Prognostic value of longitudinal vasoreactivity in pediatric pulmonary hypertension

Patrick D. Evers¹ | Patrick Quinn¹ | Paul J. Critser² | Benjamin S. Frank³ | Mohammad Alnoor¹ | Laurie B. Armsby¹

¹Division of Pediatric Cardiology, Oregon Health and Sciences University, Portland, Oregon, USA
²Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA
³Department of Pediatrics, University of Colorado, Denver, Colorado, USA

Correspondence
Patrick D. Evers, Division of Pediatric Cardiology, Oregon Health and Sciences University, 707 SW Gaines St. CDRC-P, Portland, OR 97239, USA.
Email: eversp@ohsu.edu

Abstract
Upon diagnosis of pulmonary hypertension in pediatrics, standard practice often involves acute vasoreactivity testing (AVT) in the cardiac catheterization laboratory. However, the importance of repeated AVT testing in a given patient thereafter remains unclear. This study sought to describe serial AVT results in pediatric patients and understand the prognostic significance of longitudinal AVT results in pediatric pulmonary hypertension. A retrospective chart review was performed for pediatric pulmonary hypertension patients diagnosed between 2008 and 2021. Patients were included if they had two or more catheterizations with AVT. The study cohorts were patients who were AVT negative upon initial catheterization then AVT positive at any subsequent catheterization (AVT−/+), compared to those who were AVT negative upon initial and all subsequent catheterizations (AVT−/−). A positive AVT was defined by Sitbon criteria. The analyzed outcome was event-free survival. The relationship between study cohorts and event-free survival was analyzed by log-rank Kaplan–Meier survival as well as Cox proportional hazard regression to control for confounders. There were 35 patients who met inclusion criteria in this time period. Patients who were AVT(−/+), had statistically significantly better event-free survival than AVT(−/−) (p = 0.002). In univariate and multivariate Cox regressions, a subsequent AVT positive result amongst those who were initially AVT negative was a positive prognostic factor, hazard ratio 0.03 (95% confidence interval: 0.02–0.35). For patients with negative AVT upon initial cardiac catheterization, this data supports that continuing AVT should be performed as any subsequent AVT positive result may indicate improved expectations for event-free survival.

KEYWORDS
hemodynamics, hypertension, pediatrics, pulmonary
INTRODUCTION

Pulmonary hypertension (PHTN) in pediatrics implicates a diverse array of pathogenesis with natural history expectations that are similarly diverse. The majority of cases in pediatrics are caused by World Health Organization (WHO) Group I idiopathic/heritable pulmonary arterial hypertension (IPAH/HPAH), WHO Group I congenital heart disease associated pulmonary artery hypertension (CHD-PAH), or WHO Group III PHTN related to hypoxemia or developmental lung diseases. Before the initiation of pulmonary vasodilator therapy, current American and European guidelines for the care of children with PHTN recommend acute vasodilator testing (AVT) whereby one administers pulmonary vasodilators in the cardiac catheterization laboratory and observes for a significant improvement in hemodynamic metrics of disease severity. While the definitions used for AVT responsiveness vary, multi-institutional data of pediatric patients with WHO Group I and III disease illustrates high covariance between results regardless of the definition (Sitbon, Barst, or Modified Barst) and that there is approximately a 5%-36% AVT response rate, depending on the cohort examined and the definition for AVT responsiveness used. Acute vasoreactivity testing has several purposes: determining the appropriateness of calcium-channel blocker (CCB) therapy, prognostic clarity in PHTN, precardiac transplantation assessment, and judging the operability of closing an intracardiac shunt. Regarding the prognostic value of AVT results from initial catheterization, research findings are conflicting and uncertainty remains. The multinational TOPP registry of pediatric pulmonary arterial hypertension patients illustrated that Sitbon responders have statistically significantly improved transplant-free survival compared to Barst responders or nonresponders. In addition, a large meta-analysis of pediatric PHTN patients illustrated AVT responsiveness (various definitions) engendered a protective effect with improved transplant-free survival at a hazard ratio of 0.27 (95% confidence interval [CI]: 0.14–0.54). Acute vasoreactivity testing was further incorporated into a pediatric WHO Group I risk-prediction tool that performs well at predicting 1-year transplant-free survival. While historically emphasized in older WHO Group I patients, this prognostic value extends into infants: a single-center study of premature infants with bronchopulmonary dysplasia and WHO Group III related PHTN, Frank et al. established that patients with a positive AVT response on an initial catheterization had a decreased risk of death or tracheostomy. On the other hand, a recent multi-institutional retrospective analysis failed to show prognostic value of initial AVT results in a diverse cohort of pediatric PHTN patients. Furthermore, the performance of pediatric PHTN cardiac catheterization with AVT implicates significant cost, risk, and prolongation of procedural time which must be weighed accordingly.

To date, this body of literature describes a patient’s AVT identity in static terms: a patient is or is not responsive. Yet, despite the recommendations that AVT be performed serially, the longitudinal natural history of AVT response in pediatric PHTN has not been illustrated at a patient-by-patient level, nor has the clinical relevance of any AVT change been quantified. In an adult WHO Group I observational cohort (n = 174) published as an abstract in 2016, Sweatt et al. illustrated that it was the longitudinal maintenance of AVT positivity that portended improved survival, not the initial AVT result. The absence of additional exploratory analyses on this topic may be due to lack of routine repeat AVT at many centers if the result is not felt to inform prognosis or a management change, such as if patient is on a CCB and show signs of waning CCB response. The lack of data relating longitudinal hemodynamic parameters and outcomes in children has recently been highlighted. At Oregon Health and Sciences University, AVT is performed in a standard manner as a part of initial and subsequent PHTN assessments, regardless of the WHO Group or therapeutic approach. This provides a unique examination of AVT results at an individual level longitudinally across WHO classifications. Similarly, this data set affords the opportunity to understand the prognostic value of a positive AVT response at a subsequent catheterization amongst a cohort who had an initial negative AVT response, an aspect of pediatric PHTN care that has not been characterized. We hypothesized that a subset of children will illustrate a conversion from a negative to a positive AVT result and those who do so would demonstrate a more favorable clinical course than those who never illustrated a positive AVT response.

METHODS

Study population

A retrospective chart review was performed of all pediatric PHTN patients cared for at Oregon Health and Sciences University between 2008 and 2021. The patient’s medical records were reviewed for demographic data, PHTN etiology, medication administration, catheterization hemodynamic data, and outcome data. Inclusion criteria were pediatric patients less than 18 years of age with invasive hemodynamic data meeting criteria for PHTN characterized by a mean pulmonary artery pressure (mPAP)
≥20 mmHg. Patients were excluded from analysis if catheterization data was available for less than two catheterizations with AVT phases included, they were on an inhaled pulmonary vasodilator at baseline (inhaled nitric oxide or fractional oxygen content >50%), or their initial hemodynamic catheterization was not available.

**Catheterization elements**

Institutional practice involved AVT testing in all PHTN catheterizations, regardless of the presence or absence of a CCB in the medication regimen. There were three phases of hemodynamic assessment: baseline phase, an oxygen phase in which 100% inspired fraction of oxygen was used, and a phase in which 40 ppm of nitric oxide was administered in addition to oxygen. For the purposes of this analysis, this final nitric oxide phase was defined as the AVT phase. Hemodynamic data extracted from each catheterization and phase included respiratory or inotropic support, systemic pressures, mPAP, indexed pulmonary vascular resistance (PVR), indexed systemic vascular resistance (SVR), indexed pulmonary blood flow (Qp), indexed systemic blood flow (Qs), and oxygen consumption assumption. Cardiac output calculations were uniformly based on Fick method with measured PO2 incorporated when appropriate. The oxygen consumption assumption was made by the interventional cardiologist at the time of the catheterization based on the patient’s age, heart rate, and body surface area. Hemodynamic catheterizations were performed under conscious-sedation with the subject free-breathing except when a patient age, development or any anticipated procedural risk demanded general anesthesia with assisted ventilation or airway support.

For patients without a systemic-to-pulmonary shunt, the Sitbon criteria was used to define AVT responsiveness per recent consensus guidelines and was defined as a decrease in mPAP by ≥10 mmHg to a mPAP value ≤40 mmHg while maintaining a normal cardiac output (or no fall in cardiac output if cardiac output was pathologically low during baseline conditions) during the AVT phase. For patients with a systemic-to-pulmonary shunt diagnosed as having CHD-APA, a positive AVT was defined as a resultant decrease of at least 20% in PVR and PVR/SVR ratio during the AVT phase with final values of <6 IWU PVR and <0.3 PVR/SVR ratio.

The primary outcome of interest was event-free-survival using a composite adverse outcome metric constituted by the following hard-outcomes: death, atrial septostomy, unplanned pulmonary hypertension-related hospitalization, or lung transplantation. For patients in which more than one hard-outcome occurred, the chronologically first event was used for time-to-event analysis.

**Statistical analysis**

The date of diagnosis was defined as the first cardiac catheterization meeting requirement for PHTN. Subjects were divided into three subgroups: AVT(+), AVT(−/+), and AVT(−/−). These groups were patients who were Sitbon positive on their initial presentation catheterization, those who were not Sitbon positive on their initial catheterization but were positive on any of the subsequent catheterizations, and patients who were at no point Sitbon positive, respectively. Demographic, hemodynamic, therapeutic, and outcome data were tabulated for each cohort. Continuous data was described as medians and interquartile ranges. Categorical variables were described as counts and percentages of each cohort. Continuous variables were tested for normality of distribution by the Kolmogorov–Smirnov test. These cohort characteristics were compared using Student t-test for parametric continuous variables, Mann–Whitney test for nonparametric continuous variables, and Chi-squared test for categorical variables. An alpha value of 0.05 was used to define statistical significance. A Kaplan–Meier analysis was performed to compare freedom from composite adverse outcomes of these three cohorts with a log-rank (Mantel-Cox) test comparing survival distributions of the populations.

Given that the focus of this manuscript was to understand the implication of subsequent Sitbon positivity, patients who were AVT positive upon initial catheterization were thereafter excluded and the remaining analyses pertained to only those subjects who were Sitbon negative on their initial catheterization: AVT(−/+)) and AVT(−/−)). A Kaplan–Meier analysis was performed and log-rank analysis was used to compare freedom from composite adverse outcomes between AVT(−/+)) and AVT(−/−)) patients. A Cox proportional hazard regression was used to control for the impact of initial hemodynamic characteristics and therapeutic strategy to better isolate the influence of Sitbon positivity subsequent to the initial catheterization upon the dependent variable being the occurrence of a composite adverse outcome. Regressors that were significant to a p < 0.05 in a univariate regression were included in a multivariate regression. Since patients with severe disease are likely to receive more catheterizations and as CCB are known to be effective in primarily those patients who are AVT positive, the a priori decision was made to adjust the multivariate regression by the mPAP upon initial catheterization and the utilization of a CCB at any time in the clinical course, regardless of these regressors statistical significance at the univariate level. A sensitivity analysis was
performed whereby this multivariate regression was repeated with cardiac index, PVR and right atrial pressure included as alternative metrics to control for disease severity. Given the unique impact that AVT results have on clinical decision making in CHD-APAH patients, such as shunt closure, a sensitivity analysis was performed wherein CHD-APAH patients were excluded and the aforementioned analysis was repeated. For these analysis, SPSS 25 by IBM (Armonk) was used.

RESULTS

Between 2008 and 2021, there were 77 unique new-diagnosis pediatric PHTN patients undergoing cardiac catheterization at Oregon Health and Sciences University in Portland, Oregon. Applying the exclusion criteria, 32 subjects were excluded due to absence of two or more catheterizations with an AVT phase, followed by six subjects excluded due to incomplete catheterization data available, followed by an additional four subjects excluded due to presence of pulmonary vasodilators in the baseline phase. This left 35 patients who met criteria to constitute the final study cohort (Table 1). The median age at PHTN diagnosis was 1.7 years with a range between 0.0 and 14.8 years. The cohort contained 18 (51%) females. The NICE Classifications of the cohort included 23 (66%) WHO Group I and 12 (34%) WHO Group III. Of those with WHO Group I disease, 16 were IPAH/HPAH and seven were CHD-APAH. There was a mean of 3.6 catheterizations performed per patient, of which 1.1 were Sitbon positive, although not to a statistically significant degree (Figure 3). This analysis was repeated among only AVT(−/−) and AVT(−/+). This Kaplan–Meier analysis performed on the cohort of interest (those who were Sitbon negative on initial catheterization) illustrated that AVT(−/−) patients had statistically significant superior event-free-survival than those that were AVT(−/+). (Figure 4, log-rank p = 0.002). Similarly, the unadjusted univariate Cox proportional hazard regression (Table 2) illustrated that amongst those who were Sitbon negative at the first catheterization, the occurrence of any subsequent AVT positivity conferred a protective advantage with a hazard ratio (HR) of 0.07 (95% CI: 0.01–0.59). In an adjusted multivariate Cox regression analysis controlling for the baseline mPAP as a proxy variable for disease severity and the influence of a calcium channel blocker, the statistical significance of subsequent Sitbon positivity was maintained, HR of 0.03 (95% CI: 0.02–0.35). This multivariate regression finding remained similar with only the CCB and AVT positive test meeting criteria for statistical significance regardless of the hemodynamic metric for disease severity included in the regression. Last, this Cox proportional hazard regression in those who were AVT negative on initial catheterization was repeated, excluding those with congenital heart disease. Results from this repeated hazard regression were similar, indicated that a subsequent AVT positive catheterization illustrated a HR 0.08 (95% CI: 0.01–0.63) at the univariate analysis and a HR 0.03 (95% CI: 0.01–0.34) in the multivariate regression.
In the care of pediatric patients with PHTN, cardiac catheterization for invasive hemodynamic assessment remains a key diagnostic element, informing an understanding of pathophysiology, disease severity, and treatment approaches. As a part of these catheterizations, AVT at disease diagnosis plays a role in determining the appropriateness of CCB therapy, guides correction of a congenital heart malformation, as well as improves prognostic understanding for the providers and families. However, for patients who are AVT positive on their

### TABLE 1 Description of study cohort demographic, hemodynamic, and clinical characteristics

| Patient characteristics (% or IQR) | Total cohort (n = 35) | Analysis cohort (n = 28) | AVT (+/-) | AVT (−/-) | p |
|-----------------------------------|----------------------|--------------------------|-----------|-----------|---|
| **Female**                        | 18 (51%)             | 5 (50%)                  | 10 (56%)  | 3.3 (5)   | - |
| **Age at PH diagnosis (years)**   | 4.5 (9)              | 5.4 (10)                 | 7 (70%)   | 17 (94%)  | - |
| **Race and ethnicity**            |                      |                          |           |           |   |
| Asian                             | 2 (6%)               | 1 (10%)                  | 0 (0%)    | -         | - |
| White (Hispanic or Latino)        | 5 (14%)              | 2 (20%)                  | 1 (6%)    | -         | - |
| White (non-Hispanic or Latino)    | 28 (80%)             | 7 (70%)                  | 17 (94%)  | -         | - |
| **Etiology**                      |                      |                          |           |           |   |
| WHO I CHD-APAH                    | 7 (20%)              | 1 (10%)                  | 3 (17%)   | -         | - |
| WHO I IPAH/HPAH                   | 16 (46%)             | 5 (50%)                  | 9 (50%)   | -         | - |
| WHO Group III                     | 12 (34%)             | 4 (40%)                  | 6 (33%)   | -         | - |
| **Catheterizations (IQR)**        |                      |                          |           |           |   |
| Total catheterizations            | 3 (3)                | 3 (3)                    | 3 (2)     | -         | - |
| Second catheterization interval (years) | 0.5 (0.7) | 0.5 (1.0) | 0.5 (0.4) | -         | - |
| AVT+ catheterizations             | 1 (1)                | 1 (1)                    | 0 (0)     | 0.002     | - |
| Baseline phase mRAP (mmHg)        | 7.0 (3.0)            | 7.0 (3.0)                | 7 (3.0)   | -         | - |
| Baseline phase mPAP (mmHg)        | 50.0 (24.0)          | 36.5 (39.0)              | 53.0 (22.8)| -        | - |
| Baseline phase CI (L/min/m²)      | 3.6 (1.5)            | 3.8 (1.1)                | 3.9 (1.7) | -         | - |
| Baseline phase PVR (iWU)          | 8.2 (10.3)           | 4.8 (10.6)               | 8.1 (9.2) | -         | - |
| **Treatment (%)**                 |                      |                          |           |           |   |
| Calcium-channel blocker           | 8 (23%)              | 3 (30%)                  | 3 (17%)   | -         | - |
| Mono therapy                      | 11 (31%)             | 3 (30%)                  | 6 (33%)   | -         | - |
| Dual therapy                      | 11 (31%)             | 3 (30%)                  | 5 (28%)   | -         | - |
| Triple therapy                    | 13 (37%)             | 4 (40%)                  | 7 (39%)   | -         | - |
| **Adverse outcome (%)**           |                      |                          |           |           |   |
| Composite adverse outcome         | 13 (37%)             | 1 (10%)                  | 11 (61%)  | 0.009     |   |
| Atrial septostomy                 | 2 (6%)               | (0%)                     | 2 (11%)   | -         | - |
| Lung transplantation              | 1 (3%)               | (0%)                     | 1 (6%)    | -         | - |
| Unplanned PH-related hospitalization | 5 (14%)            | 1 (10%)                  | 3 (17%)   | -         | - |
| Death                             | 5 (14%)              | (0%)                     | 5 (28%)   | -         | - |

**Note:** Significance value displayed only for p < 0.05.

Abbreviations: AVT, acute vasoreactivity testing positive; CHD-APAH, congenital heart disease associated pulmonary arterial hypertension; CI, cardiac index; IPAH/HPAH, idiopathic or heritable pulmonary arterial hypertension; IQR, interquartile range; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PH, pulmonary hypertension; PVR, indexed pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization.
initial catheterization, there is little data describing the longitudinal consistency of these findings for a given patient. Furthermore, for patients who are AVT negative on their initial catheterization, there is little understanding as to the utility of continued vasoreactivity testing in subsequent catheterizations. In this study, we provide the first descriptive insight into longitudinal AVT results for pediatric PHTN patients. Contrary to common parlance in which patient’s AVT results are described in static terms, we find that many individual’s AVT results are dynamic, intermittently Sitbon positive or negative. Second, while prior literature focuses on the prognostic value of AVT result on initial catheterization, our study indicates that even for patients who are Sitbon negative upon their initial catheterization, any subsequent AVT where Sitbon positivity can be illustrated engenders a positive prognosis, even when controlling for initial disease severity and the utilization of CCB therapy.

While serial catheterizations are often performed to assess disease severity and inform treatment approach, the results described point to the continued relevance of vasoreactivity testing in patients during these catheterizations to inform prognosis. Importantly, in this cohort, the prognostic value of the AVT result cannot be substituted by baseline hemodynamics alone; Figure 2 illustrates that the AVT(−/+ and AVT(−/−) cohorts did not have divergent baseline hemodynamic features. As such, the pathophysiologic basis for AVT results implicating prognosis warrants description. Pulmonary hypertension has long been known to be a spectrum of disease, at its mildest involving reversible vasoconstriction and endothelial dysfunction and at its most severe implicating fixed resistance through neointimal proliferation, plexus formation, and adventitial fibrosis. Pulmonary vasodilator testing may therefore identify patients with less severe disease driven primarily by vasoconstriction and less so by a fixed obstruction. Supporting this, AVT positive patients have been illustrated to have higher cardiac index values and lower PVR than AVT negative patients and children generally have higher rates of AVT positivity than adults. With this paradigm, one may suspect that this study’s findings that an absence of a positive AVT response on any catheterization identifies patients with more aggressive vascular disease or disease refractory to therapy due to genetic or environmental influences. However, the significantly dynamic individual AVT results described herein (Figure 1) and the similarities between the two cohort’s disease-severity metrics and therapeutic approaches (Table 1) points to influences on AVT results beyond

![Figure 1](image-url)
**FIGURE 2**  Box and whiskers plot for baseline hemodynamics up to 1 year following discharge, 5 years following discharge and 10 years following discharge. Groups compared are those who at any catheterization subsequent to the first were AVT positive (AVT\(-/+)\) compared to those who never illustrated AVT positivity (AVT\(-/-\)).

**FIGURE 3**  Kaplan–Meier of freedom from composite adverse outcomes based on acute vasoreactivity testing (AVT) results at initial diagnostic catheterization. Log-rank = 0.149
simply disease severity which warrant future exploration in larger cohort studies.

The results of vasodilator testing may have been in the causal pathway to event-free survival outside the reasons theorized above in those patients with congenital heart disease associated pulmonary arterial hypertension. Specifically, given that both the American\(^2\) and European guidelines\(^3\) include AVT results as a criterion for operability of congenital heart lesions, one may suspect that this clinical decision may influence the results of the analysis above. Given these authors’ uncertainty in this historic cohort regarding the clinical decision-making surrounding AVT results in the setting of CHD-APAH for a given patient, a sensitivity analysis

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**Table 2**

| Variables                  | Unadjusted univariate | Adjusted multivariate (covariates: CCB) | Adjusted multivariate (covariates: mPAP, CCB) |
|----------------------------|-----------------------|----------------------------------------|---------------------------------------------|
|                            | HR (95% CI)           | HR (95% CI)                            | HR (95% CI)                                 |
| Baseline phase mRAP (mmHg) | ns                    | 0.98 (0.95–1.01)                       | 0.005 (0.02–0.35)                            |
| Baseline phase mPAP (mmHg) | ns                    |                                        |                                            |
| Baseline phase CI (L/min/m\(^2\)) | ns          |                                        |                                            |
| Baseline phase PVR (iWU)   | ns                    |                                        |                                            |
| WHO I CHD-APAH             | ns                    |                                        |                                            |
| WHO I IPAH/HPAH            | ns                    |                                        |                                            |
| WHO III                    | ns                    |                                        |                                            |
| AVT(−/+                    | 0.07 (0.01–0.59)      | 0.05 (0.01–0.49)                       | 0.03 (0.02–0.35)                            |
| Calcium-channel blocker    | ns                    | 3.84 (1.07–13.83)                      | 1.24 (1.24–18.87)                           |
| Mono therapy               | ns                    |                                        |                                            |
| Dual therapy               | ns                    |                                        |                                            |
| Triple therapy             | ns                    |                                        |                                            |

Note: Univariate significance value displayed only for \(p < 0.05\), bold font. Independent variables binary unless otherwise specified.

Abbreviations: AVT(−/+), acute vasoreactivity testing positive on any catheterization subsequent to the first; CHD-APAH, congenital heart disease associated pulmonary arterial hypertension; CCB, calcium-channel blocker; CI, cardiac index; CI, confidence interval; HR, hazard ratio; IPAH/HPAH, idiopathic or heritable pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; WHO, World Health Organization.
was performed in which the Cox proportional hazard analysis above was repeated, but with the four WHO Group I CHD-APAH patients excluded. Including only WHO I IPAH/HPAH and WHO Group III patients who were Sitbon negative on their first catheterization, a subsequent Sitbon positive result continued to have statistically significant explanatory power over event-free survival.

Limitations of this analysis include the fact that the cohort was constituted by only patients with serial clinically indicated catheterizations, this enriched the cohort for more severe disease. This may explain why few variables quantifying disease-severity in Table 2 met criteria for statistical significance: smaller hemodynamic differences between individuals with or without the outcome of interest. In addition, the retrospective nature of the analysis allows for heterogeneity in the manner in which patients were treated, allowing for omitted variable bias. However, Table 1 illustrates that the pharmacologic treatments are not skewed across the study cohorts.

CONCLUSION

This retrospective analysis of WHO Group I and Group III pediatric PHTN patients adds both descriptive and prognostic understanding to the field. This analysis indicates that AVT results are dynamic for a significant portion of patients and the illustration of AVT positivity, whether that be upon the initial catheterization or any subsequent catheterization, portends a favorable prognosis. This finding supports a role for serial vasoreactivity testing in the pediatric PHTN population.

AUTHOR CONTRIBUTIONS

Patrick D. Evers: conceptualized and designed the study, assisted in data acquisition, performed the data analysis, interpreted the analysis, and drafted portions of the initial manuscript. Patrick Quinn: conceptualized and designed the study, assisted in data acquisition, and drafted portions of the initial manuscript. Paul J. Critser and Benjamin S. Frank: conceptualized and designed the study, interpreted the analysis and drafted portions of the initial manuscript. Mohammad Alnoor and Laurie B. Armsby: assisted in data acquisition and drafted portions of the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

This retrospective analysis was approved by the institutional review board of Oregon Health and Sciences University. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ORCID

Patrick D. Evers http://orcid.org/0000-0002-9299-1926

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