Research Square

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Residual Pulmonary Hypertension After Pulmonary Endarterectomy Is Associated With Female Sex, Absence of Prior Venous Thromboembolism, and Higher Preoperative Mean Pulmonary Artery Pressure

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Abstract

Purpose

Residual pulmonary hypertension (RPH) after pulmonary endarterectomy (PEA) is associated with adverse functional and long-term outcomes. We investigated preoperative factors associated with RPH, defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at follow-up right heart catheterization (RHC).

Methods

This single-centre cohort included 205 consecutive patients with chronic thromboembolic pulmonary hypertension who underwent PEA tertiary referral centre (2015–2024). Among 174 hospital survivors, 149 (85.6%) underwent follow-up RHC at a median of 6.0 months (IQR 4.3–9.9) and comprised the primary analysis. Multivariable logistic regression was complemented by bootstrap internal validation (1,000 resamples).

Results

RPH was present in 80 of 149 patients (53.7%). Female sex (adjusted OR 2.21; 95% CI 1.10–4.44; p = 0.026), absence of prior venous thromboembolism (adjusted OR 3.39; 95% CI 1.12–10.23; p = 0.031), and higher preoperative mPAP (adjusted OR 1.037 per 1 mmHg; 95% CI 1.007–1.068; p = 0.016) were independently associated with RPH. The primary model showed moderate discrimination (AUC 0.693; 95% CI 0.609–0.777, DeLong method), adequate calibration (Hosmer–Lemeshow p = 0.386), and an optimism-corrected AUC of 0.675.

Conclusion

Female sex, absence of prior venous thromboembolism, and higher preoperative mPAP were independently associated with RPH after PEA. These readily available variables may help identify patients who warrant closer postoperative clinical and haemodynamic reassessment.

Highlights

• Residual PH (mPAP ≥ 25 mmHg at follow-up RHC) occurred in 53.7% of patients undergoing PEA in this referral centre.

• Female sex was independently associated with 2.2-fold higher odds of residual pulmonary hypertension (RPH), consistent with previously reported sex-related differences after PEA, although the biological basis underlying this association remains uncertain.

• The absence of a previous history of venous thromboembolism (VTE) was associated with 3.4-fold higher odds of RPH. This hypothesis-generating association is less well established in the post-PEA literature and requires external validation.

• Each 1-mmHg increase in preoperative mean pulmonary arterial pressure (mPAP) was associated with a 3.7% increase in the odds of RPH, supporting the interpretation of preoperative mPAP as a continuous marker of haemodynamic burden.

• These readily available preoperative factors may help identify patients who warrant closer postoperative clinical and haemodynamic reassessment.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is classified within Group 4 of the clinical classification of pulmonary hypertension and is characterised by a pre-capillary haemodynamic phenotype resulting from incomplete resolution and fibrous transformation of thromboembolic material in the pulmonary arterial vasculature after at least three months of effective anticoagulation [1]. Without therapeutic intervention, the five-year prognosis is poor, reaching approximately 10% survival in patients with mPAP > 50 mmHg [2].

Pulmonary endarterectomy (PEA) is the gold-standard treatment for eligible patients with CTEPH, providing sustained symptomatic relief and prognostic benefit [3, 4]. In high-volume centres, PEA is associated with operative mortality below 5%, significant reductions in pulmonary vascular resistance (PVR), and improvements in functional class and exercise tolerance [5, 6]. Yet a non-negligible proportion of patients fail to achieve complete haemodynamic normalisation after surgery.

Residual pulmonary hypertension (RPH) after PEA is clinically relevant and may adversely affect functional recovery and long-term outcomes. Historically, many PEA series defined RPH as mPAP ≥ 25 mmHg at follow-up right heart catheterization (RHC), with reported incidences ranging from 5% to 47% depending on the diagnostic threshold, timing of postoperative catheterisation, case selection, and centre experience [7–13]. Current ESC/ERS criteria define pre-capillary pulmonary hypertension as mPAP > 20 mmHg with pulmonary vascular resistance (PVR) > 2 Wood units and pulmonary arterial wedge pressure ≤ 15 mmHg [4]. Proposed mechanisms of post-PEA RPH include persistent fibrothrombotic obstruction in distal surgically inaccessible vessels and superimposed pulmonary microvasculopathy that is not directly corrected by endarterectomy [14–16].

Despite its clinical relevance, the preoperative factors associated with RPH after PEA remain incompletely characterised, and data from Latin American centres are particularly scarce. Identifying such factors may help select patients for closer postoperative clinical and haemodynamic reassessment and timely evaluation for multimodal treatment when residual disease is confirmed. This study aimed to identify independent preoperative factors associated with RPH in a single Latin American referral-centre cohort undergoing PEA for CTEPH.

Methods

Study design and population

This was a single-centre analytical cohort study. Data were obtained through a review of medical records and the institutional database of the Pulmonary Endarterectomy Research Group. The study was

approved by the institutional Research Ethics Committee (CAAE: 86861525.9.0000.0068; Approval No. 7,557,226). The study design is presented in Fig. 1.

Of the 205 patients who underwent PEA, 56 (27.3%) were not included in the follow-up RHC analysis. Thirty-one patients (15.1% of the overall cohort) died postoperatively before undergoing right heart catheterisation; these deaths were distributed as follows: 13 (6.3%) within the first 7 days after surgery, 9 (4.4%) between postoperative days 8 and 30, and 9 (4.4%) after 30 days of hospitalization, yielding a 30-day operative mortality of 22 of 205 (10.7%) and a median time from surgery to in-hospital death of 14 days (IQR 5–41 days).

Among the 174 patients who survived the index hospitalization, 25 (14.4%) did not undergo follow-up RHC. Six were lost to follow-up with no recorded outpatient contact after discharge; 11 had not yet completed catheterization at database closure (8 with follow-up < 90 days and 3 awaiting scheduling at 90–180 days); and 8 remained under longer-term follow-up without RHC because of refusal of the invasive procedure after clinical improvement, transfer of care to regional centres, or geographic barriers. The primary inference of this study is therefore restricted to patients with CTEPH who survived the index admission and underwent follow-up RHC.

Definitions

The primary endpoint was residual pulmonary hypertension, defined as mPAP ≥ 25 mmHg at follow-up RHC performed at a median of 6 months postoperatively (IQR 4.3–9.9 months). Although current ESC/ERS criteria define pre-capillary pulmonary hypertension using mPAP > 20 mmHg together with PVR > 2 Wood units and pulmonary arterial wedge pressure ≤ 15 mmHg, the historical mPAP ≥ 25 mmHg threshold was retained for the primary endpoint to preserve comparability with established PEA outcome literature [4]. Prior venous thromboembolism (VTE) was defined as a clinically documented episode of deep vein thrombosis or pulmonary embolism preceding CTEPH diagnosis. Absence of prior VTE was coded as a binary exposure variable.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 22.0. Three multivariable logistic regression models were evaluated: (1) a full model including all pre-selected candidate variables; (2) a backward stepwise model; and (3) a forward stepwise parsimonious model, which was used for the primary analysis, with the full and backward models retained as sensitivity analyses. Entry and retention in stepwise modelling were based on the Wald statistic with $p < 0.05$. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and discrimination using the area under the receiver operating characteristic (ROC) curve (AUC; DeLong 95% CI). Internal validation used bootstrap resampling (B = 1,000; Harrell method) to estimate optimism-corrected discrimination and calibration slope; bootstrap distributions of the final-model coefficients were also examined for directional stability. Statistical significance was set at $p < 0.05$. Reporting followed relevant TRIPOD recommendations [17].

Results

Study population

Of 205 patients with CTEPH who underwent PEA between January 2015 and January 2024, 149 (85.6% of hospital survivors) underwent postoperative RHC and constituted the analytic cohort. Of these, 90 (60.4%) were female and 59 (39.6%) were male. Eighty patients (53.7%) met the criterion for RPH (mPAP ≥ 25 mmHg), while 69 (46.3%) achieved haemodynamic normalisation. The preoperative population was characterised by high haemodynamic burden: mean preoperative mPAP was 48.94 mmHg (median 50 mmHg), and more than 74% of patients presented in NYHA functional class III–IV.

Univariable analysis

Univariable logistic regression identified several variables nominally associated with RPH (Table 1). Female sex (OR 2.14; 95% CI 1.10–4.17; p = 0.026), absence of prior VTE (OR 3.20; 95% CI 1.11–9.26; p = 0.032), distal disease of the left pulmonary artery (OR 2.29; 95% CI 1.18–4.45; p = 0.014), and preoperative mPAP per 1 mmHg increment (OR 1.032; 95% CI 1.003–1.062; p = 0.030) reached statistical significance.

Table 1
Univariable and multivariable logistic regression analyses of factors associated with residual pulmonary hypertension after pulmonary endarterectomy (n = 149) Primary multivariable model performance (n = 147 complete cases; 80 events)

Variable	Comparison / unit	Univariable OR	95% CI	p value	Adjusted OR†	95% CI	p value
Demographic and clinical characteristics							
Female sex	**Female vs. male**	**2.14**	**1.10–4.17**	**0.026**	**2.21**	**1.10–4.44**	**0.026**
Absence of prior VTE‡	**Absent vs. present**	**3.20**	**1.11–9.26**	**0.032**	**3.39**	**1.12–10.23**	**0.031**
History of syncope	Yes vs. no	1.31	0.66–2.59	0.444	—	—	—
Lower-limb edema	Yes vs. no	1.18	0.60–2.31	0.632	—	—	—
NYHA functional class I–II	vs. III–IV	1.42	0.68–2.96	0.351	—	—	—
Thrombophilia	No vs. yes	1.24	0.63–2.48	0.534	—	—	—
Age at surgery, per year	Continuous	1.013	0.987–1.040	0.315	—	—	—
BMI, per kg/m²	Continuous	0.967	0.907–1.031	0.307	—	—	—
Comorbidities	Yes vs. no	1.22	0.64–2.32	0.553	—	—	—
Oxygen use and anatomical thrombus distribution							
Preoperative O_2 use	Yes vs. no	2.05	0.99–4.25	0.055	—	—	—
Distal disease, left PA	Yes vs. no	2.29	1.18–4.45	0.014	—	—	—
Proximal disease, left PA	Yes vs. no	1.83	0.95–3.51	0.070	—	—	—
Pericardial effusion (echocardiography)	Yes vs. no	1.62	0.69–3.82	0.272	—	—	—
Preoperative hemodynamics							
Preoperative mPAP, per 1 mmHg	**Continuous**	**1.032**	**1.003–1.062**	**0.030**	**1.037**	**1.007–1.068**	**0.016**
Preoperative PVR, per 100 dyn·s·cm^{-5}	Continuous	1.08	0.99–1.19	0.096	—	—	—

Variable	Comparison / unit	Univariable OR	95% CI	p value	Adjusted OR†	95% CI	p value
Demographic and clinical characteristics							
Female sex	**Female vs. male**	**2.14**	**1.10–4.17**	**0.026**	**2.21**	**1.10–4.44**	**0.026**
Cardiac output, per L/min	Continuous	0.94	0.72–1.23	0.660	—	—	—
Right atrial pressure, per mmHg	Continuous	1.02	0.94–1.11	0.605	—	—	—
Operative variables							
CPB time, per 30 min	Continuous	1.00	0.78–1.28	0.994	—	—	—

Events / n	**80 / 147 (54.4%)**	**Events per predictor (EPV)**	**26.7**
Apparent AUC	0.693 (bootstrap 95% CI, 0.608–0.777)	**Optimism-corrected AUC**	0.675 (optimism = 0.0177; B = 1,000)
Calibration slope	0.904 (bootstrap 95% CI, 0.509–1.533)	**Hosmer–Lemeshow test**	p = 0.386
Nagelkerke R^2	0.139	**Predictor directional stability**	> 98.8% for all three retained predictors

OR, odds ratio; CI, confidence interval; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PA, pulmonary artery; VTE, venous thromboembolism; BMI, body mass index; CPB, cardiopulmonary bypass; NYHA, New York Heart Association modified functional class; EPV, events per variable; AUC, area under the receiver operating characteristic curve.

† Multivariable model: forward stepwise logistic regression (entry criterion $p < 0.05$, Wald statistic); n = 147 complete cases; 80 events. Only variables retained in the final model are shown in the adjusted OR columns. Bootstrap internal validation used 1,000 repetitions according to the Harrell method.

‡ Absence of prior VTE was defined as no documented episode of deep vein thrombosis or pulmonary embolism before the diagnosis of CTEPH.

Multivariable analysis — Primary model (Forward Stepwise)

In the final multivariable model (forward stepwise, n = 147 with complete data), three variables remained independently associated with RPH: female sex (adjusted OR 2.21; 95% CI 1.10–4.44; p = 0.026), absence of prior VTE (adjusted OR 3.39; 95% CI 1.12–10.23; p = 0.031), and preoperative mPAP per 1 mmHg increment (adjusted OR 1.037; 95% CI 1.007–1.068; p = 0.016). The model demonstrated adequate calibration (Hosmer–Lemeshow p = 0.386), Nagelkerke R^2 = 0.139, and moderate discrimination (AUC = 0.693; 95% CI 0.609–0.777, DeLong method) (Table 1, Fig. 2).

Bootstrap internal validation

Bootstrap internal validation (B = 1,000 repetitions; Harrell method) yielded an optimism-corrected AUC of 0.675 (optimism = 0.018), indicating limited apparent optimism in model discrimination. The calibration slope was 0.904 (95% CI 0.509–1.533), consistent with some uncertainty in calibration at this sample size. All three predictors retained the same direction of association in > 98.8% of bootstrap resamples (Fig. 3). Recent PEA risk-modelling studies have similarly used bootstrap internal validation when evaluating residual PH models [28].

Sensitivity analyses

Sensitivity analyses using the full and backward stepwise models showed similar directional and magnitude patterns for the three primary associations, with apparent AUCs of 0.730–0.731. Paired DeLong comparisons did not demonstrate a statistically significant difference in discrimination from the primary model. After bootstrap correction, however, the sensitivity models yielded lower corrected AUCs (~ 0.627), reflecting greater optimism (~ 0.050) associated with the more complex, data-driven specifications (model-selection bootstrap; instability index = 0.913).

Discussion

The central finding of this study is that residual pulmonary hypertension after PEA was independently associated with three readily available preoperative characteristics: absence of prior VTE, higher preoperative mPAP, and female sex. RPH occurred in 53.7% of patients who underwent follow-up RHC. This proportion is higher than many historical series but is close to contemporary data from systematic post-PEA reassessment, including the UK CURATE registry, which reported mPAP ≥ 25 mmHg in 47% of patients after PEA [13]. Differences across studies likely reflect variation in haemodynamic definitions, timing and completeness of postoperative catheterisation, case mix, and referral-centre characteristics.

Preoperative mPAP as a predictor of RPH

Each 1 mmHg increment in preoperative mPAP was associated with 3.7% higher odds of RPH (adjusted OR 1.037; 95% CI 1.007–1.068; p = 0.016). In our cohort, the 4.5 mmHg difference between the mean preoperative mPAP of patients with and without RPH (51.1 vs 46.6 mmHg) corresponds, under the fitted log-linear model, to approximately 18% higher odds of RPH. Rather than defining a single threshold, this finding supports interpretation of preoperative mPAP as a continuous marker of haemodynamic burden. Prior PEA studies have similarly linked greater preoperative haemodynamic severity with less complete postoperative haemodynamic recovery [18, 21, 24, 26]. Figure 4 illustrates the cumulative OR implied by the fitted model across the observed mPAP range and should be interpreted as a model-based illustration of the assumed linear effect on the log-odds scale, not as a validated clinical threshold.

Female sex

Female sex was associated with 2.2-fold higher odds of RPH (adjusted OR 2.21; p = 0.026). The direction of this association is consistent with previous PEA cohorts. Kunihara et al. identified male sex as a predictor of more favourable haemodynamic response, de Perrot et al. reported female sex among factors associated with residual PH in severe CTEPH, and Chan et al., in 401 patients, found that women had higher postoperative PVR and a greater long-term need for targeted PH therapy, with female sex remaining independently associated with treatment requirement [8, 24, 27]. The biological basis of this sex-related difference remains uncertain. Sex-specific pulmonary vascular remodelling and a greater distal or microvascular component are plausible hypotheses, but these mechanisms were not directly measured in the present study and require dedicated prospective investigation.

Absence of prior VTE

The association between absence of prior VTE and RPH (adjusted OR 3.39; 95% CI 1.12–10.23; p = 0.031) is less well established in the post-PEA literature and should be considered hypothesis-generating. Patients with CTEPH without a clinically documented thromboembolic event may represent a clinically distinct phenotype, as suggested by population-level data comparing CTEPH with and without previous VTE [25]. One possible explanation is a more insidious course with a relatively greater contribution from distal pulmonary vascular remodelling or microangiopathy; however, the present study did not directly assess microvascular disease, and the wide confidence interval indicates uncertainty in the magnitude of this association.

This interpretation also highlights the distinction between surgically accessible distal fibrothrombotic disease and non-surgical small-vessel remodelling. The latter may persist despite technically successful endarterectomy and provides part of the rationale for multimodal CTEPH management, including pharmacological therapy and balloon pulmonary angioplasty when residual disease is confirmed [14, 20, 21].

Clinical implications

Together, these findings suggest that female sex, absence of prior VTE, and higher preoperative mPAP may help identify patients who merit closer postoperative reassessment. The primary model showed only moderate discrimination (AUC 0.693), and these variables should therefore not be used as a stand-alone clinical decision rule or as criteria to withhold PEA. Their potential value is in complementing clinical judgement and supporting timely clinical, functional, and haemodynamic reassessment, with evaluation for multimodal treatment if residual PH is confirmed. This is clinically relevant because contemporary registry data indicate that residual haemodynamic abnormalities after PEA are common and treatment patterns remain heterogeneous [13].

Limitations

The limitations of this study are primarily related to its single-centre cohort design, which is inherently susceptible to information and recall bias. It is also important to acknowledge that the reference population comprised patients with a high degree of clinical and haemodynamic severity, which may limit the generalisability of our findings to other PEA populations. In addition, the identified predictors of

residual pulmonary hypertension after PEA showed only moderate discriminatory performance, reflecting limited sensitivity for accurately identifying patients at risk of postoperative residual pulmonary hypertension.

Conclusion

Female sex, absence of prior venous thromboembolism, and higher preoperative mean pulmonary artery pressure were independently associated with residual pulmonary hypertension after pulmonary endarterectomy for CTEPH. In this PEA cohort from a tertiary referral centre, with systematic invasive haemodynamic reassessment, these readily available clinical characteristics identified patients at greater risk of persistent postoperative haemodynamic impairment. Their clinical role should be limited to supporting closer postoperative reassessment and evaluation for multimodal therapy when residual PH is confirmed, pending external validation in larger prospective cohorts.

Statements and Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: The authors declare no known financial or personal competing interests.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committee of the Heart Institute (InCor), Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil [Protocol No. CAAE: 86861525.9.0000.0068; Approval No. 7,557,226; Date: June 2025]. Informed consent was waived by the Ethics Committee in view of the retrospective design of the study.

Data availability: De-identified individual participant data supporting the findings are available from the corresponding author upon reasonable request.

AI disclosure: During the preparation of this manuscript, the authors used ChatGPT (OpenAI) and Claude (Anthropic) to assist with manuscript organisation, language refinement, and formatting. These tools were not used to generate or modify the underlying research data, statistical results, or scientific conclusions. All AI-assisted content was critically reviewed and verified by the authors.

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Figures

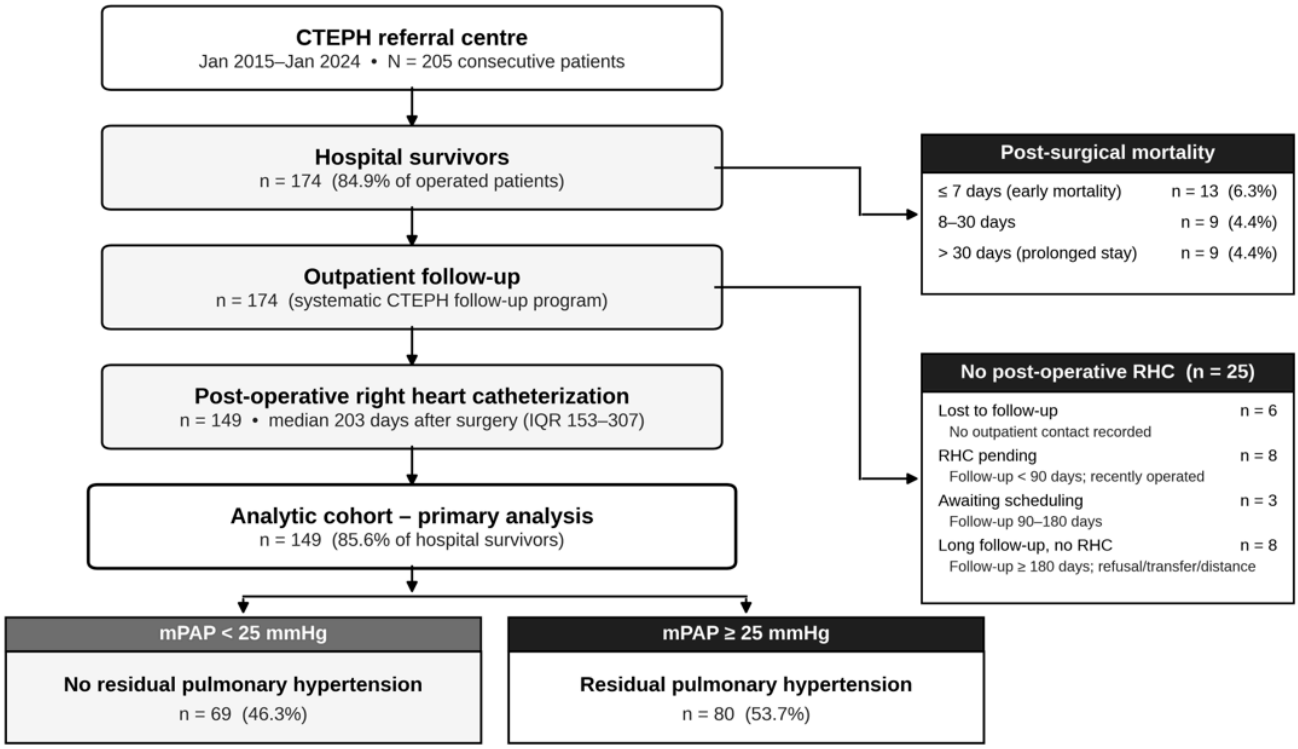

Figure 1

Study design and patient flow. Of 205 consecutive patients undergoing pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) at InCor-HCFMUSP between January 2015 and January 2024, 174 survived the index hospitalization and 149 (85.6% of hospital survivors) completed post-operative right heart catheterization (RHC), constituting the analytic cohort. Post-surgical mortality occurred in 31 patients (15.1%): ≤7 days, n = 13 (6.3%); 8–30 days, n = 9 (4.4%); and >30 days, n = 9 (4.4%). Among 25 hospital survivors without follow-up RHC, 6 were lost to follow-up, 8 had follow-up <90 days with RHC pending, 3 were awaiting scheduling at 90–180 days, and 8 remained without RHC after ≥180 days because of refusal, transfer, or geographic barriers. mPAP, mean pulmonary artery pressure; RHC, right heart catheterization; RPH, residual pulmonary hypertension.

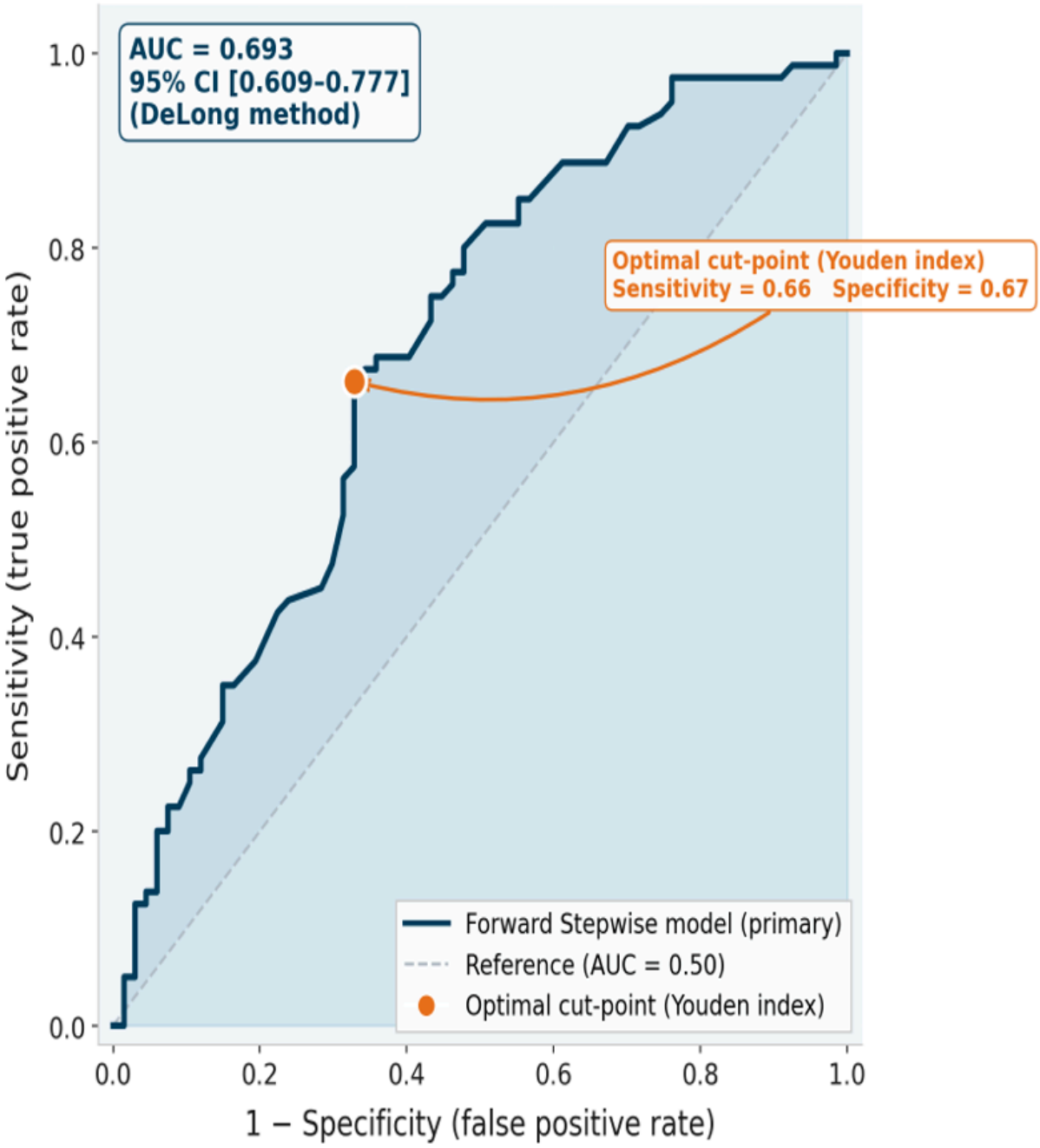

Figure 2

Receiver operating characteristic (ROC) curve for the primary multivariable model (forward stepwise; female sex + absence of prior VTE + preoperative mPAP; n = 147 complete cases; 80 events). AUC = 0.693 (95% CI 0.609–0.777, DeLong method). The orange circle marks the optimal discrimination threshold by the Youden index (sensitivity = 0.66; specificity = 0.67). AUC, area under the curve; CI, confidence interval; VTE, venous thromboembolism; mPAP, mean pulmonary artery pressure.

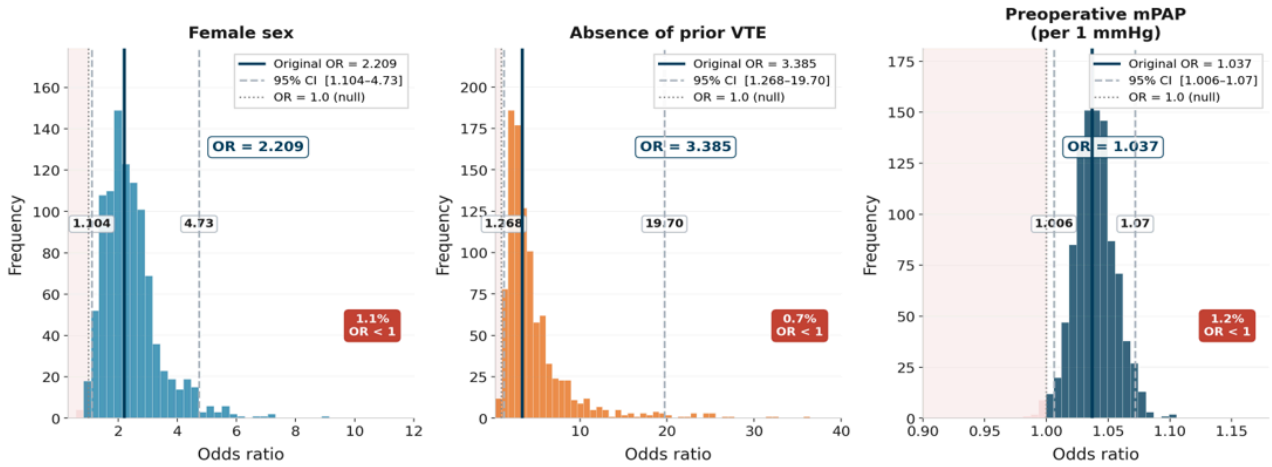

Figure 3. Bootstrap distributions of adjusted odds ratios for the three clinical predictors (B = 1,000).
Vertical solid navy line = original OR; dashed grey lines = bootstrap 2.5th–97.5th percentiles (95% CI); dotted line = OR 1.0 (null).

Figure 3

Bootstrap distributions of adjusted odds ratios for the three clinical factors in the primary model (B = 1,000 repetitions). Each histogram shows the distribution of odds ratios across bootstrap resamples. The vertical solid navy line marks the original adjusted OR; dashed grey lines mark the 2.5th and 97.5th bootstrap percentiles (95% CI); and the dotted line marks OR = 1.0 (null). Only 0.7%–1.2% of bootstrap estimates were <1.0 across the three predictors, supporting directional stability. The right-skewed distribution for absence of prior VTE reflects greater uncertainty for this less common binary exposure. OR, odds ratio; VTE, venous thromboembolism; mPAP, mean pulmonary artery pressure.

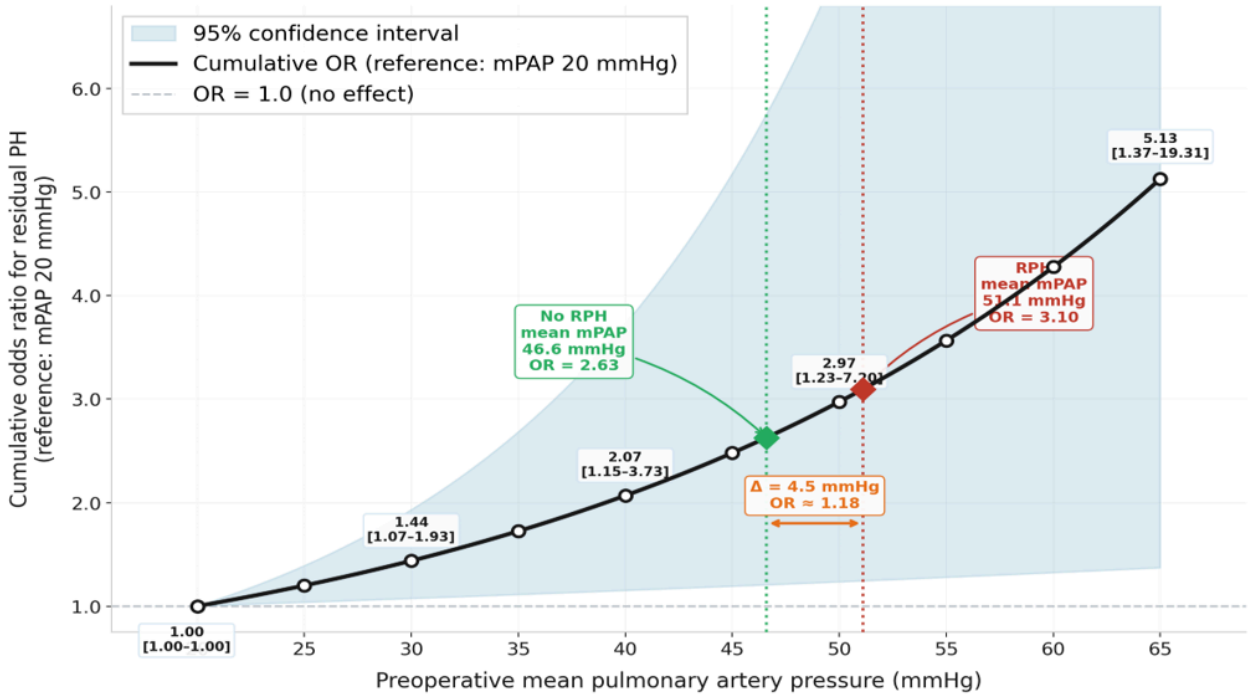

Figure 4. Cumulative odds ratio for residual pulmonary hypertension by preoperative mPAP. Adjusted OR per 1 mmHg increment = 1.037 (95% CI 1.007–1.068; p = 0.016).

Figure 4

Cumulative odds ratio for residual pulmonary hypertension (mPAP ≥ 25 mmHg at 6-month follow-up RHC) across the observed preoperative mPAP range, derived from the adjusted OR per 1 mmHg increment (1.037; 95% CI 1.007–1.068; p = 0.016) in the primary multivariable model. The shaded area represents the propagated 95% confidence interval. Green and red diamond markers indicate the observed mean preoperative mPAP in patients without (46.6 mmHg) and with (51.1 mmHg) residual pulmonary hypertension, respectively; the 4.5 mmHg difference corresponds to a cumulative OR of approximately 1.18. The curve illustrates the cumulative change in odds implied by the fitted log-linear model and should not be interpreted as a validated clinical threshold. OR, odds ratio; mPAP, mean pulmonary artery pressure; RHC, right heart catheterization.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ResidualPHPEAStatisticalReport.xlsx
- ResidualHPPEASTROBEChecklistLung.docx