The Aristotle Score Predicts Mortality After Surgery of Patent Ductus Arteriosus in Preterm Infants

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Background. Outcomes after surgical ligation of patent ductus arteriosus (PDA) in preterm infants are often complicated by prematurity associated comorbidities. The Aristotle comprehensive complexity score (ACCS) has been proposed as a useful tool for complexity adjustment in the analysis of outcome after congenital heart surgery. The aims of this study were to define preoperative risk factors for mortality and to demonstrate the usefulness of ACCS to predict mortality after surgical ligation of PDA in the preterm.

Methods. Included were 49 preterm babies (≤35 weeks of gestation) who had surgical ligation of PDA between May 2009 and July 2012. Median gestational age was 27.6 weeks (range, 23 to 35 weeks) and median birth weight was 1,040 g (range, 520 to 2,280 g). Median age at operation was 15 days (range, 4 to 44 days) and median weight was 1,120 g (range, 400 to 2,880 g). Initial oral ibuprofen was ineffective in 24 patients and contraindicated in 25. All surgical ligations were done at bedside in the neonatal intensive care unit. Preoperative clinical and laboratory profiles were reviewed and ACCS was derived.

Results. Eight of 49 patients (16.3%) died at a median of 14 days (range, 2 to 73 days) after PDA ligation. Patients who had contraindications for oral ibuprofen (odds ratio [OR] 8.94; \( p = 0.049 \)), coagulopathy (OR 12.13; \( p = 0.025 \)), renal dysfunction (OR 28.88; \( p = 0.003 \)), intraventricular hemorrhage greater than grade II or seizure (OR 34.00; \( p = 0.002 \)), and ACCS points (OR 29.594; \( p < 0.05 \)) were significantly associated with an increased risk for mortality. Among the risk factors, ACCS showed the largest area under curve (0.991) by receiver-operating characteristic curve analysis. Optimal cutoff value of ACCS for mortality were 15 or greater, with sensitivity of 87.5%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 97.6%.

Conclusions. The ACCS, especially for procedure-independent complexity factors, is a useful tool to predict mortality after ligation of PDA in preterm infants.
define preoperative risk factors for mortality and to
demonstrate the usefulness of ACCS to predict mortality
after surgical ligation of PDA in preterm infants.

Patients and Methods
Preterm infants with a gestational age of 35 weeks or less
who had surgical PDA ligations from May 2009 to July 2012
at the Seoul St. Mary’s Hospital were enrolled retro-
spectively in this study. The Institutional Review Board
of Seoul St. Mary’s Hospital approved this study. Surgical
ligation was done in preterm infants with a hemody-
namically significant ductus arteriosus (HSDA) who had
failed to respond to medical therapy (one or two cycles of
oral ibuprofen) or had contraindications to COX inhibitor.
Excluded are patients with either intracardiac anomalies
or chromosomal abnormalities. The PDA was screened in
all preterm infants within 4 days of life and confirmed by
two-dimensional and color Doppler echocardiography.
By definition, HSDA in this study was a PDA that meets
at least moderate stage (stage 3 or greater) clinical and
echocardiographic criteria as proposed by NcNamara and
colleagues [9]. Echocardiographic criteria for HSDA
included transductal diameter greater than 1.5 mm with
a continuous left-to-right shunt; unrestrictive pulsatile
transductal flow; more than mild to moderate left-side
heart volume loading (eg, left atrium to aortic diameter
ratio greater than 1.5); more than mild to moderate left-
side heart pressure loading; and decreased or absent
diastolic flow in the superior mesenteric artery, middle
cerebral artery, or renal artery [9]. Medical failure was
defined as a persistent HSDA with a ductal size greater
than 1.5 mm after two courses of oral ibuprofen or any
cases in which oral ibuprofen was unable to be used
after the first course owing to acute renal failure or to
positive disseminated intravascular coagulation labora-
tory findings.

Surgical PDA ligation was done at the bedside in the
neonatal intensive care unit by one designated surgeon.
After left posterolateral thoracotomy, the highest inter-
costal vein was divided and the mediastinal pleura was
opened from the subclavian artery to the middle
descending aorta. For left lung retraction, instead of using
a lung retractor, several sutures on mediastinal pleura
were applied and pulled to minimize a lung injury (Fig 1).
The left recurrent laryngeal nerve was identified and
protected by keeping it medially, and after minimal
dissection above and below the aortic ends of the ductus,
one medium or large clip was applied to obliterate the
PDA. The chest wall was closed gently to avoid rib cage
deformity after surgery. No patient had a chest tube in
situ after surgery.

For risk analysis of mortality, preoperative demo-
graphic, laboratory, and clinical variables including
gestational age, sex, and birth weight, preoperative and
postoperative systemic blood pressure, duration of
mechanical ventilator support, echocardiographic data
such as PDA diameter and left atrium to aorta diameter
ratio, use of COX inhibitor, and the presence of coagul-
opathy, intraventricular hemorrhage, seizure, and renal
dysfunction were analyzed. In addition, ACCS was
computed for each patient at the time of PDA diagnosis
and PDA ligation [8]. The published Aristotle method-
ology was modified in this study by not limiting (or
capping) the contribution of “procedure-independent
factors” to only 5 points when the actual sum of all factors
was more than 5. Coagulopathy was defined according to
the corrected age of each infant [10]. Intracranial
hemorrhage variable was substituted by intraventricular
hemorrhage, as all subjects were premature infants.

All of the statistical analyses were performed with
SPSS, version 15.0 (SPSS-PC, Chicago, IL), and SAS,
version 9.2 (SAS Institute, Cary, NC). Continuous vari-
ables were reported as median (range) or mean (standard

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**Figure 1.** Method to expose patent ductus arteriosus using several sutures on mediastinal pleura. (Prolene; Ethicon, a subsidiary of Johnson & Johnson, Somerville, NJ.)
deviation) as appropriate. Categorical variables were presented as number (percentage). A paired samples t test, Wilcoxon signed rank test, and McNemar test were used to compare demographic and hemodynamic variables before and after ligation, as appropriate. We used the univariate logistic analysis to detect the risk factors of in-hospital mortality and the results were presented as odds ratio and 95% confidence interval. A penalized likelihood estimation was used to resolve the semi-complete separation problem for ACCS. To compare the diagnostic abilities among risk factors, we provided area under the curve and 95% confidence interval using receiver-operating characteristics curve analysis. Finally, we obtained the optimal cutoff for ACCS and its sensitivity, specificity, positive predictive value, and negative predictive value. Statistical significance was taken as \( p < 0.05 \).

**Results**

A total of 49 preterm infants who had surgical ligation of PDA during this study period were enrolled in this study. Patient characteristics are summarized in Table 1. The median age at PDA ligation was 15 days (range, 4 to 44 days) and median body weight was 1,120 g (range, 400 g to 2,880 g). Initial medical therapy with oral ibuprofen failed in 24 patients, whereas primary surgical ligation was done in 25 patients owing to contraindications for COX inhibitors such as acute renal failure or to disseminated intravascular coagulation laboratory profile. Preoperative mechanical ventilator support was required in 39 patients (79.6%).

The mean operation time was 65 ± 15.6 minutes (range, 40 to 110 min). Systemic diastolic blood pressure increased significantly just after PDA ligation, from 30.3 ± 8.95 mm Hg to 38.5 ± 10.98 mm Hg \( (p < 0.001) \). There was no case of pneumothorax, hemothorax, infection, or recurrent laryngeal nerve injury after surgery. In 1 patient, a chylothorax developed 3 days after surgery and was managed with supportive care.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (Range) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>27.6 (23–35)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1.040 (520–2.280)</td>
</tr>
<tr>
<td>Male</td>
<td>21 (42.9%)</td>
</tr>
<tr>
<td>Age at PDA ligation, days</td>
<td>15 (4–44)</td>
</tr>
<tr>
<td>Weight at PDA ligation, g</td>
<td>1.120 (400–2.880)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Preoperative mechanical ventilation</td>
<td>39 (79.6)</td>
</tr>
<tr>
<td>Use of COX inhibitor</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>22 (44.9)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>IVH more than grade II or seizure</td>
<td>14 (28.6)</td>
</tr>
</tbody>
</table>

COX = cyclooxygenase; IVH = intraventricular hemorrhage; PDA = patent duc tus arteriosus.

The mean ACCS at the time of PDA ligation was 11.8 ± 2.26 (range, 9 to 16). Among procedure-independent factors except for prematurity factor (all were prematurity), mechanical ventilation to treat cardiorespiratory failure was the most common factor (39 of 49, 79.6%), followed by coagulation disorder (22 of 49, 44.9%), renal dysfunction (15 of 49, 30.6%), IVH greater than grade II or seizure (14 of 49, 28.6%), NEC (2 of 49, 4.1%), Hirshsprung’s disease (2 of 49, 4.1%), and septicemia (1 of 49, 2.0%; Fig 2).

There were 8 of 49 in-hospital deaths (16.3%), which occurred at a median of 14 days (range, 2 to 73 days) after PDA ligation. Low birth weight, low gestational age, contraindications for COX inhibitor, and lower increase in systemic blood pressure were associated with mortality. In addition, procedure-independent factors in ACCS including coagulopathy, renal dysfunction, IVH more than grade II or seizure, and ACCS points (odds ratio 29.594; \( p = 0.029 \)) were significantly associated with an increased risk for mortality at a univariate analysis (Table 2). Among the risk factors, ACCS showed the largest area under curve (0.991) by receiver-operating characteristic curve analysis (Table 3). Optimal cutoff value of ACCS for mortality was greater than or equal to 15 with sensitivity of 87.5%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 97.6% (Fig 3). All 7 patients whose ACCS was 15 or more died, whereas 41 of 42 (98%) with ACCS less than 15 survived to discharge (Fig 4). Echocardiographic PDA diameter and left atrium to aortic diameter ratio were not associated with mortality.

**Comment**

In this study, we report that in-hospital mortality after surgical ligation of PDA in the preterm infants was related to procedure-independent systemic factors associated with prematurity. In addition, an ACCS of 15 or more was an independent risk factor of mortality. The ACCS, especially procedure-independent complexity factors, is a useful tool to predict mortality after ligation of PDA in the preterm.

The role of surgical ligation of PDA in the preterm still remains controversial. Although surgical ligation can definitely close PDA immediately, it is associated with its own set of morbidities: lung injury, pneumothorax, hemothorax, infection, or recurrent laryngeal nerve injury after surgery. In addition, recent observational studies indicated an increased risk of outcomes associated with PDA ligation: chronic lung disease, retinopathy of prematurity, and neurodevelopmental impairment [11–13]. These adverse effects of surgical ligation may be associated with several factors including unfavorable perioperative general conditions such as renal impairment, IVH, or coagulopathy that preclude the use of COX inhibitor; direct mechanical injuries to the immature lungs that impedes improvement of pulmonary mechanics and lung growth after surgery; and waiting-time or delay in...
surgical intervention that could make clinical condition worse and affect clinical outcomes.

To improve benefits and to minimize adverse effects of surgical ligation, it is important to refine target population, to perform timed surgical ligation if indicated, and to use gentle and modified surgical techniques to minimize lung injury. At our center, we adopted the HSDA criteria based on the clinical and echocardiographic staging system proposed by McNamara and Hellman and considered medical or surgical treatment for patients who meet at least moderate stage (stage 3 or greater) [9].

A PDA size of more than 1.5 mm has been considered to be significant on the basis that, at this cutoff, systemic end-organ hypoperfusion develops [14, 15]. However, to understand hemodynamic impact of a PDA resulting from a large magnitude of left to right shunt (not only the size of PDA, but also systemic effects such as end-organ hypoperfusion), various echocardiographic variables should be assessed including Doppler patterns of the PDA, renal artery, mesenteric artery, and cerebral artery, and the size of left ventricle and left atrium to assess volume or pressure overload [9].

In addition, clinical factors such as patient size, gestational age, and clinical symptoms should be taken into account to maximize surgical benefit [9, 16]. Regarding surgical timing, we consider timed surgical intervention without delay if medical treatment (oral ibuprofen) fails or COX inhibitors are contraindicated.

Because of low compliance and high friability of the lungs in the preterm, a subtle mechanical injury or

Table 2. Risk Factors of In-Hospital Mortality After Patent Ductus Arteriosus Ligation in the Preterm Infants, Univariate Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, days</td>
<td>0.945 (0.894–0.998)</td>
<td>0.043</td>
</tr>
<tr>
<td>Birth weight, 100 g</td>
<td>0.560 (0.347–0.903)</td>
<td>0.018</td>
</tr>
<tr>
<td>BP increase after PDA ligation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>0.894 (0.809–0.987)</td>
<td>0.026</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>0.897 (0.807–0.997)</td>
<td>0.043</td>
</tr>
<tr>
<td>Preoperative MV support, days</td>
<td>1.091 (1.011–1.179)</td>
<td>0.026</td>
</tr>
<tr>
<td>Contraindication for COX inhibitor</td>
<td>8.94 (1.007–79.457)</td>
<td>0.049</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>12.13 (1.359–108.364)</td>
<td>0.025</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>28.88 (3.095–269.373)</td>
<td>0.003</td>
</tr>
<tr>
<td>IVH more than grade II or seizure</td>
<td>34.00 (3.592–321.831)</td>
<td>0.002</td>
</tr>
<tr>
<td>ACCS,a points</td>
<td>29.594 (1.409–621.635)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a Penalized likelihood estimation [21].

ACCS = Aristotle comprehensive complexity score; BP = blood pressure; CI = confidence interval; COX = cyclooxygenase; IVH = intraventricular hemorrhage; MV = mechanical ventilation; PDA = patent ductus arteriosus.
compression during operation may cause hemodynamic instability and postoperative complications such as hemothorax, pneumothorax, and atelectasis, which are associated with long-term adverse outcomes. To minimize these complications during operation, instead of using a lung retractor, we applied several sutures on mediastinal pleura and pulled them to expose the PDA. Using this method in this series of patients, we did not experience any procedure-related complications. However, despite every effort to minimize postoperative morbidity and mortality, significant in-hospital mortality (16.3%) was recorded in our patients, and was mostly associated with prematurity-related comorbidities. Gestational age has been a major risk factor for outcomes, but it is reasonable to analyze other factors related to prematurity for stratifying patients at risk systemically [7, 17, 18].

The ACCS has been proposed for complexity adjustment in the analysis of outcome after congenital heart surgery and considered to be a useful tool to evaluate outcomes [8, 19, 20]. The score is the sum of basic complexity score (procedure-adjusted complexity) and the comprehensive complexity score (patient-adjusted complexity) and takes into account comorbidities and procedure-specific and anatomic variability. The patient-adjusted complexity score consists of procedure-dependent factors and procedure-independent factors. For PDA, the basic score is 3 points and the procedure-dependent factor is 0 points, which were the same for all patients in this study. Conversely, procedure-independent factors such as mechanical ventilation, coagulation disorder, renal dysfunction, IVH or seizure, NEC, Hirshsprung’s disease, and septicemia accounted for a high proportion of the score and recorded 6 to 13

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**Table 3. Area Under The Receiver-Operating Characteristic (ROC) Curves for Each Risk Factor**

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC</th>
<th>SE</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, days</td>
<td>0.762</td>
<td>0.080</td>
<td>0.619–0.872</td>
<td>0.0011</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>0.829</td>
<td>0.066</td>
<td>0.695–0.921</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BP increase after PDA ligation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>0.739</td>
<td>0.089</td>
<td>0.592–0.855</td>
<td>0.0075</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>0.700</td>
<td>0.096</td>
<td>0.551–0.824</td>
<td>0.0376</td>
</tr>
<tr>
<td>Preoperative MV support, days</td>
<td>0.758</td>
<td>0.105</td>
<td>0.614–0.868</td>
<td>0.0139</td>
</tr>
<tr>
<td>Contraindication for COX inhibitor</td>
<td>0.718</td>
<td>0.089</td>
<td>0.571–0.837</td>
<td>0.0139</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>0.755</td>
<td>0.105</td>
<td>0.611–0.866</td>
<td>0.0155</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0.840</td>
<td>0.091</td>
<td>0.707–0.929</td>
<td>0.0002</td>
</tr>
<tr>
<td>IVH more than grade II or seizure</td>
<td>0.852</td>
<td>0.088</td>
<td>0.722–0.937</td>
<td>0.0001</td>
</tr>
<tr>
<td>ACCS, points</td>
<td>0.991</td>
<td>0.024</td>
<td>0.910–0.992</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ACCS = Aristotle comprehensive complexity score;  AUC = area under curve;  BP = blood pressure;  CI = confidence interval;  COX = cyclooxygenase;  IVH = intraventricular hemorrhage;  MV = mechanical ventilation;  PDA = patent ductus arteriosus;  SE = standard error.

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**Fig 3. Area under receiver-operating characteristic curve (AUC) for Aristotle comprehensive complexity score (ACCS). Optimal cutoff is 15 or greater, with sensitivity 87.5%, specificity 100%, positive predictive value 100%, and negative predictive value 97.6%. (CI = confidence interval.)**

**Fig 4. The Aristotle comprehensive complexity scores for each patient. The black stars (★) indicate in-hospital deaths.**
points (ACCS 9 to 16 points) in this series. Because the minimal value of the procedure-independent factors was 6, the published Aristotle methodology was modified in this study by not limiting (or capping) the contribution of procedure-independent factors to only 5 points.

In our cohort, low birth weight, low gestational age, contraindications for COX inhibitor, lower increase in systemic blood pressure after ligation, and procedure-independent factors were significantly associated with an increased risk for mortality. Moreover, ACCS point was the most significant risk factor with the highest specificity and sensitivity to predict mortality after PDA ligation. When considering surgical management of PDA in the preterm infant, these findings should be taken into account in clinical decision making. Individualized meticulous risk-benefit assessment of surgical or conservative management of PDA and careful family counseling should be done.

In conclusion, the outcome measure after surgical ligation of PDA in preterm infants is often complicated by prematurity-associated comorbidities. To improve outcomes, it is important to refine target population, to perform timed surgical ligation, and to use gentle surgical technique. The ACCS, especially procedure-independent factors, appears to be a useful tool to predict outcome and to stratify patients at risk preoperatively.

References