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Incidence of postoperative thrombosis in children with surgical and non-surgical heart diseases
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Thesis

INCIDENCE OF POSTOPERATIVE THROMBOSIS IN CHILDREN WITH SURGICAL
AND NON-SURGICAL HEART DISEASES

by

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DEDICATION

I would like to dedicate this work to my parents and grandparents for always supporting me in all of my endeavors.
INCIDENCE OF POSTOPERATIVE THROMBOSIS IN CHILDREN WITH SURGICAL AND NON-SURGICAL HEART DISEASES

KATHERINE M. GARDELLA

ABSTRACT

Objectives: Congenital heart disease or CHD is a condition that affects 8 out of every 1,000 newborns. Every year more than 35,000 newborns are diagnosed with a congenital heart disease in the United States. Neonates and children with congenital heart disease are at increased risk for thrombotic events, especially those with a single ventricle physiology. The objective of this study was to assess the incidence and to identify the predictors of thrombosis in neonates and children with surgical and non-surgical heart diseases.

Methods: We performed a retrospective analysis of the Health Care and Cost Use Project Kid’s Inpatient Database. Neonates and children with a congenital heart disease were identified using the international classification of disease, 9th revision, clinical modification (ICD-9 CM) diagnostic codes, and grouped into two subcategories of surgical heart and non-surgical heart diseases. These groups were further divided into four types of lesions: septal defects, single ventricle physiology, right ventricle outflow tract obstruction, and left ventricle outflow tract obstruction. Demographic characteristics, the presence of co-morbidities, the incidence of any thrombotic events, mortality rate, and the presence of additional complications such as acute kidney injury, sepsis, neurologic complications, the need for extracorporeal membrane oxygenation or ventricular assist device were also collected using ICD-9
CM codes. After propensity-matched analysis, neonates and children with a surgical congenital heart disease were compared with those with a non-surgical heart disease. We used uni- and multivariable logistic regression analysis to identify the predictors associated with the incidence of thrombotic events in both sub-group.

**Results:** In children with surgical heart disease, the incidence of thrombosis was 3.90%, compared with 2.13% in children with non-surgical heart disease. Furthermore, those with single ventricle physiology (surgical 2.13%; non-surgical 3.41%) or right ventricle outflow tract obstruction (surgical 1.54%; non-surgical 1.66) had the highest incidence of thrombosis. In addition to demographic characteristics (e.g. age) and the type of congenital heart disease, we observed that extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD), the presence acute kidney injury, sepsis, and coagulopathy were strong predictors for the development of thrombotic events.

**Conclusions:** Children with both surgical and non-surgical heart disease have an increased risk for thrombotic events, but those with a single ventricle physiology or a right ventricle outflow tract obstruction had a further increased risk.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Septal Defects (SD)</td>
<td>1</td>
</tr>
<tr>
<td>Single Ventricle Physiology (SVP)</td>
<td>3</td>
</tr>
<tr>
<td>Right Ventricle Outflow Tract Obstruction (RVOTO)</td>
<td>9</td>
</tr>
<tr>
<td>Congenital Heart Disease and Thrombotic Events</td>
<td>13</td>
</tr>
<tr>
<td>Specific Aims and Objectives</td>
<td>14</td>
</tr>
<tr>
<td>METHODS</td>
<td>17</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>19</td>
</tr>
<tr>
<td>RESULTS</td>
<td>21</td>
</tr>
</tbody>
</table>
DISCUSSION .................................................................................................................................29

Limitations ........................................................................................................................................32

Future Directions ..............................................................................................................................33

Conclusions ........................................................................................................................................35

REFERENCES ..................................................................................................................................37

CURRICULUM VITAE .......................................................................................................................43
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Characteristics of children with surgical and non-surgical heart disease diagnosed with a thrombotic complication</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Variables obtained from multivariate logistic regression analysis associated with thrombotic complication in the surgical population</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Variables obtained from multivariate logistic regression analysis associated with thrombotic complications in the non-surgical population</td>
<td>25</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypoplastic Left Heart Syndrome Heart</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Comparison of RVPA Shunt and MBT Shunt</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Heart after Completion of Fontan Procedure</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Heart at Each Palliative Stage</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Repaired Tetralogy of Fallot</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Flow chart and description of the propensity-matched analysis</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>Incidence of thrombotic complications in children with surgical and non-surgical heart disease based on the type of lesion</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>Mortality in children with surgical or non-surgical heart disease with or without thrombotic complications</td>
<td>28</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

AKI .......................................................................................................................... Acute Kidney Injury
Ao............................................................................................................................. Aortic
CHD .......................................................................................................................... Congenital Heart Disease
ECMO ....................................................................................................................... Extracorporeal Membrane Oxygenation
GEE .......................................................................................................................... Generalized Estimating Equations
HCUP ......................................................................................................................... Health Care Cost and Use Project
HD ............................................................................................................................... Heart Disease
HLHS ......................................................................................................................... Hypoplastic Left Heart Syndrome
ICD-9 CM ................................................................................................................. International Classification of Diseases,

9th Revision, Clinical Modification Codes
IRQ ............................................................................................................................ Interquartile Range
KID ........................................................................................................................... Kid’s Inpatient Databases
LOS .......................................................................................................................... Length of Stay
LVOTO ....................................................................................................................... Left Ventricle Outflow Tract Obstruction
RMBT ....................................................................................................................... Right Modified Blalock-Taussig
ROC .......................................................................................................................... Receiver Operating Characteristic
RVOTO ....................................................................................................................... Right Ventricle Outflow Tract Obstruction
RVPA ....................................................................................................................... Right Ventricle to Pulmonary Artery
SD ............................................................................................................................ Septal Defect
SVP .......................................................................................................................... Single Ventricular Physiology
Ventricular Assist Device
INTRODUCTION

Congenital heart disease or CHD is a condition that affects 8 out of every 1,000 newborns (National Heart, Lung, and Blood Institute, 2013). Every year, a diagnosis of congenital heart disease is made in more than 35,000 babies in the United States (National Heart, Lung, and Blood Institute, 2013). Congenital heart disease can take many forms; it can range from a ‘simple’ malformation that does not require any intervention, and will resolve within the first 6 months of life (e.g. atrial septal defect or ventricular septal defect) to an extremely complex disease that will require a long series of surgical interventions. Examples of simple CHDs would include atrial and ventricle septal defects, patent ductus arteriosus, or narrowed valves. Complex CHDs can include tetralogy of Fallot, single ventricle defects, hypoplastic left heart syndrome, transposition of great arteries, or aortic arch anomalies (National Heart, Lung, and Blood Institute, 2013).

Septal Defects (SD)

Septal defects, or holes in the heart, are simple congenital heart defects that correspond to different forms of incomplete junction and closure of embryologic structures leading to abnormal persistent communication between the left and the right sides of the heart. Such communications could be found in either the atrial or ventricular septum (National Heart, Lung, and Blood Institute, 2013). This condition will usually correct itself without the need for any surgical or interventional procedures. However, in the absence of spontaneous closure, an intervention will be
required to close the communication, and avoid long-term complications associated with this non-physiologic shunt of the blood from the left part of the heart to the right (e.g. cardiomyopathy, cardiac failure, pulmonary artery hypertension). In case there is a need for an intervention to close the communication, the patient can either undergo a surgical repair, corresponding to an open-heart surgery with cardiopulmonary bypass, or a closure using an interventional cardiology technique, or a hybrid procedure using both techniques (Mayo Clinic, 2014). Patients will usually require an intervention only if the hole is medium or large in size because they have a higher risk of not closing on their own through growth (National Heart, Lung, and Blood Institute, 2013).

As reported by the National Heart, Lung, and Blood Institute, an atrial septal defect is a hole in the wall of the septum that separates the upper chambers of the heart (National Heart, Lung, and Blood Institute, 2013). It is a congenital heart disease that has few, if any, symptoms. A ventricular septal defect is a hole in the wall of the septum that separates the lower chambers of the heart. Unlike atrial defects, having a ventricular septal defect will cause symptoms if it is large or medium in size. Because of the large opening there is an extra workload on the heart and this can cause heart failure and poor growth along with high blood pressure (National Heart, Lung, and Blood Institute, 2013).
Single Ventricle Physiology (SVP)

There are three common types of single ventricle defects; hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum, and tricuspid atresia. Single-ventricle heart defects are often diagnosed during pregnancy or immediately after birth (American Heart Association, 2015). The underlying causes of single ventricle defects are usually unknown and are not completely modifiable. Children with these conditions can often have other heart defects along with their SVP (American Heart Association, 2015). Children with single ventricle physiology are at an increased risk for short and long-term complications, both during the perioperative period of the different surgical procedures required and a decreased standard of living when compared to other patients in their age group (Center for Disease Control, 2016; Idorn et. al., 2013). Neonates and children with SVP will require a series of surgical procedures usually defined as follow: right modified Blalock-Taussig shunt within the first days or weeks after birth, Glenn procedure at the age of 3-6 months, and the Fontan surgery usually performed at the age of 2-3 years old. Even though, the introduction of this series of surgical procedure has significantly improve survival in those patients, the procedures should be considered as palliative options, with a congenital heart disease that will never been completely solved, and will require lifetime medical treatments.

Hypoplastic left heart syndrome (Figure 1) is one of the most complex diseases where the entire left side of the heart, and sometimes the aorta are underdeveloped. Patients present with a severe cyanotic with poor peripheral
pulses, rapid breathing, and cold hands and feet to name a few symptoms (Cincinnati Children’s Hospital, 2013). As described above, such a SVP requires three palliative surgeries to allow for correct blood to flow through out the body, while in some patients a heart transplant will be the only option. The three palliative surgeries are the Norwood procedure, the bi-directional Glenn shunt procedure, and the Fontan procedure (American Heart Association, 2015).

Between birth and two weeks of life the patient will undergo the first of three palliative surgeries (Figure 4). The Norwood procedure (Figure 2) is carried out to create a new aorta, of normal size, and a shunt. The atrial septum is opened and the old aorta and coronary arteries are connected to the new enlarged aorta. There are two types of shunts typically used in the Norwood procedure, the right modified Blalock-Taussig shunt (RMBTS) or the right ventricle to pulmonary artery shunt (RVPA). The Blalock-Taussig shunt is the original shunt that was performed with success in this procedure (Center for Disease Control, 2016). The RMBTS, is a modified approach of the original Blalock-Taussig shunt, and is created between the right subclavian artery, and the right pulmonary artery to generate flow into the pulmonary arteries. The RVPA shunt provides the same flow to the pulmonary arteries except it connects the pulmonary artery directly to the right ventricle (Ohye et. al., 2010). This technique is not routinely used, as the RMBTS is usually preferred (Ohye et. al., 2010).
Figure 1: Hypoplastic Left Heart Syndrome. As seen in the figure the left ventricle is under developed along with the aorta. The direction of the blood flow causes mixture of oxygenated and deoxygenated blood through an atrial septal defect. (Adapted from Ohye et. al., 2010)
Figure 2: Comparison of MBT shunt and RVPA shunt. The raised dashed lines represent the new enlarged aorta and new connections. The shunts are whiter in color to emphasize the different types of shunts placements. The only difference between the two surgeries is the type of shunt. (Adapted from Ohye et. al., 2010)
Following the Norwood procedure, between 3 to 6 months of age the bi-directional Glenn shunt procedure, or the hemi-Fontan procedure is performed (Center for Disease Control, 2016). This surgery is necessary to reduce the amount of strain placed on the right ventricle. Creating a direct connection between the superior vena cava and pulmonary artery, which reduces the workload on the right ventricle, and allows the oxygenation of the venous blood before it goes back to the systematic circulation. Though the child may still appear cyanotic the survival rate is about 90% if they can make it to this surgery (Cincinnati Children’s Hospital, 2013).

Lastly, between 2 and 3 years the patient will undergo the Fontan procedure (Figure 3), where the inferior vena cava is connected to the pulmonary artery using a prosthetic tube. Following the completion of the Fontan procedure the deoxygenated blood flows passively to the lungs and the patient is no longer cyanotic (Center for Disease Control, 2016). The Norwood procedure, has the highest rate of mortality of the three surgeries at a 75% survival rate (Cincinnati Children’s Hospital, 2013). Many pediatric patients have difficulty making it through to the next surgery. These patients may also not be able to complete the three surgeries and need to receive a heart transplant. Patients who have not completed the palliative surgery to correct their congenital heart disease often experience failing circulation, acute cardiac failure, or respiratory failure. Extracorporeal membrane oxygenation (ECMO) has been found to be a useful bridge to heart transplant or surgery for these patients (Bautista-Hernandez et. al., 2014). While it
has been found to be helpful in getting patients through to their next surgery, ECMO is not without its complications. In a study performed by Tajik et. al. (2008), found that while there was a higher survival to discharge of 12-23% when compared to CPR alone, there were high incidences of complications. These complications they found were neurological and renal in nature and had a strong influence on the survival of the patient (Tajik et. al., 2008).

Pulmonary atresia is characterized by the absence of the pulmonary valve and the right ventricle and tricuspid valve are often developed poorly (American Heart Association, 2015). In these patients the only source of lung blood flow is the patent ductus arteriosus and if this closes the patient experiences severe cyanosis, and dies (American Heart Association, 2015). Depending on the size of the pulmonary artery and the right ventricle a complete repair of this defect could be possible by placing a shunt between the aorta and the pulmonary artery. If the pulmonary artery and the right ventricle were too small, the repair would then be to connect the body veins directly to the pulmonary arteries (American Heart Association, 2015). These patients can also undergo the Glenn and Fontan procedures if necessary to alleviate symptoms and cyanosis. Tricuspid Atresia is a condition where no tricuspid valve is present. This gives a patient abnormal circulation and causes cyanosis. Treatment is again a shunt or the Glenn and Fontan procedures (American Heart Association, 2015).
Figure 3: Heart after Completion of Fontan Procedure. The left side of the heart has been completely bypassed and now deoxygenated blood flows freely to the lungs. (Adapted from Asirvatham, 2008)
Figure 4: Heart at Each Palliative Stage. a) Stage 1 is the Norwood Procedure. b) Stage 2 is the Bi-Directional Glenn Shunt Procedure. c) Stage 3 is the Fontan Procedure. d) Stage 4 is the closure of the fenestration. (Adapted from Fruitman, 2000)
Right Ventricle Outflow Tract Obstruction (RVOTO)

Right ventricle outflow tract obstruction, is an obstruction in the blood flow from the right ventricle of the heart to the lungs. While RVOTO can occur on its own, is more commonly seen in conjunction with another condition such as tetralogy of Fallot (Nevil Thomas Adult Congenital Heart Library, 2001).

Tetralogy of Fallot (Figure 5) is a combination of four defects; a ventricular septal defect, right ventricle outflow tract obstruction, right ventricular hypertrophy or a thickening of the muscles surrounding the lower right chamber of the heart, and a displaced aorta that lies over the ventricular septal defect (National Heart, Lung, and Blood Institute, 2013). Neonates and children with tetralogy of Fallot are prone to episodes of cyanosis and is now treated in infancy to prevent additional health complications. The palliative care as a neonate is the placement of a shunt to provide a temporary repair to the problem of poor blood flow to the lungs. This technique is not widely used since most surgeons now prefer to perform the complete repair as soon as possible (National Heart, Lung, and Blood Institute, 2013). The complete repair consist in the closure of the septal defect, and either the opening or removal of the RVOTO, that sometimes requires the placement of a prosthetic pulmonary conduit. This approach is now very successful, leading to extremely good outcomes (American Heart Association, 2015).
Figure 5: Repaired Tetralogy of Fallot. Ventricular septal defect is closed using a patch and the RVOTO is opened and lung flow from right ventricle to lungs is repaired. (Adapted from Diller et al., 2011)
*Congenital Heart Disease and Thrombotic Events.*

Children with congenital heart disease are at an increased risk for thrombosis. Data shows that post-operative complications involving thrombosis in children with congenital heart disease varies in the range of 100/10,000 and 3,500/10,000 incidences reported (Giglia *et. al.*, 2013). This is relatively high when the prevalence of thrombosis in pediatric CHD is compared to the prevalence of thrombosis in the non-cardiac pediatric population. The non-cardiac pediatric population has a relatively low prevalence of thrombosis at 20-50/10,000 hospital admissions (Raffini *et. al.*, 2009; Bouet *et. al.*, 2009). The incidence is further increased when the prevalence of symptomatic thrombosis is taken into account giving a range of 160-1,600/10,000 in children with cancer (Piovesan *et. al.*, 2014).

Children with cyanotic congenital heart diseases have differences in their blood compilation and coagulation profiles from normal children leading to multiple complications such as high incidence of intraoperative hemorrhage, and high rate of thrombosis in the postoperative period (Zabala *et. al.*, 2015). Another study conducted by Giglia *et. al.* also states that thrombosis has been recognized as a condition with potentially life-threatening complications in children with congenital heart diseases, especially those with shunt-dependent single ventricles and Fontan circulation. Their study found that with shunt-dependent single ventricles the incidence of thrombosis was 8-12%, and with the Fontan circulation the incidence was higher at 17-33% (Giglia *et. al.*, 2013).
The findings of Giglia et al. are further supported by a study completed by Odegard et al. that looked at coagulation profiles in children with hypoplastic left heart syndrome (HLHS) through all three procedures. The study completed by Odegard et al. found that children with single ventricle physiology, either before or after the Fontan procedure, appear to have the highest risk for thrombosis. This study concluded that coagulation abnormalities could put patients at a higher risk for clotting or bleeding complications (Odegard et al., 2002). Another study completed by Odegard et al. reported that there were significantly lower levels of both pro-coagulation and anticoagulation factors, specifically factor VIII, in patients through the completion of the Fontan procedure (Odegard et al., 2009). Though the deficiency was present through the Fontan procedure, the study found that after the Fontan the levels of factor VIII increased. The researchers in this study thought that the monitoring of increase in factor VIII after the Fontan procedure in patients could help to indicate the patients at risk for thrombosispost-Fontan (Odegard et al., 2009).
Specific Aims and Objectives

There is a profound lack of research regarding thrombotic complications in children with congenital heart disease and prophylactic therapies for these complications. This study aims to identify factors that contribute to thrombosis in children with surgical and non-surgical congenital heart disease to better understand the incidences and the predictors for thrombosis in this high-risk population.

Using a sample of children with surgical and non-surgical CHD from the Health Care Cost and Use Project Kid's Inpatient Database the specific aims of this study are:

1. To assess the incidence and predictors for thrombosis in children with surgical and non-surgical heart disease by performing a retrospective analysis of the database. Some of the variables tested as predictors included age group, type of cardiac lesion, coagulopathy, ECMO, VAD, AKI, sepsis, elective hospital admission, Elixhauser co-morbidity score, and length of stay.

2. To compare the incidence in children with CHD with another high-risk non-cardiac pediatric population. In this study the incidences observed in CHD patients were compared with a control group of children with cancer. As mentioned above the prevalence in non-cardiac pediatric population is relatively low, but the prevalence of symptomatic thrombosis in patients with cancer is between 160/10,000 to
1,600/10,000 (Piovesan et. al., 2014) which is comparable to children with CHD which has a prevalence of thrombosis between 100/10,000 and 3,500/10,000 incidences reported (Giglia et. al., 2013).

By completing this study, the goal would be to have a better understanding of predictors for thrombotic complications. By furthering the research in this study the hope would be to better define optimal prophylactic approaches to treating thrombosis based on the predictors for thrombotic complications.
METHODS

The retrospective analysis was performed using the 2009 and 2012 Health Care Cost and Use Project (HCUP) Kid’s Inpatient Databases (KID). The KID data set is a national database that encompasses more than 100 clinical and non-clinical variables. The database has a range of hospitals that include specialty hospitals, public hospitals, and academic medical centers. The size of the hospitals were categorized by HCUP using the number of beds and this categorization was also specific to hospital’s location and teaching status. A small hospital was defined as 1-99 beds, medium was 100-399 beds, and large was more than 400 beds. Their region, such as, Northeast, Mideast, South, and West, further categorized the hospitals in the database (Health Care Cost and Use Project Kid’s Inpatient Database, 2009). This work was approved by the International Review Board.

Using the database and International Classification of Diseases, Ninth Revision, Clinical Modification codes (IDC-9 CM) diagnostic codes, neonates and children with CHD were identified for analysis. Each case was reviewed using the IDC-9 CM diagnostic codes and separated into surgical and non-surgical groups. Cases that were assigned to multiple diagnostic code categories were excluded from the study. The surgical group included hospitalized CHD patients that underwent cardiac surgery procedures such as, cardiac catheterization procedures, cardiac surgery, or non-cardiac surgery. All other hospitalized CHD patients were categorized into the non-surgical group. The cases were further sub-divided into
four additional groups looking at the type of lesion: septal defects (SD), single ventricle physiology (SVP), right ventricle outflow tract obstruction (RVOTO), and left ventricle outflow tract obstruction (LVOTO).

Patient’s age and length of hospital stay were also assessed as factors for increased thrombosis risk. Each patient’s age at admission was categorized into one of five age groups: neonates (less than 1 month of age), 1 to 12 months old, 1 to 6 years old, 6 to 12 years old, and older than 12 years old. In addition to age and length of stay, demographic information, co-morbidities, and outcomes were also identified. Using the ICD-9 CM procedure codes the outcomes identified were: mortality, acute kidney injury (AKI), sepsis, neurologic complications, thrombotic complications, extracorporeal membrane oxygenation (ECMO) use in neonates, and ventricular assist device (VAD) use in neonates. Thrombotic complications were classified by the ICD-9 CM diagnostic codes and defined as intravascular thrombosis, either venous, atrial, or intra-cardiac including shunts, cardioembolic strokes, or pulmonary embolisms. To identify co-morbidities a combination of the ICD-9 CM diagnostic codes and a modified Elixhauser comorbidity score was used. (Quan et al., 2005) The primary diagnostic code was not considered a complication, as it was the reason for hospital admission not a result of the hospital stay.
**Statistical Analysis**

Propensity matched analysis and multivariable logistic regression analysis were used to determine the predictors for thrombosis. All data are presented as a number and a percentage. Each group of surgical and non-surgical heart disease children were further sub-divided into groups of those with thrombotic complications and those without thrombotic complications. These groups were compared using a Chi-square test for categorical variables.

Multivariable logistic regression using backward selection was used to obtain variables associated with thrombosis. A pre-defined univariate was used with cut off values of P<0.10 for variable inclusion and P>0.05 for removal from the model. The association of hospital identification with the incidence of thrombotic complications was evaluated after adjusting for cluster by center using hospital identification number by using a logistic regression model using generalized estimating equations (GEE). To assess the strength of the association between thrombosis and the independent variables the cumulative area under the receiver operating characteristic (ROC) curve was calculated.

Furthering our statistical analysis a logistic regression model was used to identify demographic and co-morbidity (including Elixhauser score) variables predicting surgical vs. non-surgical heart disease. From these variables consequently a propensity score can be determined by completing a propensity-matched analysis (Deb et. al., 2015). For the propensity score model the following characteristics were included: age, gender, elective hospital admission, type of
cardiac lesion, Elixhauser co-morbidity score, and length of stay. The propensity matched analysis done used a nearest-neighbor-1:1-greedy matching algorithm. The algorithm was applied to match children with surgical and non-surgical heart disease on the basis of the logit of their propensity score. This matching was completed using a caliper width equal to 0.2 times the standard deviation of the logit of their propensity score (Austin et. al., 2014; Austin, 2011). The balance of baseline covariates between the exposed and control groups in the matched sample was assessed using standard differences, with standardized differences of less than 0.1 for each covariate. This test was completed to show that there was a good balance in the match cohort (Austin, 2009).

As a secondary objective the incidence of thrombotic complications in children with surgical and non-surgical heart disease was compared with a matched group of children with cancer. A logistic regression model to define demographic and co-morbidity variables predicting surgical heart disease vs. cancer diagnosis was performed with the same methods as mentioned previously. After this analysis was completed a second propensity-matched analysis was completed as mentioned above using the same characteristics as when comparing surgical vs. non-surgical heart disease.

A P value of <0.05 was considered statistically significant for all tests. All reported values in this study are absolute values measured from the data set. All statistical analyses were performed using STATA version 14.1 for Mac OS.
RESULTS

The 2009 and 2012 KID HCUP databases included 6,386,928 children. From this database, 274,583 children were identified with CHD totaling to 4% of the database. Of the 274,583 CHD patients, 27,492 or 10% of the patients had surgical heart disease and 247,091 or 90% had non-surgical heart disease. In the general population of children with CHD, the incidence of thrombotic complications was found to be 0.28%. The incidence of thrombosis became 3.62% in children with surgical heart disease. For the children with non-surgical heart disease, the incidence of thrombosis was lower at 0.85% (P<0.001).

The first propensity-matched analysis, using 24,251 children with surgical heart disease match with an equal number of children with non-surgical heart disease, found that the incidence of thrombotic complications was 3.90% in children with surgical heart disease and 2.13% in children with non-surgical heart disease (P<0.001). In the second propensity-matched analysis, children with surgical heart disease were matched with an equal number of children with cancer. The incidence of thrombotic complications was found to be significantly higher in children with surgical heart disease at 3.75% when compared to 1.19% incidence of thrombosis in children with cancer. Non-surgical heart disease patients also had a higher incidence of thrombosis at 2.13% when compared to children with cancer (P<0.001).
Figure 6: Flow chart and description of the propensity-matched analysis. A significant difference is seen between patients with surgical heart disease and those patients with non-surgical heart disease. There is also a significant difference between cancer patients and patients with surgical heart disease.
Among the surgical and non-surgical heart disease populations, demographic characteristics and outcomes were compared between children with and without thrombotic complications.

Table 1: Characteristics of children with surgical and non-surgical heart disease diagnosed with a thrombotic complication

<table>
<thead>
<tr>
<th>Variables</th>
<th>Surgical HD (n=24,251)</th>
<th>Non-Surgical HD (n=24,251)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombotic complications (n=947)</td>
<td>Controls (n=23,304)</td>
</tr>
<tr>
<td>Age group (%)</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 1 month</td>
<td>284 (30)</td>
<td>2,855 (12)</td>
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<td>1-12 months</td>
<td>491 (52)</td>
<td>9,661 (41)</td>
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<td>1-6 years</td>
<td>100 (11)</td>
<td>5,720 (25)</td>
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<td>6-12 years</td>
<td>24 (2)</td>
<td>2,321 (10)</td>
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<td>&gt; 12 years</td>
<td>48 (5)</td>
<td>2,747 (12)</td>
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<td>Female (%)</td>
<td>388 (41)</td>
<td>10,505 (45)</td>
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<tr>
<td>Elective (%)</td>
<td>295 (31)</td>
<td>14,686 (63)</td>
</tr>
<tr>
<td>Cardiac lesions (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVP/RVOTO</td>
<td>534 (56)</td>
<td>8,117 (35)</td>
</tr>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 days</td>
<td>241 (25)</td>
<td>17,851 (77)</td>
</tr>
<tr>
<td>20-50 days</td>
<td>306 (32)</td>
<td>3,740 (16)</td>
</tr>
<tr>
<td>50-100 days</td>
<td>242 (26)</td>
<td>1,210 (5)</td>
</tr>
<tr>
<td>&gt; 100 days</td>
<td>158 (17)</td>
<td>503 (2)</td>
</tr>
<tr>
<td>ECMO (%)</td>
<td>119 (13)</td>
<td>677 (3)</td>
</tr>
<tr>
<td>VAD (%)</td>
<td>13 (1.4)</td>
<td>43 (0.2)</td>
</tr>
<tr>
<td>Elixhauser Score (IQR)</td>
<td>3 (0-5)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>127 (13)</td>
<td>749 (3)</td>
</tr>
</tbody>
</table>

Note. Data are presented as number (%), or median and interquartile range (IQR) when appropriate.
Furthering the comparison, demographic characteristics, co-morbidities, and outcomes in children with non-surgical and surgical heart disease were compared using before and after propensity-match analysis. Seen in Tables 2 and 3 are the results of the multivariate logistic regression analysis.

Table 2: Variables obtained from multivariate logistic regression analysis associated with thrombotic complications in the surgical population

<table>
<thead>
<tr>
<th>Variables</th>
<th>B (SE)</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
<th>ROC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 month</td>
<td>1.43 (0.16)</td>
<td>&lt;.001</td>
<td>4.16</td>
<td>3.01-5.75</td>
<td>0.674</td>
</tr>
<tr>
<td>1-12 months</td>
<td>0.85 (0.16)</td>
<td>&lt;.001</td>
<td>2.35</td>
<td>1.72-3.20</td>
<td></td>
</tr>
<tr>
<td>1-6 years</td>
<td>-0.04 (0.18)</td>
<td>.840</td>
<td>0.96</td>
<td>0.68-1.37</td>
<td></td>
</tr>
<tr>
<td>6-12 years</td>
<td>-0.45 (0.25)</td>
<td>.073</td>
<td>0.63</td>
<td>0.39-1.04</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Type of lesion (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.712</td>
</tr>
<tr>
<td>Septal defects</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td>0.75 (0.09)</td>
<td>&lt;.001</td>
<td>2.12</td>
<td>1.79-2.53</td>
<td></td>
</tr>
<tr>
<td>RVOTO</td>
<td>0.43 (0.09)</td>
<td>&lt;.001</td>
<td>1.54</td>
<td>1.30-1.83</td>
<td></td>
</tr>
<tr>
<td>LVOTO – Ao.</td>
<td>0.08 (0.14)</td>
<td>.550</td>
<td>1.09</td>
<td>0.83-1.43</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (%)</td>
<td>0.22 (0.03)</td>
<td>&lt;.001</td>
<td>1.25</td>
<td>1.17-1.33</td>
<td>0.730</td>
</tr>
<tr>
<td>ECMO (%)</td>
<td>0.47 (0.12)</td>
<td>&lt;.001</td>
<td>1.61</td>
<td>1.27-2.04</td>
<td>0.741</td>
</tr>
<tr>
<td>VAD (%)</td>
<td>1.40 (0.36)</td>
<td>&lt;.001</td>
<td>4.07</td>
<td>2.03-8.17</td>
<td>0.743</td>
</tr>
<tr>
<td>AKI (%)</td>
<td>0.74 (0.10)</td>
<td>&lt;.001</td>
<td>2.10</td>
<td>1.72-2.58</td>
<td>0.756</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>1.34 (0.10)</td>
<td>&lt;.001</td>
<td>3.82</td>
<td>3.16-4.63</td>
<td>0.775</td>
</tr>
</tbody>
</table>

* Cumulative areas under the receiver operative characteristics (ROC) curve are used to assess the accuracy of logistic regression model to predict thrombotic complications.

Note. Data are presented as B, regression coefficient; SE, standard error; OR, odds ratio; 95 CI, 95% confidence interval.
Table 3: Variables obtained from multivariate logistic regression analysis associated with thrombotic complications in the non-surgical population

<table>
<thead>
<tr>
<th>Variables</th>
<th>B (SE)</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
<th>ROC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 month</td>
<td>-0.43 (0.18)</td>
<td>.017</td>
<td>0.65</td>
<td>0.46-0.93</td>
<td>0.525</td>
</tr>
<tr>
<td>1-12 months</td>
<td>-0.28 (0.14)</td>
<td>.047</td>
<td>0.76</td>
<td>0.57-0.99</td>
<td></td>
</tr>
<tr>
<td>1-6 years</td>
<td>-0.22 (0.15)</td>
<td>.151</td>
<td>0.80</td>
<td>0.59-1.08</td>
<td></td>
</tr>
<tr>
<td>6-12 years</td>
<td>-0.42 (0.21)</td>
<td>.043</td>
<td>0.66</td>
<td>0.44-0.99</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Type of lesion (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.631</td>
</tr>
<tr>
<td>Septal defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td>1.23 (0.13)</td>
<td>&lt;.001</td>
<td>3.41</td>
<td>2.65-4.40</td>
<td></td>
</tr>
<tr>
<td>RVOTO</td>
<td>0.51 (0.13)</td>
<td>&lt;.001</td>
<td>1.66</td>
<td>1.28-2.15</td>
<td></td>
</tr>
<tr>
<td>LVOTO – Ao.</td>
<td>0.03 (0.13)</td>
<td>.825</td>
<td>1.03</td>
<td>0.80-1.33</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (%)</td>
<td>0.31 (0.05)</td>
<td>&lt;.001</td>
<td>1.36</td>
<td>1.24-1.50</td>
<td>0.661</td>
</tr>
<tr>
<td>ECMO (%)</td>
<td>1.39 (0.17)</td>
<td>&lt;.001</td>
<td>4.03</td>
<td>2.89-5.62</td>
<td>0.687</td>
</tr>
<tr>
<td>VAD (%)</td>
<td>1.85 (0.56)</td>
<td>.001</td>
<td>6.33</td>
<td>2.11-19.02</td>
<td>0.688</td>
</tr>
<tr>
<td>AKI (%)</td>
<td>0.42 (0.18)</td>
<td>.019</td>
<td>1.52</td>
<td>1.07-2.16</td>
<td>0.690</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>1.06 (0.14)</td>
<td>&lt;.001</td>
<td>2.89</td>
<td>2.20-3.80</td>
<td>0.712</td>
</tr>
</tbody>
</table>

* Cumulative areas under the receiver operative characteristics (ROC) curve are used to assess the accuracy of logistic regression model to predict thrombotic complications.

Note. Data are presented as B, regression coefficient; SE, standard error; OR, odds ratio; 95 CI, 95% confidence interval.
From the multivariate logistic regression analysis of the surgical population, children less than 1 month old and children between 1 month to 1 year had a significant increased risk of thrombotic complications. It is also observed that SVP, RVOTO, and the presence of a coagulopathy were associated with an increased risk of thrombotic complications in both non-surgical and surgical congenital heart disease populations. Furthermore, children supported with ECMO or VAD, and those who developed AKI or sepsis, also had an increased risk of thrombosis in both surgical and non-surgical heart disease populations. In an attempt to better understand why surgical heart disease was significantly higher than the non-surgical heart disease the type of lesions were compared (Figure 7). The correlation between the presence of a thrombotic complications and mortality rate was also compared (Figure 8).

In a graphical representation the incidence of thrombotic complications was significantly higher in children with SVP and RVOTO when compared to those with septal defects and LVOTO (P<0.001) (Figure 7). The presence of thrombotic complications was associated with a significant increase in mortality in both populations (P<0.001) (Figure 8).
Figure 7: Incidence of thrombotic complications in children with surgical and non-surgical heart disease based on the type of lesion. Highest incidence of thrombosis is seen in SVP and RVOTO for both surgical and non-surgical heart disease when compared to septal defects and LVOTO aortic arch repair (Ao).
Figure 8: Mortality in children with surgical or non-surgical heart disease with or without thrombotic complications. The mortality rate is increased in the presence of a thrombotic complication when compared to controls.
DISCUSSION

Upon completion of the retrospective analysis, we observed a high incidence of thrombotic complications in children with CHD. We observed that when compared to children with non-surgical heart disease and children with cancer, those with surgical heart disease had a higher incidence of thrombosis reported. Looking further we also reported that children with SVP and RVOTO had the highest incidence of thrombosis overall. This result is likely because children with SVP remain with a non-physiologic palliative circulation throughout all the palliative surgical stages, and will be implemented with a prosthetic conduit that require adequate anticoagulation in order to avoid any thrombotic event, while children with RVOTO will become non-cyanotic with a congenital heart disease fully repaired to a physiologic circulation after the surgery (American Heart Association, 2015).

This study also found that those children with coagulopathy, children placed on ECMO or VAD, children who developed postoperative complications such as sepsis or AKI, and children who had a prolonged length of stay (LOS>20 days) also had a higher risk of thrombotic complications that lead to a significant increase in mortality rates.

In a study completed by Manlhiot et. al. a retrospective analysis was performed using 1542 children undergoing cardiac surgical procedures with or without cardiopulmonary bypass. The incidence of thrombosis in patients was confirmed by diagnostic imaging. The study concluded that there was an 11%
incidence of thrombosis (Manlhiot et al., 2011). In contrast, we observed a lower incidence of thrombotic complications with surgical heart disease at 3.90%. The difference in the incidence of thrombotic complications can be explained by the fact that we used a database that encoded for thrombotic complications as means for analysis. This means that we cannot account for center variability in systematic surveillance and screening for the incidence of a thrombotic event, and for reporting of sub-clinical thrombosis in our patients.

In an additional study completed by Manlhiot et al., found that oxygen saturation of <85%, previous thrombosis, history of a heart transplant, the use of deep hypothermic circulatory arrest, the presence of a central venous catheter for >5 days, and postoperative use of ECMO and VAD, were significantly associated with a higher risk of thrombosis. Also supporting our findings they reported that a prolonged LOS was an indicator for increased mortality and risk of thrombotic complications. Lastly, the study by Manlhiot et al. also showed that patients with single ventricle physiology had a higher risk of thrombotic complications at an incidence rate of 40% after initial palliative therapy, 28% after the superior cavopulmonary connection, and ultimately 21% after the Fontan procedure (Manlhiot et al., 2012). The results of our study are in concurrence with the study completed by Manlhiot et al. As reported in previous studies, we found that neonates with surgical heart disease had a significantly higher incidence of thrombotic complications.
The multivariate model in our study indicated that children over the age of 12 had an increased risk of thrombotic complications for children with non-surgical heart disease, indicating that age was a predictor for thrombotic complication. We believe that this result could be because the older children admitted to the hospital are likely children with marginal hemodynamic status, sometimes inadequate chronic anticoagulation therapy, and other risk factors for thrombotic complications.

In a longitudinal study performed by Odegard et al. (2009), children with hypoplastic left heart syndrome had a significant decrease in the level of both procoagulant and anticoagulant factors through the completion of the Fontan procedure (Odegard et al., 2009). In a recent study completed by Emani et al. (2013) thrombin generation, plasminogen activator inhibitor, and thrombin activatable fibrinolysis inhibitor, were found to be significantly elevated in SVP patients experiencing postoperative thrombosis (Emani et al., 2013). While there is a consensus that there is a relatively high thrombotic complication rate before and after the Fontan procedure, there is distinct lack of consensus on the thromboprophylactic strategy needed in these cases. Though new research from Tomkiewicz et al. (2014) indicated that a combination of antiplatelet therapy and anticoagulation thromboprophylaxis could be beneficial for patients who have undergone the Fontan patients and are experiencing enhanced platelet activation, endothelial injuries, increased thrombin formation, and impaired fibrinolysis (Tomkiewicz-Pajak et al., 2014).
Another aspect of our study was to compare the incidence of thrombotic complications between children with surgical and non-surgical heart disease with a matched group of children with cancer. Previous studies have shown that those with cancer are known to have a higher incidence of thrombotic complications ranging from 2.1%-16% symptomatic events to 40% for asymptomatic events with varying types of cancer (Piovesan et al., 2014). We found that in our study the incidence of thrombosis observed in the cancer population was not significantly different that of those with congenital heart disease, but when comparing the cancer to patients with surgical heart disease to those with surgical heart disease we found a significant difference.

Limitations

While there were significant findings in our research, our study includes some major limitations. Most hospitals do not systematically screen cardiac patients for thrombosis, which means that the incidences reported is more than likely lower than what it would be if hospitals used a screening process. This limits our ability to assess incidences of thrombotic complications. The national database used to complete the retrospective chart review, HCUP KID, is large and more than likely included missing data, miscoded diagnosis, and miscoded procedures. Many children had overlapping ICD-9-CM codes, which may have made us misclassify some cases as we used the codes to classify patients into different diagnostic groups. The HCUP database is administrative data and only includes clinically detected and
coded thrombotic complications. A study conducted by Wright et. al. (2011), observed that when using an administrative database, like HCUP, that the incidence of thrombosis in the pediatric population was often miscalculated (Wright et. al., 2011).

Using the HCUP KID’s database patient history is only seen as it is reported and a lot of details could have been missing. For example, we were unable to establish causality and any time related relationship between the hospital admission and the thrombotic complications, as we were only able to see the outcomes. In some patients cases we were unable to determine if the patient was admitted with thrombosis or if they developed thrombosis during the course of their hospitalization. This meant that we were unable to assess how treatment of the thrombosis was applied to these patients, when they were diagnosed, how central venous access contributed to the thrombotic complication risk. In other words, we were unable to assess the entirety of the incidence of thrombosis from diagnosis through treatment. For this reason further studies are needed to validate the predictive model found in this study through institutional databases.

Future Directions

As reported by Faraoni et. al. (2015), there is an independent association of increased hospital cost with four categories; hospital bed size, the number of procedures performed, hospital length of stay, and the incidence of major complications (Faraoni et. al., 2015). Our study found that the longer the length of
stay (>20 days) was a predictor for thrombotic complications which would increase hospital costs according to the study by Faraoni et al. Understanding the predictors for thrombotic complications could potentially reduce hospital costs by reducing the incidence rate. The study conducted by Faraoni et al. (2015) also found that children with CHD consume 23% of national hospital resources, but they only account for 4% of hospitalizations (Faraoni et al., 2015). Further studies are needed to better define the optimal prophylactic approach and to better monitor the response to the prophylactic therapies. The next part of the project would to examine at the incidence of thrombosis at a more local level by completing a retrospective chart review of patients at Boston Children’s Hospital. In addition to a retrospective chart review, a prospective analysis of patients’ coagulation factors will be completed to further investigate the theory that coagulation factors may be a predictor for thrombotic complications as indicated in the study completed by Odegard et al. (2009).

Thromboprophylaxis for SVP patients both before and after the Fontan procedure was a top research priority according to a report from the National Heart, Lung and Blood Institute/National Institutes of Health Working Group on Thrombosis in Pediatric Cardiology and Congenital Heart Disease (National Heart, Lung and Blood Institute, 2014). A trial completed by Monagle et al. concluded that there was no advantage to using antiplatelet therapy over anticoagulation therapy or vice versa (Monagle et al., 2011). With this information, the therapies should be tailored to an individuals response as a prophylactic treatment option for those
patients with congenital heart disease and complications with their coagulation factors.

Investigating the impact that congenital heart disease with single ventricle physiology and related incidences of thrombosis has on quality of life is another aspect that will be included in the next part of the project. A study completed by Idorn et. al. found that the quality of life is reduced in Fontan children when comparing them to normal children (Idorn et. al., 2013). This study also found that over the age of 16 the quality of life was only diminished physically where as the younger children experienced diminished quality of life both physically and psychosocially as well. Lastly, this study found that cognitive speed was significantly reduced in patients of all ages (Idorn et. al., 2013). Supporting the finding of Idorn et. al., a study by Uzark et. al. found that children with cardiovascular diseased has a lower perceived quality of life when compared to children who were healthy and those with severe cardiovascular disease have worse physical and psychosocial quality of life (Uzark et. al., 2015).

Conclusions

In conclusion, our study confirmed that children with both surgical and non-surgical heart disease have an increased risk for thrombotic complications when compared to other pediatric populations. The risk for thrombotic complications is significantly increased when a patient has a cyanotic heart disease. The highest risk
for thrombotic complications is seen in patients who have the presence of single ventricle physiology.
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CURRICULUM VITAE

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Current Address: 205 Kent Street, Apt 41 • Brookline, MA, 02446
Permanent Address: 7 Davis Park • Plaistow, NH 03865

EDUCATION
Boston University School of Medicine, Boston, MA
M.S. in Medical Sciences
• Coursework: Human Physiology, Biochemistry and Cell Biology, Histology, Basic Human Anatomy, Pathology

Boston University, Boston, MA
B.A. in Chemistry: Biochemistry
• Coursework: General Chemistry, Organic Chemistry, General Biology, Cell Biology, Instrumentation and Analysis, Molecular Biology, Statistics, Single Variable Calculus, Multivariable Calculus, General Physics, Biochemistry

LABORATORY EXPERIENCE:
• Extensive laboratory experience from laboratory courses taken at Boston University
  o Trained to work with radioactive materials, to use Gaussian View, chromatography, gel electrophoresis, use of several spectroscopy and analytical chemical instrumentation such as HPLC, MALDI-TOF, SPR, and have a beginner understanding of Matlab

CLINICAL
Boston Children’s Hospital, Boston, MA
Pediatric Anesthesia Clinical and Research Internship (PACaRI) May 2015-Present
• Performed cardiac anesthesia research with a Boston Children’s Hospital cardiac anesthesiologist and researcher and also worked as an anesthesia technician.
• Worked as an anesthesia technician which included duties such as, preparing the operating room for the anesthesiologist, making IV's, restocking anesthesia carts, and preparing anesthesia circuits

Brigham and Women’s Hospital, Boston, MA
Brigham and Women’s Medical Career Exploration Program Volunteer Fall 2013-Spring 2016
• Work directly with patients that required assistance navigating the hospital while placed in the Patient Access Services Department
• Work as a transport assistant in the Central Transport Department as an ambassador
• Visit with patients, ask them questions to stimulate their memory, and perform mental stimulation exercises with those that are bed ridden for a long period of time as part of the MOSAICS program.

Children’s Hospital Boston, Boston, MA
Volunteer
• Assisted in helping the staff attend to the children’s needs by creating short term activities to occupy patients and siblings.
• Help to keep areas safe and healthy

EXTRACURRICULAR ACTIVITIES
• Boston University’s Global Day of Service
• Boston Universities Premedical Society
SUMMARY

• Skilled at learning new concepts quickly, working well under pressure, and communicating ideas clearly and effectively.
• Beginner understanding of Spanish as well as an Intermediate understanding of American Sign Language