Early View

Original article

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A Novel Approach to Perioperative Risk Assessment for Patients with Pulmonary Hypertension

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Take-home message:

For patients with pulmonary hypertension undergoing non-cardiac surgery, perioperative risk can be estimated using a model that combines inherent procedural risk with composite PAH risk assessment scores.

Abstract

Rationale: Pulmonary hypertension (PH) is associated with significant perioperative morbidity and mortality. We hypothesized that pulmonary arterial hypertension (PAH) composite risk assessment scores could estimate perioperative risk for PH patients when adjusted for inherent procedural risk.

Methods: We identified patients in the Johns Hopkins PH Center Registry that had non-cardiac surgery (including endoscopies) between September 2015 and January 2020. We collected information on preoperative patient-level and procedural variables and used logistic regression to evaluate associations with a composite outcome of death within 30 days or serious post-operative complication. We generated composite patient-level risk assessment scores for each subject and used logistic regression to estimate the association with adverse surgical outcomes. We adjusted multivariable models for inherent procedural risk of major cardiovascular events, and used these models to generate a numerical PH perioperative risk (PHPR) score.

Results: Among 150 subjects, 19 (12.7%) reached the primary outcome including seven deaths (4.7%). Individual patient-level and procedural variables were associated with the primary outcome (all *P*<0.05). A composite patient-level risk assessment score built on three non-invasive parameters was strongly associated with reduced risk for poor outcomes (OR=0.4, *P*=0.03). This association was strengthened after adjusting the model for procedural risk. A PHPR score derived from the multivariable model stratified patients into low (0%), intermediate (≤10%), or high (>10%) risk of reaching the primary outcome.

Conclusion: Composite PAH risk assessment scores can predict perioperative risk for PH patients after accounting for inherent procedural risk. Validation of the PHPR score in a multi-center, prospective cohort is warranted.

Introduction

Perioperative risk assessment presents a formidable challenge for providers managing patients with pulmonary hypertension (PH). Multiple studies have demonstrated increased risk of mortality and serious morbidity among PH patients undergoing non-cardiac surgery [1-6], and some have identified PH as an independent risk for perioperative complications and death [6-8]. This clinical challenge becomes increasingly relevant for patients with pulmonary arterial hypertension (PAH) as advances in medical therapy expand the population of patients requiring invasive procedures [9]. Current PH guidelines [10, 11] provide limited guidance for assessing perioperative risk. Better risk assessment tools may assist providers and patients in complex perioperative decision-making.

Previous studies have identified preoperative variables associated with poor surgical outcomes for patients with PH [1, 3, 5, 8]. The clinical utility of these associations has been limited, as they have been inconsistent among studies with differing patient populations, surgical procedures, and small samples sizes. In parallel, there is a growing effort to address longitudinal clinical risk assessment for PAH patients, unrelated to surgery. Several approaches have been used to combine multiple clinical variables into composite risk assessment scores [11-16]. These scoring systems have been validated in predicting clinical [12-14, 17, 18] and patient-centered [19] outcomes in diverse PAH groups. We hypothesized that composite risk assessment scores could estimate perioperative risk for PH patients when adjusted for procedural risk. Moreover, we present "proof-of-concept" data that this approach can be used to develop a clinically pragmatic perioperative risk assessment tool.

Methods

Study Population and Data Extraction: We included participants in the Johns Hopkins Pulmonary Hypertension Center Registry (IRB# NA_00027124), which enrolls consecutive patients from all World Symposium on Pulmonary Hypertension (WSPH) groups [20]. From September 2015 to January 2020, we identified upcoming surgical procedures among Registry participants during weekly meetings, including all non-cardiac surgical procedures (excluding lung transplantation) requiring at least moderate sedation. Some patients had multiple procedures during the study period; only the last procedure was analyzed.

Preoperative Patient-level Risk Variables of Interest: Individual patient-level risk variables were selected *a priori* from previous studies evaluating operative risk in PH [1-4, 7, 8] and studies evaluating predictors of overall survival in PAH [11, 13-16, 21, 22]. These included American Society of Anesthesiologists' (ASA) classification, World Health Organization functional class (WHO FC), serum brain natriuretic peptide (BNP) or N-terminal pro-hormone BNP (NT-proBNP) level, six-minute walking distance (6-MWD), echocardiographic parameters (right atrial and ventricular dilation, tricuspid annular plane systolic excursion (TAPSE), maximum Doppler tricuspid regurgitant velocity), and right heart catheterization parameters (right atrial pressure (RAP), cardiac index (CI), mixed venous oxygen saturation (SvO_2)). We used multiple approaches to generate composite risk assessment scores [12-14] from patient-level risk variables as defined in current PAH guidelines [11]. In one approach ("low-risk focused"), we quantified the number of "low-risk" features present among three non-invasive parameters (WHO FC I or II, 6-MWD>440 m, BNP<50 ng/L or NT-proBNP<300 ng/L) or a combination of four invasive and non-invasive parameters (WHO FC I or II, 6-MWD>440 m, RAP<8 mmHg, CI≥2.5 L/min/m^2) to generate composite scores [14]. In another approach ("score and average"), we assigned a

value of 1 (low-risk), 2 (intermediate-risk), or 3 (high-risk) for each of six clinical parameters (**Supplemental Table 1**), then averaged the values to generate a composite score [13]. In all cases, we used the closest measurement before the surgical procedure for analyses or composite risk assessment score calculation.

Procedural Risk Variables of Interest: We identified procedural risk variables of interest using American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines [23] and previous studies [3, 4, 7, 8, 24]. These included inherent risk of major cardiovascular events ("elevated" or ≥1% risk *vs.* "low" or <1% risk), emergency procedure (patient requires access to the operating room within 24 hours of the decision to operate [25]), length of procedure (>3 hours), and location of patient immediately prior to procedure (inpatient *vs.* outpatient).

Outcome of Interest: The primary outcome was the composite of death within 30 days or serious post-operative complication. Serious post-operative complications required intensive care unit (ICU) admission and included any of the following: 1) hemodynamic instability requiring inotropes and/or vasopressors; 2) respiratory failure requiring invasive mechanical ventilation ≥48 hours; 3) initiation of inhaled pulmonary vasodilators; 4) acute coronary syndrome; 5) cerebrovascular accident; 6) arrhythmia; 7) renal failure (serum creatinine >2 mg/dl for patients with normal preoperative levels, or a 50% increase in serum creatinine, or initiation of dialysis); 8) hepatic injury (elevation of aspartate aminotransferase and/or alanine aminotransferase by 50% or more); and 9) sepsis [1-3, 8, 26]. Secondary outcomes included post-operative hospital length of stay (LOS), ICU LOS, and hospital readmission for a medical deterioration within 30 days of the procedure.

Statistical Analysis: For descriptive analyses, we used the independent t-test for normally distributed continuous variables, the Wilcoxon rank-sum test for skewed continuous variables, and the chi-square test for categorical variables. We used univariable logistic regression to evaluate associations between

preoperative variables and the primary outcome. For secondary outcomes, we used linear regression to estimate associations between preoperative variables and hospital or ICU length of stay and logistic regression to estimate the association with readmission within 30 days.

We used logistic regression to estimate associations between composite risk assessment scores ("low-risk focused" and "score and average") and the primary outcome. We used multivariable regression to account for differences in procedural risk based on inherent risk of major cardiovascular events (elevated *vs.* low) [23]. We selected this variable to capture procedural risk because it had the strongest association with the primary outcome, potentially incorporates the other procedural risk variables, and is known to the perioperative physician prior to surgery. We generated receiver-operating characteristics (ROC) curves to quantify the discriminatory power of multivariable models, and used the DeLong test to compare the area under ROC curves. In all analyses, we considered a *P*-value (two-tailed) less than 0.05 to represent statistical significance. We used Stata version 15 (College Station, TX) for all analyses.

Risk Assessment Tool Development: We used the multivariable model including the three-parameter non-invasive "low-risk focused" score to develop a risk assessment tool (PH Perioperative Risk or PHPR Score) that can be calculated before surgery. We used this model to develop the PHPR Score because of its superior performance characteristics and because additional invasive procedures are not required. The PHPR Score (range=0-7) is calculated by adding a patient-level component and a procedural component. The patient-level component is the number of features in the composite score that do not reach "low-risk" thresholds (0-3). The procedural component is binary. "Low" risk procedures are assigned a value of 0 (no added risk). "Elevated" risk procedures are assigned a value of 4, derived from the ratio of odds ratios for "elevated" procedural risk and number of composite score features that do not reach "low-risk" thresholds in the multivariable regression model ($e^{2.7}/e^{1.3} = e^{1.4} = 4$). For example, a patient with WHO FC II symptoms, NT-proBNP = 600 ng/L, and 6-MWD = 250 m undergoing an

endoscopy ("low" risk) would have a PHPR Score of [2 + 0] = 2, while the same patient undergoing a total knee replacement ("elevated" risk) would have a PHPR Score of [2 + 4] = 6. We used the distribution of PHPR scores to assign three risk categories (0-2 = low, 3 = intermediate, 4-7 = high). Thresholds were intentionally set to include all patients having an "elevated" procedural risk procedure in the highest category.

Results

Study Population, Surgical Procedures, and Preoperative Evaluation: During the study period, we prospectively identified 150 subjects undergoing non-cardiac surgery (**Table 1**). The cohort was predominantly female (76%) with an average age of 59.7 years. Approximately half (52%) had PAH, and 47.4% of these had connective tissue disease-associated PAH (**Supplemental Table 2**). Most subjects were receiving PAH-specific therapy at the time of surgery (72%), and nearly all were deemed ASA classification of 3 or higher.

Most procedures (82%) were performed at the Johns Hopkins Hospital, and 73.3% were classified as "low" risk using ACC/AHA guidelines [23]. Of 110 procedures classified as "low" risk, 54 (49%) were endoscopies, primarily of the gastrointestinal tract (**Supplemental Table 3**). Endoscopic procedures are routinely staffed by Cardiac Anesthesiology providers for PH patients at our institution [27]. Forty procedures (26.7%) classified as "elevated" risk included primarily intraperitoneal, orthopedic, or intrathoracic surgeries. Six percent of all procedures were emergency procedures, 32% were performed during inpatient hospitalization, and 28% lasted longer than 3 hours.

Outpatient clinical assessment by a PH specialist (67.3%) or anesthesiologist (21.3%) was completed within 90 days of surgery for most patients. Among procedures performed at the Johns Hopkins Hospital, 75.6% were referred to the Cardiac Anesthesiology liaison for case review. Most patients had WHO FC assessment (63%), natriuretic peptide (NT-proBNP or BNP) measurement (55%),

and echocardiography (53%) within 3 months before surgery, while fewer had 6-MWD testing (23%) or right heart catheterization (21%) in this interval **(Fig. 1)**. Average values for the closest measurement before surgery are shown in **Supplemental Table 4**.

Surgical Outcomes: The primary outcome was observed in 19 patients (12.7%; **Table 2**), including seven deaths (4.7%). Median time from surgery until death was 13 days (IQR 5-23 days), with causes listed in **Supplemental Table 5**. Seventeen patients (11.3%) developed serious post-operative complications. Among these, hemodynamic instability and respiratory failure were most common. Median hospital length of stay was 1 day (IQR 0-6 days). Of the 37 patients (24.7%) admitted to the ICU after surgery, 20 were planned (enhanced monitoring) and 17 were unplanned. Intensive care unit LOS was longer for unplanned admissions (median 4 *vs.* 1 day; *P*<0.001, **Supplemental Fig. 1)**. Nineteen patients (12.7%) were readmitted to the hospital within 30 days of surgery for clinical deterioration (**Supplemental Table 6**).

Associations Between Individual Risk Variables and Surgical Outcomes: Associations between individual preoperative variables and the primary outcome are shown in **Table 3**. Among patient-level variables, we observed no associations between patient age, sex, presence of systemic sclerosis, WSPH Group, or use of PAH-specific therapy and the primary outcome. Patients with the highest ASA classification (4 or 5) had increased risk compared to those with ASA classification 2 or 3. We did not find associations between preoperative evaluation by a PH specialist, anesthesiologist, or case review by the Cardiac Anesthesiology liaison and the primary outcome. WHO functional class was associated with the primary outcome; subjects with WHO FC 3 or 4 limitations had greater risk than those with WHO FC 1 or 2 limitations (OR 5.87; *P*=0.02). Natriuretic peptide levels were also associated with the primary outcome; subjects with NT-proBNP>1400 ng/L (or BNP>300 ng/L) had higher odds of adverse events compared to those with NT-proBNP<300 ng/L (or BNP<50 ng/L) (OR 7.08; *P*=0.01). We did not find associations between RA dilation, TAPSE, or pericardial effusion and the primary outcome. However,

severe RV dilation (OR 6.27; *P*=0.01) and maximum Doppler TR velocity (OR 1.5 for every increase of 0.5 m/sec; *P*=0.02) were associated with increased risk. We found no associations between 6-MWD or invasive hemodynamic measurements and the primary outcome.

All procedural variables examined were associated with the primary outcome. The strongest association was observed with procedures designated as "elevated" risk for major cardiovascular events, with an odds ratio of 8.35 (*P*<0.001) compared to "low" risk procedures. Emergency procedures, those lasting >3 hours, and procedures performed on inpatients were also associated with increased odds of the primary outcome (**Table 3**).

Associations Between Composite PAH Risk Assessment Scores and Surgical Outcomes: We used three approaches to generate composite PAH risk assessment scores, then used univariable logistic regression to estimate associations with the primary outcome. Only the three-parameter non-invasive "low-risk focused" score was significantly associated with the primary outcome (OR 0.4, *P*=0.03) (**Table 4**). When the models were adjusted for procedural risk, all three composite PAH risk assessment scores were significantly associated with the primary outcome. In multivariable models, the strongest association was with the three-parameter non-invasive "low-risk focused" score where each additional "low-risk" feature was associated with a 70% reduction in the estimated odds of an adverse surgical outcome (*P*=0.01). We generated ROC curves to assess the discriminatory power of the multivariable models. Each had robust discriminatory power for the primary outcome, with a c-statistic at or above 0.8 (**Supplemental Fig. 2**). However, when these multivariable ROC curves were compared to ROC curves for their component patient-level and procedural risk scores, only the three-parameter non-invasive "low-risk focused"-based multivariable model had better discrimination than both univariable models (**Fig. 2** and **Supplemental Fig. 3**). Finally, we used regression analyses to evaluate associations between the composite PAH risk assessment scores and secondary outcomes (**Table 5**). In univariable analyses, all approaches were associated with 30-day hospital readmission and none were associated with ICU LOS.

The three-parameter non-invasive "low-risk focused" and "score and average" methods were also associated with hospital LOS in univariable models. After adjustment for procedural risk, all three composite PAH risk assessment scores were significantly associated with hospital LOS and odds of hospital readmission, while no score was associated with ICU LOS.

Development of a Perioperative PH Risk Assessment Tool: We used the three-parameter non-invasive "low-risk focused" multivariable model to develop a risk assessment tool (PHPR), as outlined in the methods. We used the distribution of patients to stratify PHPR scores into discrete categories that assign low (0%), intermediate (≤10%), or high (>10%) perioperative risk (**Fig. 3a)**. As anticipated, the percentage of subjects reaching the primary outcome increased steadily across PHPR categories (P<0.001). ROC curve analysis showed that the discriminatory power of the PHPR categories approximated that of the original multivariable model (**Fig. 3b**). As an exploratory analysis, we used ROC curves to compare the performance of the PHPR categories among patients with PAH (WSPH Group I) and those without PAH (WSPH Group II-V). We did not observe a difference in the discriminatory power of the PHPR score categories between the groups (P=0.96; **Fig. 3c**).

Discussion

We describe a novel approach to perioperative risk assessment for PH patients undergoing non-cardiac surgery. We showed that a multivariable model combining patient-level risk (composite PAH risk assessment scores) and procedural risk strongly predicts adverse surgical outcomes with improved discriminatory power compared to either approach alone. Importantly, all data required to evaluate risk is routinely collected in clinical practice, does not require additional invasive assessment, and is known to the provider before the procedure. We also provide "proof of principle" that the model can be converted to a clinically pragmatic risk score that may be useful for patients with all forms of PH.

Several studies have described associations between individual patient-level variables and perioperative risk, but findings have been heterogeneous across studies and difficult to operationalize clinically. In a retrospective study of 145 PH patients (excluding those with left heart disease) undergoing non-cardiac procedures under general anesthesia, Ramakrishna *et al.* showed that advanced WHO FC, RV hypertrophy, elevated RV systolic pressure relative to systemic systolic blood pressure and a history of pulmonary embolism were associated with perioperative morbidity and mortality [1]. In another retrospective study of 196 PH patients (also excluding those with left heart disease) undergoing non-cardiac procedures, Deljou *et al.* showed that WHO FC and natriuretic peptide level are associated with postoperative complications [5]. A prospective multicenter study conducted on 114 patients with PAH undergoing non-cardiac non-obstetric surgeries identified elevated RAP and low 6-MWD (<399 m) as patient-level factors associated with adverse perioperative outcome [3]. In a retrospective analysis of 173 patients undergoing right heart catheterization and non-cardiac surgery (96 with PH), mean pulmonary artery pressure, ASA classification, and chronic renal insufficiency were identified as independent risk factors for post-operative morbidity [8]. We confirmed some of these relationships in our cohort (ASA classification, WHO FC, natriuretic peptide), but did not observe statistically significant associations for others. We also identified novel associations with two echocardiographic parameters (severe RV dilation, maximum Doppler tricuspid regurgitant velocity). This variability likely reflects the small sample sizes and limited statistical power for all of these studies, an inherent limitation to analyses of subjects with a rare disease who are often advised to avoid surgery [10, 11].

To address these limitations, we hypothesized that a composite "score" of variables routinely obtained in clinical practice would capture patient-level risk. Initially developed to assess prognosis in PAH patients [12-16], this approach combines clinical, functional, exercise, RV function and hemodynamic parameters to stratify patients into low-, intermediate- and high-risk for one-year mortality. Several scoring methods have been validated in estimating 1-year survival at the time of

diagnosis [13], after treatment for 1 year [12, 14], and in several PAH sub-groups [17, 18]. More recently, these composite scores have been associated with health-related quality of life and rate of hospitalizations in PAH patients [19]. Our findings now extend this approach to perioperative risk assessment. In this domain, we found the strongest associations with the three-component non-invasive "low-risk focused" composite risk assessment score. However, we may have lacked sufficient power for statistical significance in univariable models with the other approaches, as there appeared to be meaningful trends in associations with the primary outcome and all approaches showed concordant associations with secondary outcomes. It is also possible that the three-component non-invasive model had superior performance in our analysis because the other approaches include invasive hemodynamic parameters, which were often obtained more than 1 year prior to surgery in our cohort (not reflective of perioperative clinical status). We believe this reflects clinical practice, as there are currently no strong recommendations for pre-operative hemodynamic testing in patients with PAH.

Procedural factors intuitively inform perioperative risk, and procedural variables previously associated with adverse surgical outcomes among PH patients include inherent risk of major adverse cardiovascular event [1, 2, 5], emergency surgery [2-4, 7], and procedures lasting longer than 3 hours [2, 24]. We confirmed these relationships in our cohort, with the inherent procedural risk (elevated *vs.* low) having the strongest association with the primary outcome. Since this variable potentially incorporates other procedural risk factors (e.g., procedure length) and is known to the perioperative physician before the procedure, we elected to use it to adjust for procedural risk in multivariable models. This adjustment improved the discriminatory power of all three composite PAH risk assessment scores, but was significantly better than procedural risk alone at predicting adverse outcomes only when combined with the three-component non-invasive "low-risk focused" score. Although we lacked sufficient statistical power to determine whether procedural risk is an effect modifier or a confounder of the patient-level

risk, we note that 4 of the 7 deaths in our cohort occurred among patients with low procedural risk and high patient-level risk.

Clinically pragmatic risk assessment tools should aid providers in perioperative decision making. We used the three-parameter non-invasive "low-risk focused" multivariable model to develop PHPR scores and stratify patients into risk categories (low, intermediate, high). This approach requires only clinical data routinely collected at regular intervals [11] and knowledge of the type of upcoming surgery. It avoids the need for repeat invasive hemodynamic assessment, which could delay surgery or generate additional risk. Furthermore, previous analyses have suggested that the non-invasive "low-risk focused" approach may be more accurate than the "score and average" approach for identifying patients with the lowest risk (highest long-term survival) [28]. As devised, we believe the PHPR Score is most useful in identifying patients at the lowest perioperative risk that may be able to avoid additional workup or substantial adjustments to the perioperative plan. Because category thresholds intentionally restrict "elevated" risk procedures to the "high" PHPR category, the PHPR Score incorporates patient-level risk to stratify patients undergoing "low" risk procedures as low or intermediate risk. Notably, a low PHPR score differentiated the 0% of patients who reached the primary outcome from the 10% of patients with an intermediate PHPR Score who reached the primary outcome. Future studies in additional cohorts will be useful for further calibration of the PHPR Score, potentially allowing additional discrimination between intermediate and high-risk patients.

Limitations: The cohort is limited to a single PH referral center and included mostly low-risk procedures, which may limit generalizability. Other factors that may limit generalizability include the enrichment of our cohort with connective tissue disease-associated PH patients and routine incorporation of Cardiac Anesthesiology in perioperative management. However, our observed rates of perioperative mortality and morbidity (4.7% and 11.3%) are consistent with previous reports (mortality

1-9.7% [1-8]; morbidity 6.1-42% [1, 3, 5]). The small sample size limited some analyses (as outlined above), but is also consistent with prior studies [1-3, 5, 7, 8]. There was heterogeneity among subjects in the time between some pre-operative patient-level variables and surgery, which could lead to ascertainment bias. This heterogeneity reflects the observational nature of our study and highlights a key knowledge gap in the field, namely the lack of evidence-based recommendations for specific preoperative testing protocols. Future prospective trials could evaluate the predictive power of a defined preoperative testing regimen (e.g., WHO FC, 6-MWD, and NT-proBNP within 3 months of surgery). We were unable to assess the relationship between the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) 2.0 risk score, another composite PAH risk assessment tool [15, 16], and perioperative outcomes given the limited number of patients having sufficient information to calculate REVEAL 2.0 scores. Finally, we recognize that the PHPR Score will require additional prospective validation, but present it here as "proof-of-principle" that a clinically pragmatic scoring system can be used to inform perioperative risk.

Conclusion: For PH patients undergoing non-cardiac surgery, a composite PAH risk assessment score can be combined with procedural risk to improve perioperative risk assessment. When converted to a PHPR Score, this approach provides a simple and clinically pragmatic tool for perioperative risk assessment for patients with PH.

Conflicts of interest: None

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Figure 1
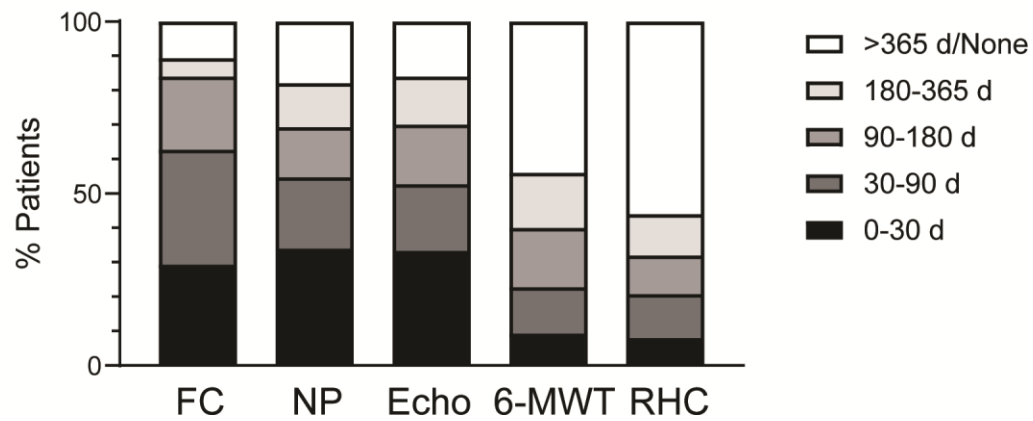
Figure 1. Percentage of patients having preoperative assessments during specified time intervals before surgery. d=days; FC=World Health Organization Functional Class; NP=Natriuretic Peptide; Echo=Echocardiography; 6-MWT=6-Minute Walk Test; RHC=Right Heart Catheterization

Figure 2
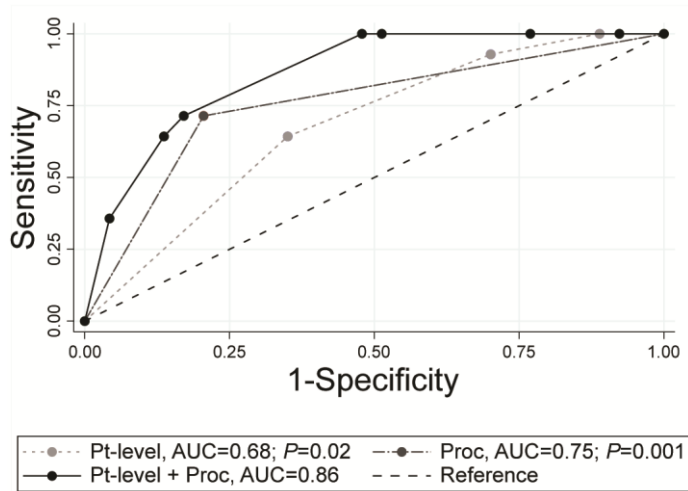
Figure 2. ROC curves for logistic regression models including only patient-level risk (Pt-level), only procedural risk (Proc), or both patient-level and procedural risk (Pt-level + Proc). The area under the curve (AUC) for each model is shown in the legend. *P*-values are for DeLong test comparing ROC curves for each univariable model with the multivariable model.

Figure 3
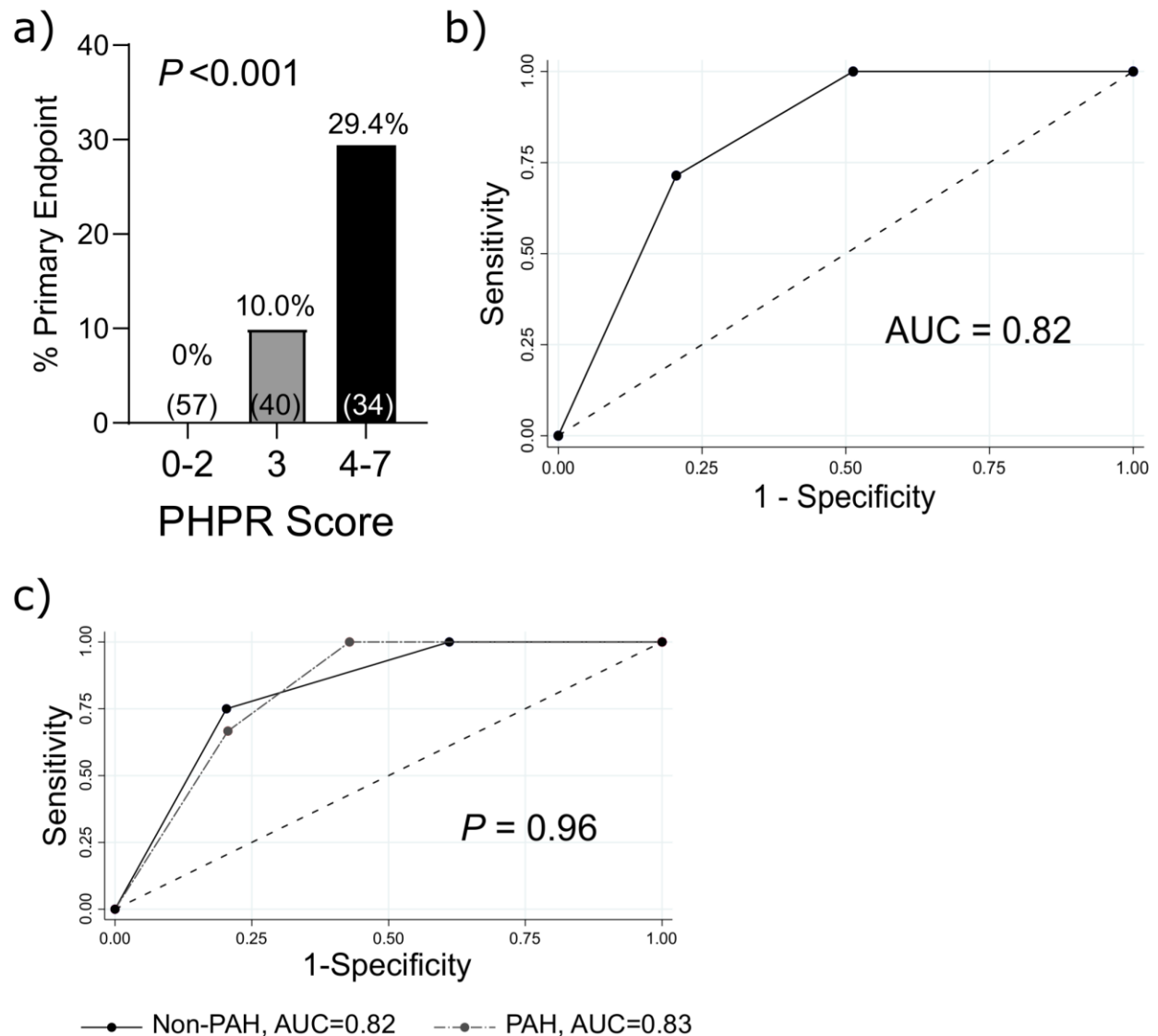
Figure 3. In a), the percentage of patients reaching the primary endpoint in each PHPR category (white=low, 0-2; grey=intermediate, 3; black=high, 4-7) is shown. The number of patients in each category is shown in parenthesis. *P*-value is for chi-square test. In b), the ROC curve for the PHPR categories is shown. In c), PHPR category ROC curves for patients with pulmonary arterial hypertension (grey) and other forms of PH (black) are compared. The AUC for each group is shown in the legend. *P*-values are for DeLong test comparing ROC curves. PHPR=Pulmonary Hypertension Perioperative Risk

Table 1 Preoperative variables

Patient Characteristics		N (%) or Mean ± SD
Age, years		59.7 ± 14.7
Female		114 (76)
SSc/MCTD		54 (36)
WSPH Group	Group 1	78 (52.0)
	Group 2	23 (15.3)
	Group 3	22 (14.7)
	Group 4	15 (10.0)
	Group 5	12 (8.0)
PAH-specific Therapy		108 (72.0)
ASA Class	1	0 (0.0)
	2	4 (2.7)
	3	78 (52.0)
	4	67 (44.7)
	5	1 (0.7)
Procedural Characteristics		
ACC/AHA Risk	Low	110 (73.3)
	Elevated	40 (26.7)
Procedure at JHH		123 (82.0)
Inpatient		48 (32.0)
Emergency		9 (6.0)
Duration >3 hours	Yes	42 (28)
	No	106 (70.7)
	Unknown	2 (1.3)
Preoperative Assessments within 3 Months of Procedure		
PH Clinic Visit		101 (67.3)
Anesthesia Clinic Visit		32 (21.3)
CA Review*	Yes	93 (75.6)
	No	27 (22.0)
	Unknown	3 (2.4)
WHO FC Assessment		94 (62.7)
BNP/pro-BNP		82 (54.7)
Echocardiography		79 (52.7)
6-MWT		34 (22.7)
RHC		31 (20.7)

* Only among procedures performed at Johns Hopkins Hospital

Abbreviations: SSc/MCTD=Systemic Sclerosis/Mixed Connective Tissue Disease; WSPH=World Symposium on Pulmonary Hypertension; ASA=American Society of Anesthesiologists'; ACC/AHA=American College of Cardiology/American Heart Association; JHH = Johns Hopkins Hospital; CA = cardiac anesthesia; WHO FC=World Health Organization Functional Class; BNP/pro-BNP=Brain Natriuretic Peptide/pro-Brain Natriuretic Peptide; 6-MWT-6-Minute Walk Test; RHC= Right Heart Catheterization

Table 2 Outcomes

	N (%) or Median [IQR]
Primary Outcome	19 (12.7)
Death, 30 days	7 (4.7)
Serious Postoperative Complication	17 (11.3)
Hemodynamic Instability	14 (9.3)
Respiratory Failure	10 (6.7)
Initiation of Inhaled Vasodilators	4 (2.7)
Acute Coronary Syndrome	0 (0.0)
Cerebrovascular Accident	1 (0.7)
Arrhythmia	5 (3.3)
Renal Failure	3 (2.0)
Hepatic Injury	1 (0.7)
Sepsis	2 (1.3)
Secondary Outcomes	
Hospital LOS, days	1 [0 - 6]
Intensive Care Unit LOS, days	3 [1 - 5]
Hospital Readmission, 30 days	19 (12.7)

Definition of abbreviations: LOS=Length of Stay

Table 3 Associations between preoperative variables and the primary outcome

		Primary Outcome Reached		
Patient Characteristics		N (%)	OR (95% CI)	*P*-value
Age, per year			1.01 (0.97 - 1.04)	0.76
Sex	Male	7 (19.4)	Reference	
	Female	12 (10.5)	0.49 (0.18 - 1.35)	0.17
SSc/MCTD	No	13 (13.5)	Reference	
	Yes	6 (11.1)	0.80 (0.28 - 2.24)	0.67
WSPH Group	1	9 (11.5)	Reference	
	2	2 (8.7)	0.73 (0.15 - 3.65)	0.70
	3	3 (13.6)	1.21 (0.30 - 4.92)	0.79
	4	3 (20.0)	1.92 (0.45 - 8.12)	0.38
	5	2 (16.7)	1.53 (0.29 - 8.14)	0.62
PAH-specific Therapy	No	6 (14.3)	Reference	
	Yes	13 (12.0)	0.82 (0.29 - 2.32)	0.71
ASA	Low (1-3)	5 (6.1)	Reference	
	High (4-5)	14 (20.6)	3.99 (1.36 - 11.74)	0.01
Procedural Characteristics				
ACC/AHA Procedure Risk	Low	6 (5.5)	Reference	
	Elevated	13 (32.5)	8.35 (2.90 - 23.99)	<0.001
Emergent Procedure	No	15 (10.6)	Reference	
	Yes	4 (44.4)	6.72 (1.62 - 27.79)	0.01
Procedure >3 hours (N=148)	No	6 (5.7)	Reference	
	Yes	13 (31.0)	7.47 (2.61 - 21.39)	<0.001
Inpatient	No	8 (7.8)	Reference	
	Yes	11 (22.9)	3.50 (1.30 - 9.37)	0.01
Preoperative Assessment				
PH Clinic within 90 days	No	6 (12.2)	Reference	
	Yes	13 (12.9)	1.06 (0.38 - 2.98)	0.91
Anesthesia Clinic within 90 days	No	16 (13.6)	Reference	
	Yes	3 (9.4)	0.66 (0.18 - 2.42)	0.53
CA Referral (N=137)*	No	1 (2.6)	Reference	
	Yes	16 (16.3)	7.41 (0.95 - 57.98)	0.06

WHO FC (N=141)	Low (I, II)	2 (3.4)	Reference	
	High (III, IV)	14 (17.1)	5.87 (1.28 - 26.90)	0.02
NT-proBNP (BNP), ng/L (N=147)	<300 (<50)	2 (4.2)	Reference	
	300 -1400 (50 - 300)	4 (8.3)	2.09 (0.36 - 12.00)	0.41
	>1400 (>300)	12 (23.5)	7.08 (1.49 - 33.56)	0.01
Echocardiography				
RA Dilation (N=146)	No	2 (4.2)	Reference	
	Yes	15 (15.3)	4.16 (0.91 - 18.98)	0.07
RV Dilation (N=147)	None	3 (6.0)	Reference	
	Mild	5 (11.1)	1.96 (0.44 - 8.71)	0.38
	Moderate	2 (8.3)	1.42 (0.22 - 9.14)	0.71
	Severe	8 (28.6)	6.27 (1.51 - 26.09)	0.01
TAPSE, cm (N=74)	≥ 1.8	5 (11.4)	Reference	
	< 1.8	6 (20.0)	1.95 (0.54 – 7.09)	0.31
Effusion (N=145)	No	11 (11.2)	Reference	
	Yes	6 (12.8)	1.16 (0.40 - 3.35)	0.79
Max TR Velocity, per 0.5 m/s (N=120)			1.50 (1.05 - 2.13)	0.02
6-MWD, m (N=131)	> 440	2 (7.7)	Reference	
	165 - 440	10 (10.6)	1.43 (0.29 - 6.97)	0.66
	< 165	2 (18.2)	2.67 (0.33 - 21.87)	0.36
RHC				
RAP, mmHg (N=144)	< 8	9 (12.7)	Reference	
	8.0 - 14	8 (14.3)	1.15 (0.41 - 3.20)	0.79
	> 14	2 (11.8)	0.92 (0.18 - 4.70)	0.92
CI, L/min/m2 (N=137)	≥ 2.5	4 (12.5)	Reference	
	2 - 2.49	6 (17.1)	1.60 (0.51; 5.05)	0.42
	< 2	8 (11.4)	1.11 (0.31; 3.98)	0.88
SvO2, % (N=137)	> 65	7 (9.5)	Reference	
	60 - 65	6 (17.1)	1.98 (0.61; 6.41)	0.25
	< 60	4 (14.3)	1.60 (0.43; 5.94)	0.49

* Only among procedures performed at Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center

Definition of abbreviations: SSc/MCTD=Systemic Sclerosis/Mixed Connective Tissue Disease; WSPH=World Symposium on Pulmonary Hypertension; ASA=American Society of Anesthesiologists; ACC/AHA=American College of Cardiology/American Heart Association;; CA=Cardiac Anesthesia; WHO FC=World Health Organization Functional Class; NT pro-BNP=N-terminal prohormone Brain Natriuretic Peptide/pro-Brain Natriuretic Peptide; RA=Right Atrial; RAP=Right Atrial Pressure; RV=Right Ventricular; TAPSE=Tricuspid Annular Plane Systolic Excursion; TR Tricuspid Regurgitant; 6-MWD=6-Minute Walk Distance; RHC= Right Heart Catheterization; CI=Cardiac Index; SvO2=Mixed Venous Oxygen Saturation

Table 4 Association between composite patient-level risk scores and the primary outcome

	Univariable		Multivariable *	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Non-invasive Low-risk Focused	0.4 (0.2; 0.9)	0.03	0.3 (0.1; 0.8)	0.01
Invasive and Non-invasive Low-risk Focused	0.7 (0.4; 1.2)	0.15	0.5 (0.3; 1.0)	0.05
Score and Average	1.9 (0.8; 4.3)	0.15	3.6 (1.2; 10.6)	0.02

* Adjusted for inherent procedural risk of major adverse cardiovascular events, per American College of Cardiology/American Heart Association guidelines

Table 5 Association between composite patient-level risk scores and secondary outcomes

	Univariable		Multivariable *	
	Hospital LOS			
	β (95% CI)	*P*-value	**β (95% CI)**	*P*-value
Non-invasive Low-risk Focused	-2.0 (-3.5; -0.5)	0.01	-2.2 (-3.6; -0.8)	0.003
Invasive and Non-invasive Low-risk				
Focused	-1.3 (-2.7; 0.1)	0.06	-1.6 (-2.9; -0.3)	0.02
Score and Average	3.4 (0.7; 6.0)	0.01	4.3 (1.9; 6.8)	0.001
	Intensive Care Unit LOS			
	β (95% CI)	*P*-value	**β (95% CI)**	*P*-value
Non-invasive Low-risk Focused	-1.0 (-4.4; 2.3)	0.53	-1.8 (-5.3; 1.6)	0.28
Invasive and Non-invasive Low-risk				
Focused	-0.4 (-3.1; 2.3)	0.77	-0.7 (-3.4; 2.0)	0.61
Score and Average	1.6 (-2.2; 5.4)	0.40	2.6 (-1.3; 6.5)	0.19
	30d Hospital Readmission			
	OR (95% CI)	*P*-value	**OR (95% CI)**	*P*-value
Non-invasive Low-risk Focused	0.5 (0.2; 0.9)	0.02	0.4 (0.2; 0.9)	0.02
Invasive and Non-invasive Low-risk				
Focused	0.6 (0.3; 1.0)	0.03	0.6 (0.3; 0.9)	0.03
Score and Average	3.2 (1.3; 7.5)	0.01	3.4 (1.4; 8.4)	0.01

* Adjusted for inherent procedural risk of major adverse cardiovascular events, per American College of Cardiology/American Heart Association guidelines

Abbreviations: LOS=Length of Stay; β = β-coefficient; OR = odds ratio

Supplemental Material, Hassan *et al*.

Supplemental Figure Legends:

Supplemental Figure 1

Supplemental Figure 1. Intensive care unit (ICU) length of stay in patients with a planned admission for monitoring (PLAN) *vs*. those admitted for management of post-operative complications (UNPLAN). Median values indicated by black bar. **** = *P*-value < 0.001 for Wilcoxon rank-sum comparison of medians. LOS=Length of Stay

Supplemental Figure 2

a) Low-Risk (3)

b) Low-Risk (4)

c) Score & Avg
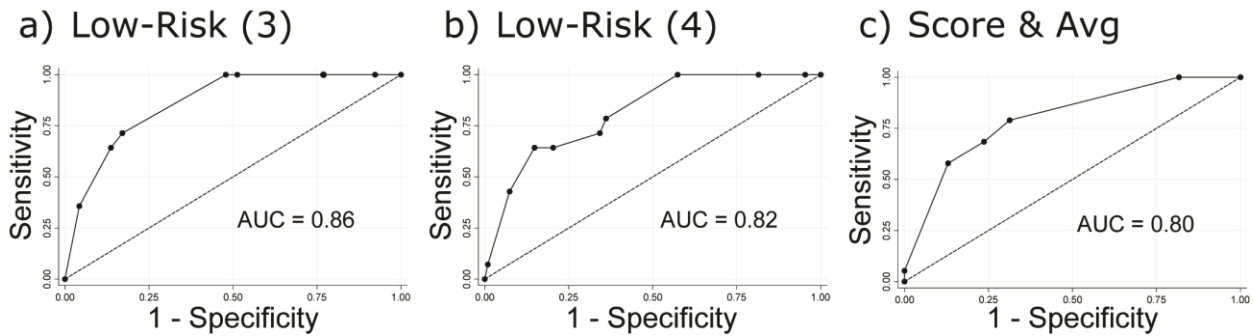
Supplemental Figure 2. ROC curves for multivariable logistic regression models that assess composite patient-level risk using a) the three-parameter non-invasive "low-risk focused" approach (Low-Risk (3)), b) the four-parameter invasive and non-invasive "low-risk focused" approach (Low-Risk (4)), and c) the "score and average" approach (Score & Avg). *P*-value for DeLong test. AUC=Area Under Curve

Supplemental Figure 3
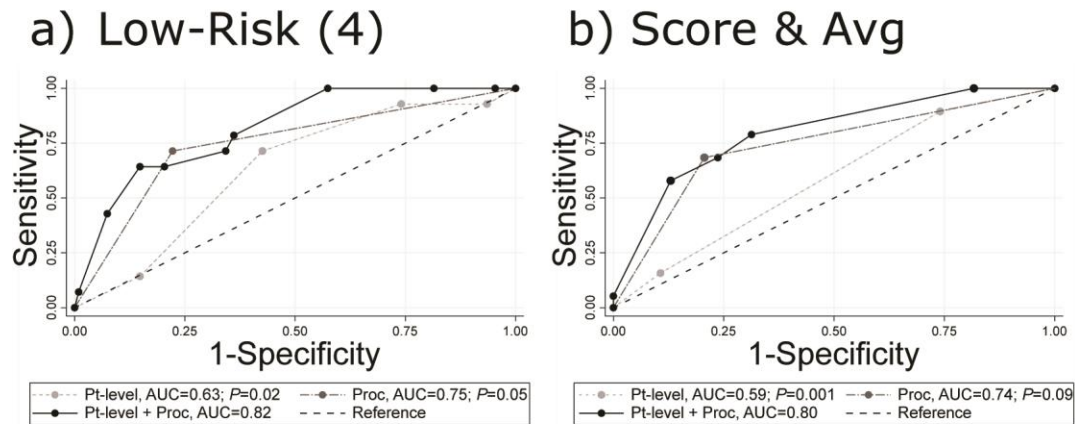
Supplemental Figure 3. ROC curves for logistic regression models including only patient-level risk (Pt-level), only procedural risk (Proc), or both patient-level and procedural risk (Pt-level + Proc) using a) the four-parameter invasive and non-invasive "low-risk focused" approach (Low-Risk (4)), and b) the "score and average" approach (Score & Avg). The area under the curve (AUC) for each model is shown in the legend. *P*-values are for DeLong test comparing ROC curves for each univariable model with the multivariable model.

Supplemental Table 1 Risk stratification of the preoperative parameters used in the "score and average" approach

Parameter	Low risk	Intermediate risk	High risk
WHO FC	1 or 2	3	4
6-MWD (m)	>440	165 - 440	<165
NT-proBNP (BNP) (ng/L)	<300 (<50)	300 -1400 (50 - 300)	>1400 (>300)
RAP (mmHg) on RHC	<8	8.0 - 14	>14
CI (L/min/m2)	≥ 2.5	2 - 2.49	<2
SvO2 (%)	>65	60 - 65	<60

Definition of abbreviations: WHO FC=World Health Organization Functional Class; 6-MWD=6-Minute Walk Distance; NT pro-BNP=N-terminal prohormone Brain Natriuretic Peptide; BNP=Brain Natriuretic Peptide; RAP=Right Atrial Pressure; CI=Cardiac Index; SvO2=Mixed Venous Oxygen Saturation

Supplemental Table 2 Preoperative variables

		N (%)		N (%)
WSPH Group (N = 150)	Group I	78 (52.0)	IPAH	21 (26.9)
			Drug/Toxin-PAH	1 (1.3)
			CTD-PAH	37 (47.4)
			HIV-PAH	3 (3.6)
			Portal HTN-PAH	7 (9.0)
			CHD-PAH	6 (7.7)
			PVOD/PCH	2 (2.6)
			HHT-PAH	1 (1.3)
	Group II	23 (15.3)	HFrEF-PH	2 (8.7)
			HFpEF-PH	18 (78.3)
			Valvular-PH	3 (13.0)
	Group III	22 (14.7)	COPD-PH	1 (4.6)
			ILD-PH	21 (95.5)
	Group IV	15 (10)	CTEPH	15 (100)
	Group V	12 (8)	Hemolytic Anemia	4 (33.3)
			MPD	1 (8.3)
			Sarcoidosis	4 (33.3)
			CKD/Dialysis	2 (16.7)
			High CO, cirrhosis	1 (8.3)
PAH-specific Therapy (N = 108)	Monotherapy	59 (54.6)	PDE5I	43 (72.9)
			Riociguat	12 (20.3)
			ERA	4 (6.8)
	Combination Therapy	49 (45.4)	PDE5I + ERA	29 (59.2)
			PDE5I + inh PC	4 (8.2)
			PDE5I + IV/SQ PC	6 (12.2)
			ERA + inh PC	1 (2)
			ERA + IV/SQ PC	2 (4.1)
			PDE5I + ERA + inh PC	5 (10.2)
			PDE5I + ERA + IV/SQ PC	2 (4.1)
ACC/AHA Procedural Risk (N = 150)	Low	110 (73.3)	Endoscopic procedure	54 (49.1)
			Superficial procedure	16 (14.6)
			Cataract surgery	7 (6.4)
			Ambulatory surgery	33 (30)
	Elevated	40 (26.7)	Intraperitoneal surgery	17 (42.5)
			Orthopedic surgery	16 (40)
			Intrathoracic surgery	5 (12.5)
			Head and neck surgery	1 (2.5)
			Peripheral vascular surgery	1 (2.5)

Definition of abbreviations: WSPH=World Symposium on Pulmonary Hypertension; IPAH=Idiopathic Pulmonary Arterial Hypertension; CTD=Connective Tissue Disease; HIV=Human Immunodeficiency Virus; HTN=Hypertension; CHD=Congenital Heart Disease; PVOD=Pulmonary Veno-Occlusive Disease; HHT= Hereditary Hemorrhagic Telangiectasia; PH=Pulmonary Hypertension; HFrEF=Heart Failure with reduced Ejection Fraction; HFpEF=Heart Failure with preserved Ejection Fraction; COPD=Chronic Obstructive Pulmonary Disease; ILD=Interstitial Lung Disease; CTEPH=Chronic Thromboembolic Pulmonary Hypertension; CKD=Chronic Kidney Disease; MPD = myeloproliferative disorder; CO=cardiac output; PDE5I=Phosphodiesterase-5 Inhibitor; ERA= Endothelin Receptor Antagonist; PC=Prostacyclin; IV/SQ=Intravenous/Subcutaneous; ACC/AHA=American College of Cardiology/American Heart Association

Supplemental Table 3 Endoscopic procedures

Endoscopic Procedure	N (%)
Colonoscopy	18 (33.3)
Esophagogastroduodenoscopy	14 (25.9)
Colonoscopy + Esophagogastroduodenoscopy	9 (16.7)
Endoscopic Retrograde Cholangiopancreatography	4 (7.4)
Enteroscopy	2 (3.7)
Bronchoscopy	2 (3.7)
Nasal endoscopy	2 (3.7)
Anoscopy	1 (1.9)
Cystoscopy	1 (1.9)
Colposcopy	1 (1.9)
Total	54 (100)

Supplemental Table 4 Comparison of preoperative assessment data for patients who reached the primary outcome and those who did not

		Primary Outcome Reached		
		Yes (n = 19; 12.7%)	**No (n = 131; 87.3%)**	***P*-value**
WHO FC	I	0 (0.0)	5 (4.0)	0.003
	II	2 (12.5)	52 (41.6)	
	III	12 (75.0)	68 (54.4)	
	IV	2 (12.5)	0 (0.0)	
NT-proBNP, ng/L*		2184 [1010 – 5939]	588 [176 – 1899]	0.002
NT-proBNP (BNP) range, ng/L	<300 (<50)	2 (11.1)	46 (35.7)	0.01
	300 -1400 (50 - 300)	4 (22.2)	44 (34.1)	
	>1400 (>300)	12 (66.7)	39 (30.2)	
Echocardiography				
RA Dilation		15 (88.2)	83 (64.3)	0.05
RV Dilation	None	3 (16.7)	47 (36.4)	0.04
	Mild	5 (27.8)	40 (31.0)	
	Moderate	2 (11.1)	22 (17.1)	
	Severe	8 (44.4)	20 (15.5)	
TAPSE, cm$^{\pm}$		1.83 ± 0.62	1.85 ± 0.54	0.90
Pericardial Effusion		6 (35.3)	41 (32.0)	0.79
Max TR Velocity, m/s$^{\pm}$		3.86 ± 0.87	3.42 ± 0.71	0.06
6-MWD, m$^{\pm}$		289.1 ± 133.6	336.8 ± 119.4	0.22
6-MWD Range, m	> 440	2 (14.3)	24 (20.5)	
	165 - 440	10 (71.4)	84 (71.8)	0.65
	< 165	2 (14.3)	9 (7.7)	
RHC				
RAP, mmHg$^{\pm}$		8.7 ± 6.0	8.0 ± 5.3	0.62
RAP Range, mmHg	< 8	9 (47.4)	62 (49.6)	0.95
	8 - 14	8 (42.1)	48 (38.4)	
	> 14	2 (10.5)	15 (12.0)	
CI, L/min/m$^{2\pm}$		2.58 ± 1.06	2.66 ± 0.93	0.75
CI range, L/min/m^2	< 2	4 (22.2)	28 (23.5)	0.72
	2-2.5	6 (33.3)	29 (24.4)	
	> 2.5	8 (44.4)	62 (52.1)	
SvO2, %$^{\pm}$		64.1 ± 10.6	65.7 ± 8.9	0.58
SvO2 Range, %	< 60	4 (23.5)	24 (20)	0.47
	60-65	6 (35.3)	29 (24.2)	
	> 65	7 (41.2)	67 (55.8)	

* Median [IQR] reported; the Wilcoxon rank-sum test used

$^{\pm}$ Mean ± SD reported; the independent t-test used

Definition of abbreviations: WHO FC=World Health Organization Functional Class; NT pro-BNP=N-terminal prohormone Brain Natriuretic Peptide; RA=Right Atrial; RAP=Right Atrial Pressure; RV=Right Ventricular; TAPSE=Tricuspid Annular Plane Systolic Excursion; TR= Tricuspid Regurgitant; 6-MWD=6-Minute Walk Distance; RHC= Right Heart Catheterization; CI=Cardiac Index; SvO2=Mixed Venous Oxygen Saturation

Subject	Age	Sex	WSPH Group	WHO FC	6-MWD (m)	NT-proBNP (ng/L)	Procedure	ACC/AHA procedural risk	Cause of Death (POD)
1	28	F	4 (CTEPH)	Unknown	Unknown	517	Mediastinal Mass Excision	Elevated	CV compromise and Hypotension (4)
2	56	M	1 (CTD-PAH)	3	331	2204	Esophagogastroduodenoscopy	Low	RV failure (23)
3	55	F	1 (CTD-PAH)	4	Unknown	12263	Gastrojejunostomy Tube Insertion by IR	Low	Sepsis + stroke, cardiac arrest (5)
4	71	F	4 (CTEPH)	4	213	1865	Cardioversion with TEE	Low	Non-responsive Hypotension (16)
5	77	F	1 (CTD-PAH)	3	189	5939	Gastrojejunostomy Tube Insertion by IR	Low	Unclear* (25)
6	64	M	3 (ILD-PH)	3	280	2164	Open Inguinal Hernia Repair (SBO)	Elevated	Unclear* (13)
7	78	F	3 (ILD-PH)	3	180	1104	Left Shoulder Hardware Removal	Elevated	Unclear* (7)

* Died after being discharged from the hospital - cause of death was unclear

Definition of abbreviations: WSPH=World Symposium on Pulmonary Hypertension; WHO FC=World Health Organization Functional Class; 6-MWD=6-Minute Walk Distance; NT-proBNP=N-terminal prohormone Brain Natriuretic Peptide; ACC/AHA=American College of Cardiology/American Heart Association; POD=Post-Operative Day of Death; CTEPH=Chronic Thromboembolic Pulmonary Hypertension; CV=Cardiovascular; CTD-PAH=Connective Tissue Disease-Pulmonary Arterial Hypertension; RV=Right Ventricular; IR=Interventional Radiology; TEE=Trans-Esophageal Echocardiography; ILD-PH=Interstitial Lung Disease-Pulmonary Hypertension; SBO=Small Bowel Obstruction

Supplemental Table 5 Causes of death

Supplemental Table 6 Reasons for 30-day hospital readmission

Reason	Frequency
RV Failure	5
Dyspnea	3
Symptomatic anemia	2
Nausea + vomiting	2
Abdominal fluid collection	1
Hypotension	1
Chest pain	1
Gastroparesis	1
SBO	1
Fever	1
Syncope	1

Definition of abbreviations: RV=Right Ventricular; SBO= Small Bowel Obstruction