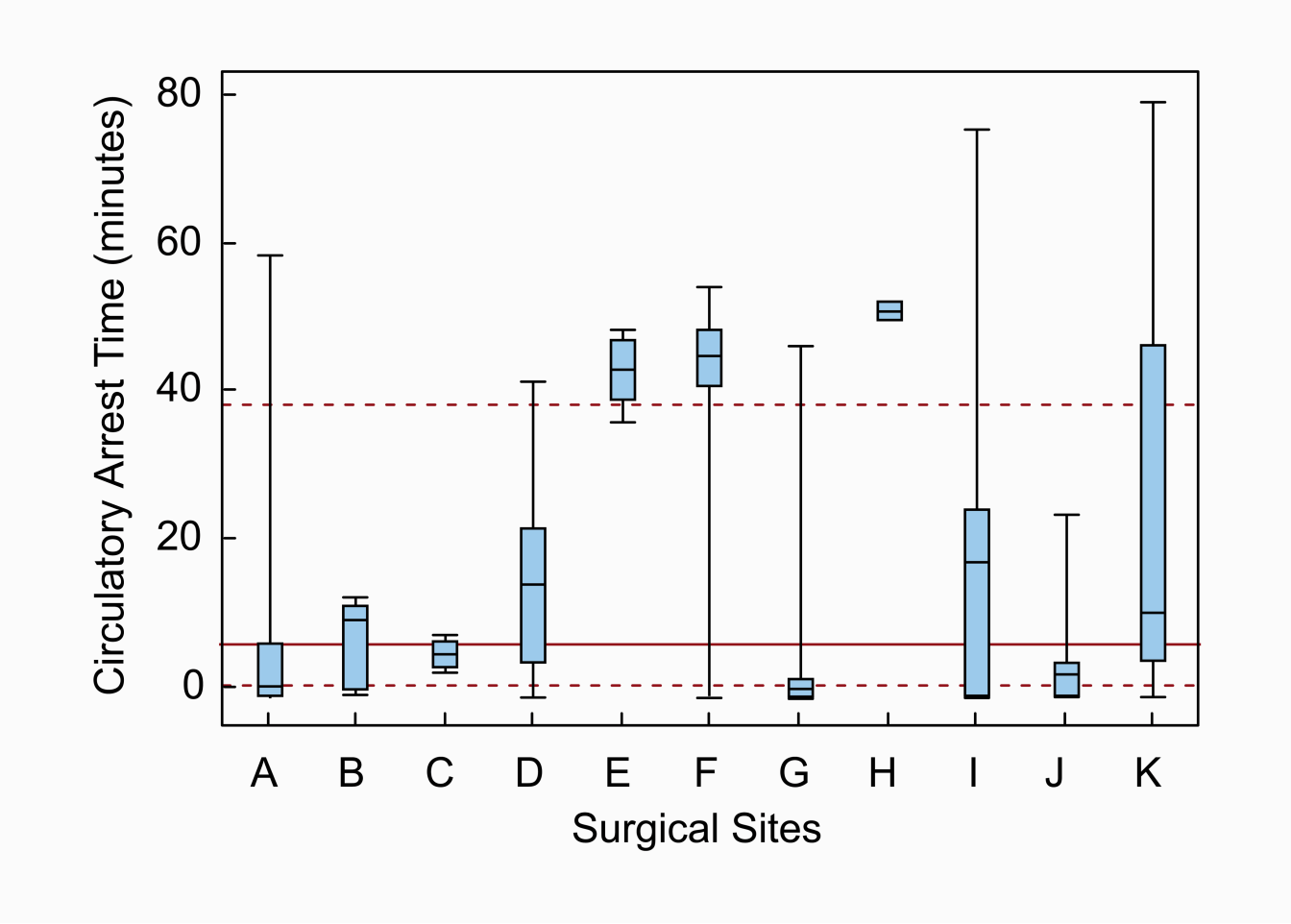

Circulatory Arrest Time (minutes)
80
60
40
20
0
A
B
C
D
E
F
G
H
I
J
K
Surgical Sites

FIGURE 5

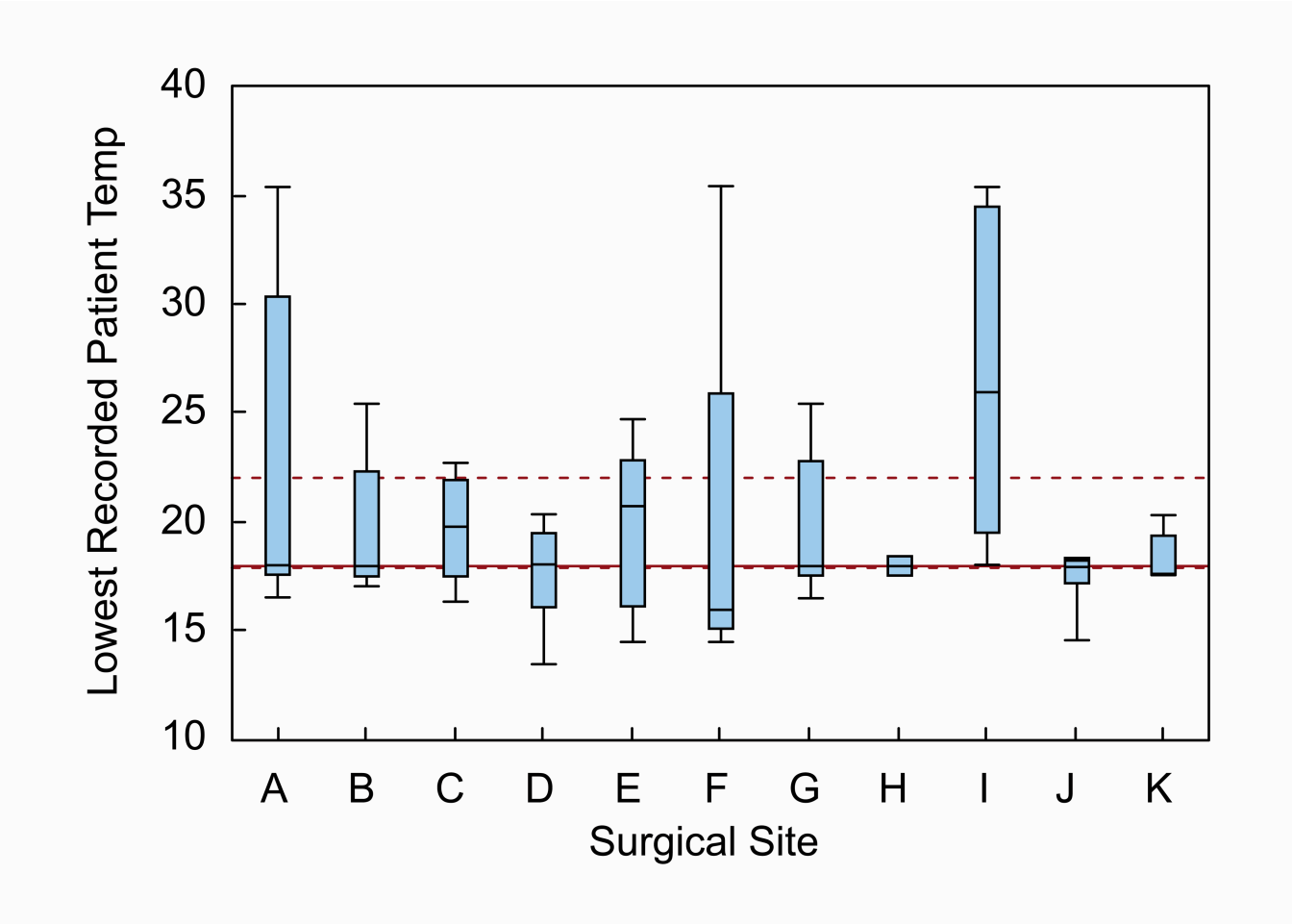
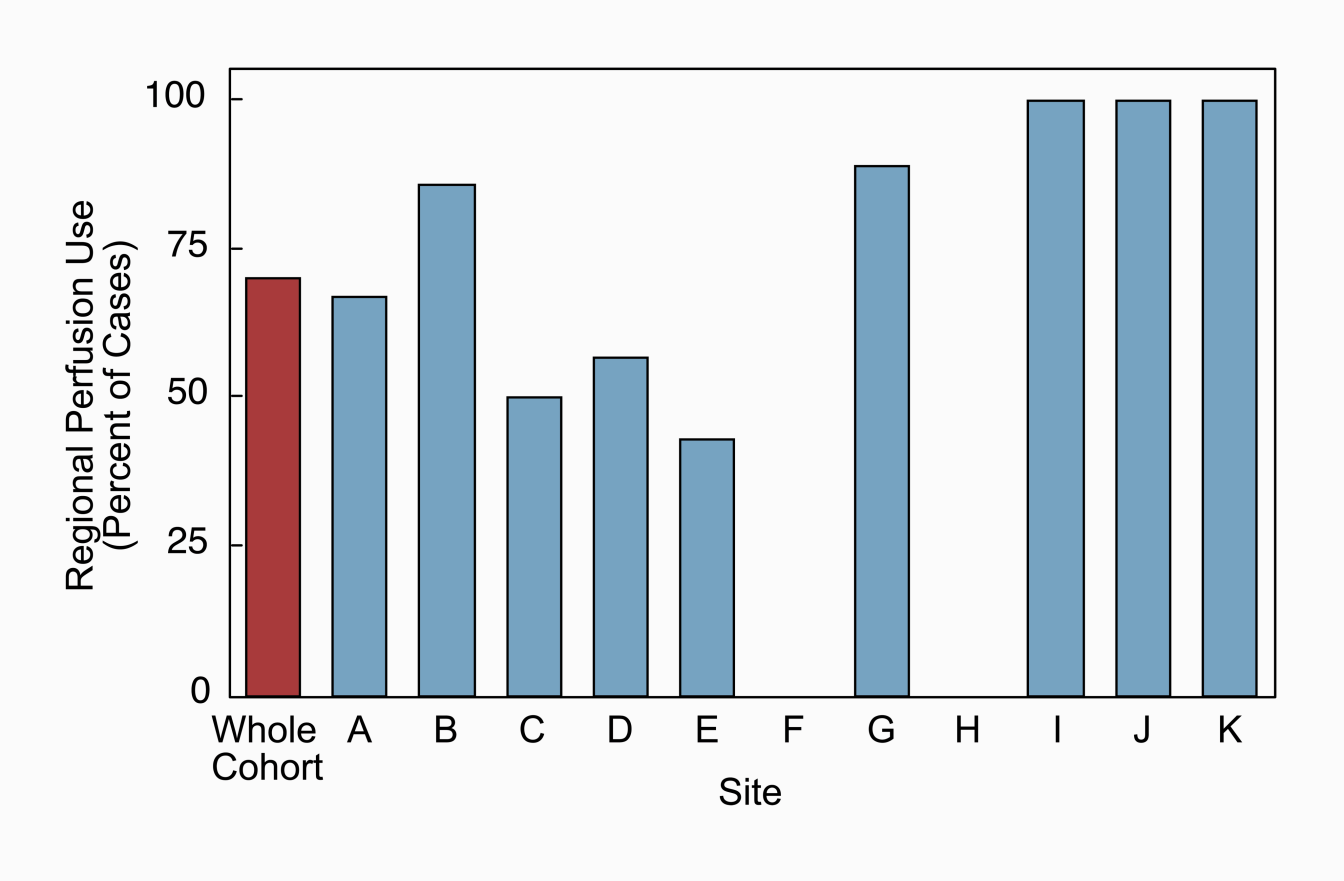

Lowest Recorded Patient Temp
40
35
30
25
20
15
10
A
B
C
D
E
F
G
H
I
J
K
Surgical Site

FIGURE 6


Regional Perfusion Use
(Percent of Cases)
100
75
50
25
0
Whole Cohort
A
B
C
D
E
F
G
H
I
J
K
Site

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