Association of Preoperative Cell Counts With Outcomes After Operation for Congenital Heart Disease

Shannon M. Jones, MD, Courtney McCracken, PhD, Bahaaldin Alsoufi, MD, William T. Mahle, MD, and Matthew E. Oster, MD, MPH

Division of Cardiology, Children's Healthcare of Atlanta, Atlanta; Department of Pediatrics, Emory University School of Medicine, Atlanta; and Division of Cardiothoracic Surgery, Emory University School of Medicine, Atlanta, Georgia

Background. We examined the association of preoperative cell count abnormalities, which have been shown to be associated with outcomes in adult cardiac patients, with morbidity and mortality after operation for congenital heart disease (CHD) in children.

Methods. We performed a retrospective cohort study on 4,865 children undergoing cardiac operation from 2004 to 2014. Our exposures of interest were presence of preoperative lymphopenia (lymphocyte count ≤ 3,000 cells/μL), thrombocytopenia (platelet count < 150 × 10^3/μL), and neutrophilia (neutrophil count ≥ 7,000 cells/μL). Our outcomes of interest were mortality status, postoperative length of stay (LOS), and occurrence of postoperative complications. We performed logistic and linear regressions to determine the associations of preoperative cell counts with mortality, LOS, and complications, adjusting for age, sex, race or ethnicity, presence of a genetic syndrome, and Society of Thoracic Surgeons and European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality category.

Results. Overall mortality was 2.8%, median LOS was 6 days, and 7.6% of patients had postoperative complications. Lymphopenia was associated with increased odds of postoperative mortality (odds ratio 1.67, 95% confidence interval: 1.15 to 2.43, $p = 0.007$). Lymphopenia, thrombocytopenia, and neutrophilia were all associated with longer postoperative LOS. Lymphopenia and thrombocytopenia were associated with increased occurrence of postoperative sepsis, and neutrophilia was associated with need for postoperative mechanical circulatory support.

Conclusions. In children undergoing CHD operation, preoperative lymphopenia is associated with increased in-hospital mortality postoperatively. Preoperative lymphopenia, neutrophilia, and thrombocytopenia are associated with longer postoperative LOS and with development of postoperative complications. Preoperative cell counts may serve as important prognostic markers in preoperative planning for patients with CHD.

(Ann Thorac Surg 2018;■:■–■)

Although advances in surgical management of congenital heart disease (CHD) have substantially improved overall patient outcomes [1, 2], CHD remains responsible for the largest proportion of infant and childhood mortality secondary to birth defects in the United States [3]. Numerous studies have been undertaken to identify institutional and patient characteristics that affect outcomes after surgical repair or palliation of CHD [1, 4–6]. These studies have shown that younger age and smaller size [7], presence of a genetic syndrome [8], and complexity of surgical repair [1] are all associated with worse outcomes after cardiac operation. Despite these findings, much remains unknown about other factors that affect morbidity and mortality after repair or palliation of CHD.

Cell line abnormalities as predictors of morbidity and mortality have been studied in numerous populations. Thrombocytopenia has been shown to be associated with increased risk of mortality in patients in the pediatric intensive care unit (ICU) [9] and has been associated with increased in-hospital mortality in adult patients after percutaneous coronary intervention [10]. In adult patients, neutrophilia and lymphopenia have been shown to be associated with worse outcomes for patients with acquired heart disease [11–13]. Relative lymphopenia has been shown to be associated with worse outcomes in pediatric and adult patients with heart failure [14, 15]. Thus far, little attention has been given to the predictive value of these preoperative laboratory findings in children undergoing surgical intervention for CHD. The few articles that have been written have reflected small study populations, but they have lent credence to the idea that preoperative cell line derangements may be associated with worse outcomes after pediatric operation [16, 17]. We sought to study the association of preoperative cell line abnormalities, including neutrophilia, thrombocytopenia,

Accepted for publication April 11, 2018.

Presented at the American Academy of Pediatrics National Conference and Exhibition, San Francisco, CA, Oct 21–25, 2016.

Address correspondence to Dr Jones, Children's Healthcare of Atlanta, 1405 Clifton Rd NE, Atlanta, GA 30322; email: joness@kidsheart.com.

Published by Elsevier Inc.

0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2018.04.022

and lymphopenia, with in-hospital mortality, development of postoperative complications, and prolonged postoperative length of stay (LOS) in pediatric patients after surgical intervention for CHD.

Patients and Methods

We performed a retrospective cohort study of pediatric patients (age < 19 years) undergoing cardiothoracic operation for CHD at Children's Healthcare of Atlanta (CHOA) from 2004 to 2014. The study included patient and surgical data from our center's surgical database and laboratory data from our center's electronic medical record. This study was approved by the Institutional Review Board for CHOA.

Variables

Variables of interest included preoperative thrombocytopenia, lymphopenia, and neutrophilia. To be consistent with prior literature, thrombocytopenia was defined as a platelet count less than 150,000 cells/μL [9, 18], and lymphopenia as a lymphocyte count of 3,000 cells/μL or less [16]. No published pediatric studies define a strict cutoff for neutrophilia. We used our laboratory normal values to define neutrophilia as a neutrophil count of 7,000 cells/μL or greater, which was in line with published values in adult literature [13]. Study laboratory data, including total white blood count, percentage of neutrophils, total neutrophil count, percentage of lymphocytes, total lymphocyte count, and platelet count, was obtained from our center's electronic medical record and was limited to the most recent laboratory data within 5 days before operation. All laboratory testing was done at CHOA. Confounding variables were chosen a priori to be consistent with prior literature and included age, sex, type of operation, Society of Thoracic Surgeons (STS) and European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality (STAT) category [19], presence of a genetic syndrome or chromosomal anomaly, and self-reported race or ethnicity. Occurrence of postoperative complications was obtained from the STS database and included postoperative cardiac arrest, wound infection (including deep and superficial wound infection and mediastinitis), sepsis, need for postoperative mechanical circulatory support, and need for prolonged postoperative respiratory support (defined as >7 days). A patient was deemed to have had a postoperative complication if it occurred within the postsurgical hospitalization, or within 30 days postoperatively. For study subjects who underwent more than one surgical intervention during the study period, all data collected, including laboratory data, occurrence of complications, and demographic data, were limited to the first surgical encounter during the study period. Individuals were excluded from the study if their surgical procedure did not have a STAT category or if they did not have preoperative laboratory data available for analysis. The primary outcome measures were survival to hospital discharge and postoperative LOS (in days). Secondary outcome measure was the development of postoperative complications.

Statistical Analysis

Descriptive statistics were calculated for all variables of interest and included means and standard deviations, medians and ranges, or counts and percentages, as appropriate. Generalized linear models (GLMs) were used to assess the association between preoperative laboratory measurements with the outcomes of postoperative mortality, LOS, and postoperative complications. In the GLM variables, LOS was modeled by using a normal distribution with the identity link, and mortality was modeled by using a binomial distribution with a logit link. Because of the right-skewed distribution for LOS, data were log-transformed before analysis. Resulting model-based estimates were back-transformed by exponentiation, and estimates are presented on the original scale (days) with associated 95% confidence intervals (CIs). In addition, the ratio of mean LOS was calculated for each preoperative laboratory measurement and can be interpreted as the percentage of increase in LOS associated with a specific level of cellular dysfunction. Risk associated with postoperative mortality or postoperative complications are expressed as odds ratios (ORs) with associated 95% CIs. For the outcomes, adjusted estimates for the three preoperative cell count variables were generated after controlling for the following variables: age, sex, race, STAT category, and presence of a genetic syndrome. Statistical significance was assessed at the 0.05 level, and analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 4,865 patients met inclusion criteria and were included in statistical analysis. Median patient age at time of operation was 5.3 months. Males accounted for 53.6% of the study population; 47.5% of the study population self-identified as white, non-Hispanic. The majority of patients (81.6%) did not have a genetic syndrome or chromosomal abnormality. Of the study population, 40.6% underwent STAT category 1 surgical intervention. Demographic data are summarized in Table 1. Incidence of preoperative lymphopenia, thrombocytopenia, and neutrophilia among various demographic groups is summarized in Figure 1.

During the study period there were 137 in-hospital deaths (2.8%). Median postoperative LOS was 6 days (range: 1 to 284 days). At least one postoperative complication occurred in 371 patients (7.6%). On unadjusted analysis, all three cell line abnormalities were associated with both increased odds of in-hospital mortality and with longer postoperative LOS. After controlling for confounders, lymphopenia alone was associated with increased odds of postoperative mortality with an OR of 1.67 (95% CI: 1.15 to 2.43, $p = 0.007$) (Table 2). Adjusted analysis for predictors of postoperative LOS revealed that lymphopenia, thrombocytopenia, and neutrophilia were all associated with longer postoperative