Preoperative C-reactive protein predicts early postoperative outcomes after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension

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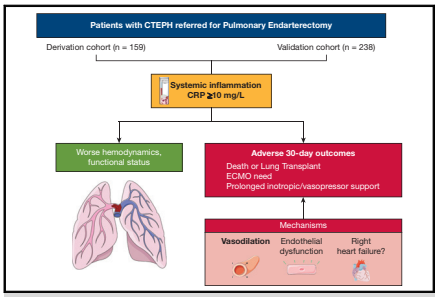
ABSTRACT

Objective: To determine whether preoperative systemic inflammation (defined by C-reactive protein [CRP] levels ≥10 mg/L) is associated with worse functional and hemodynamic status and poor early outcomes postendarterectomy in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: This study included 159 patients who underwent pulmonary endarterectomy from 2009 to 2013 (derivation cohort) and 238 patients from 2015 to 2016 (validation cohort) with CRP data from the national CTEPH registry. The correlations between proinflammatory markers (CRP, interleukins 1 and 6, fibrinogen, and leukocytes) and hemodynamics were assessed in the derivation cohort. Pre-, perioperative characteristics, and 30-day outcomes (ie, death or lung transplant or extracorporeal membrane oxygenation need or inotropic or vasopressor need ≥3 days) of patients with CRP levels ≥ or <10 mg/L were compared.

Results: Median age of the derivation cohort was 63 [52-73] years with 48% female, 80% in New York Heart Association class III/IV. The validation cohort had similar demographics and disease severity. Patients with CRP ≥10 mg/L had greater resistance levels and lower cardiac index than those with CRP <10 mg/L in both cohorts. The primary endpoint was reached in 38% (derivation) and 42% (validation) of patients. In multivariable logistic regression analysis, CRP ≥10 mg/L was associated with the primary endpoint in both the derivation cohort (odd ratio, 2.49 [1.11-5.61], independently of New York Heart class class IV and aortic clamping duration) and the validation cohort (odd ratio, 1.89 [1.09-3.61], independently of age and aortic clamping duration).

Conclusions: Preoperative CRP ≥10 mg/L is independently associated with adverse early outcomes postendarterectomy. (J Thorac Cardiovasc Surg 2021;161:1532-42)



Prognostic value of preoperative C-reactive protein for early outcomes postendarterectomy in CTEPH.

CENTRAL MESSAGE

Preoperative C-reactive protein levels ≥10 mg/L are independently associated with adverse 30-day outcomes postendarterectomy in patients with chronic thromboembolic pulmonary hypertension.

PERSPECTIVE

Pulmonary endarterectomy can be associated with perioperative hemodynamic instability in patients with CTEPH. This study demonstrates the prognostic value of preoperative CRP ≥10 mg/L for risk prediction of adverse early postoperative outcomes, potentially through inflammation-triggered systemic vasodilation. This supports closer perioperative monitoring for vasopressor initiation in these patients.

See Commentaries on pages 1543 and 1544.

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Abbreviations and Acronyms

CRP = C-reactive protein
CTEPH = chronic thromboembolic pulmonary hypertension
ECMO = extracorporeal membrane oxygenation
MPAP = mean pulmonary arterial pressure
NYHA = New York Heart Association
PEA = pulmonary arterial endarterectomy
RAP = right atrial pressure
RV = right ventricular

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Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by progressive intraluminal thrombus organization and vascular inflammatory remodeling.[1,2] While pulmonary endarterectomy (PEA) enables removal of the luminal obstruction and survival improvement,[3,4] it is frequently associated with perioperative hemodynamic instability, particularly due to profound systemic vasodilation.[5]

Patients with CTEPH often display features of systemic inflammation, including high plasma proinflammatory mediators levels (ie, fibrinogen, interleukin-1, or C-reactive protein [CRP]).[5-7] High fibrinogen levels have been associated with poor functional status and hemodynamics in 49 patients with CTEPH.[7] CRP, an acute-phase hepatic protein, is a sensitive but nonspecific marker of inflammation that responds rapidly to changes in underlying inflammatory disease activity, making it an optimal clinical biomarker to detect and monitor systemic inflammation.[8,9] There is little evidence to date on the value of preoperative CRP levels for prediction of perioperative outcomes post-PEA. We hypothesized that high preoperative CRP levels would be associated with worse early outcomes in patients undergoing PEA.

The first objective was to determine whether preoperative systemic inflammation was associated with poor functional and hemodynamics status in a derivation cohort of patients with CTEPH undergoing PEA. The second objective was to explore the association between inflammation and right ventricular (RV) adaptive phenotype in a subgroup of patients with available echocardiographic data. The third objective was to investigate the association between high preoperative CRP levels (≥10 mg/L) and early adverse outcomes post-PEA in the derivation cohort and a validation cohort.

METHODS

This retrospective cohort study is based on the prospective registry of patients with CTEPH undergoing PEA at Marie Lannelongue Hospital (Le Plessis Robinson, France), the only center in the country performing this procedure.[10] The Marie Lannelongue Hospital Institutional Review Board and the local ethics committee (CPP Ile-de- France, Le Kremlin Bicêtre: C0-09-015; Biobanking declaration: DC-2009-1032) approved this study, which was conducted in accordance with the amended Declaration of Helsinki. All patients gave written informed consent.

Derivation Cohort

Between 2009 and 2013, 529 consecutive patients underwent elective PEA for suspected CTEPH (ie, mean pulmonary arterial pressure [MPAP] ≥25 mm Hg, ≥1 segmental perfusion defect detected by lung scanning, and typical lesions of CTEPH on multidetector computed tomographic angiography and/or pulmonary angiography after ≥3 months of effective anticoagulation).[3] Indications of surgery were discussed by the CTEPH team,[10] and patients were considered operable if presenting with sufficient surgically accessible thromboembolic material relating to pulmonary hemodynamics and absence of high-risk comorbidities precluding surgery.[11] Preoperative CRP levels, clinically ordered by the treating physicians, were measured in 159 patients with confirmed CTEPH on pathology (Figure 1, *A*). The baseline characteristics of the 159 included patients (age, sex, body surface area, right atrial pressure, MPAP, cardiac index, and total pulmonary resistance) did not significantly differ from those of the total cohort (n = 529), all $P > .38$. The exclusion criterion was evidence of pulmonary artery sarcoma on pathological analysis of the surgical sample.

Validation Cohort

Between 2015 and 2016, 238 patients were included (Figure 1, *B*). Preoperative CRP levels were available in all patients, as CRP became routinely measured before PEA in our institution. Exclusion criteria were pathologic evidence of pulmonary artery sarcoma and unavailable complete postoperative inotropic or catecholamine support data.

Inflammatory Biomarkers

Blood samples were collected on ethylenediaminetetraacetic acid within 24 hours of surgery and plasma was prepared. No patient had clinically active infection at the time of blood sampling. Preoperative CRP levels were measured in the routine hospital laboratory using the integrated chemistry system Dimension Xpand Plus (Siemens, Munich, Germany) with a limit of detection of 10 mg/L during the first period, and using Dimension Vista 1500 System (Siemens) with a limit of detection of 5 mg/L during the second period. Fibrinogen was measured using the HemosIL Fibrinogen-C kit and D-dimers using HemosIL D-dimer HS 500 kit (Instrumentation Laboratory, Artarmon, Austria). Plasma levels of inflammatory cytokines (monocyte chemoattractant protein-1, interleukin-1β, and interleukin-6) were measured using Quantikine ELISA kits (R&D Systems, Minneapolis, Minn).

Preoperative Characteristics

Clinical, functional, and pulmonary functional tests data available within 1 month of surgery were collected. Hemodynamics, obtained by right heart catheterization, included mean right atrial pressure (RAP), MPAP, pulmonary artery wedge pressure, cardiac output (using thermodilution or direct Fick method in case of severe tricuspid regurgitation), total pulmonary resistance (defined as MPAP/cardiac output), and pulmonary vascular resistance. Total pulmonary resistance was preferred over

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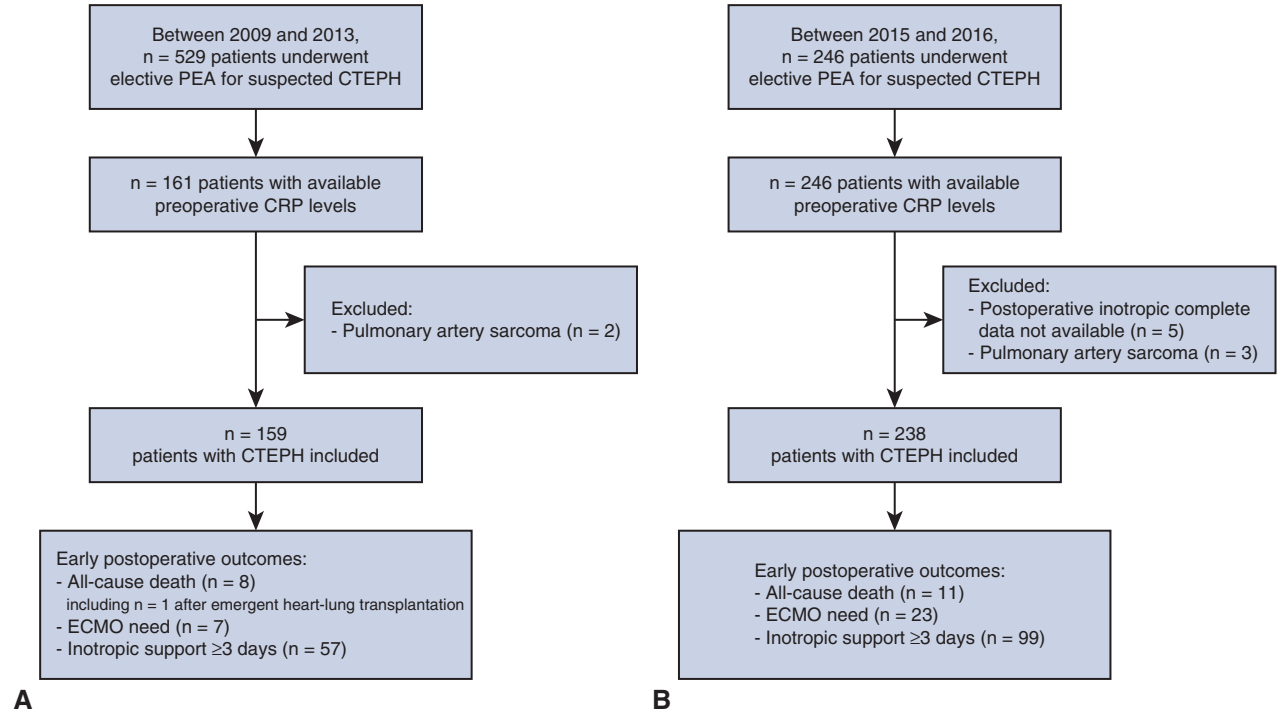


FIGURE 1. Flow chart of the derivation (A) and validation cohorts (B) and their respective early postoperative outcomes. *PEA*, Pulmonary arterial endarterectomy; *CTEPH*, chronic thromboembolic pulmonary hypertension; *CRP*, C-reactive protein; *ECMO*, extracorporeal membrane oxygenation.

pulmonary vascular resistance, as pulmonary artery wedge pressure was not obtained in all patients, particularly in those with proximal obstruction. Echocardiograms available within 1 month of surgery were interpreted offline by a certified cardiologist (M.A.) using GE EchoPAC workstation (GE Healthcare, New York, NY). Right heart metrics included RV end-systolic areas indexed on body surface area, RV fractional area change, tricuspid annular plane systolic excursion, and RV free-wall longitudinal strain.[12]

Perioperative Characteristics

The PEA procedure did not change during the study period.[13] Cardiopulmonary bypass was first established between the ascending aorta and the 2 venae cavae; body temperature was decreased to 20°C before cross clamping of the aorta. Right and then left endarterectomy procedures were performed with sequential circulatory arrests for distal pulmonary arterial recanalization. Thrombus type and location was classified according to the Jamieson's classification as part of the prospective registry design.[14] Duration of cardiopulmonary bypass, aortic clamping, circulatory arrest, and need of extracorporeal membrane oxygenation (ECMO) assistance at the end of surgery were collected. Postoperative inotropic (dobutamine) and catecholamine support (norepinephrine, epinephrine) was left at the discretion of the physicians, targeting a central venous pressure <15 mm Hg, mean arterial pressure >65 mm Hg, and cardiac index >2 L/min/m^2 in the operative room and during the postoperative phase. In case of predominant cardiogenic shock, dobutamine was initiated at the dose of 5 μg/kg/min and increased by 2.5 μg/kg/min every hour, up to 20 μg/kg/min if needed. In case of predominant or associated systemic vasodilation, noradrenaline was initiated, and in case of severe shock, adrenaline would be preferred. In the intensive care unit, inotropic and vasopressor supports were weaned as the heart recovered, based on invasive monitoring and echocardiography.

Postoperative Outcomes

The primary endpoint was the composite early (within 30-day post-PEA) outcome of postoperative hemodynamic failure defined as all-cause death, or heart-lung or double-lung transplantation for persistent pulmonary hypertension, ECMO need immediately after surgery, or inotropic or catecholamine support need for ≥3 days post-PEA. The secondary endpoints included (1) early all-cause death or heart-lung or double-lung transplantation; (2) early all-cause death, heart–lung or double-lung transplantation, or ECMO need post-PEA; and (3) inotropic or catecholamine support need for ≥3 days post-PEA. There was no loss to follow-up before 30 days postsurgery. All-cause mortality was verified through chart review.

Statistical Analysis

Continuous variables are summarized as median and interquartile range; categorical variables are presented as number (%). Comparisons between groups were performed using the nonparametric independent Mann–Whitney *U* test for continuous variables and χ^2 test for categorical data. Spearman correlation coefficients (r) were used to express the correlation between immune markers. Logistic regression analyses were performed on preoperative variables to identify correlates of outcomes occurring within 30 days of surgery. Odds ratios of continuous variables are presented per standard deviation of the considered variable for comparison purposes. The multivariate model was reduced by selecting variables with *P* value < .05. *P* values <.05 were considered statistically significant.

TABLE 1. Comparative preoperative characteristics of the derivation cohort according to preoperative CRP levels

	Total cohort, n = 159	CRP <10 mg/L, n = 122	CRP ≥10 mg/L, n = 37	*P* value*
Age, median [IQR], y	63.1 [51.7-72.9]	63.0 [52.0-73.0]	65.50 [53.0-73.9]	.49
Female sex, n (%)	76 (47.8)	60 (49.2)	16 (43.2)	.52
Body surface area, median [IQR], m^2	1.81 [1.69-1.98]	1.84 [1.69-1.99]	1.75 [1.70-1.92]	.56
History of deep venous thrombosis or acute pulmonary embolism, n (%)	117 (73.6)	92 (75.4)	25 (67.6)	.35
Inferior venous cava filter, n (%)	9 (5.7)	9 (7.4)	0	.18
Presence of endovascular device, n (%)†	10 (6.3)	6 (4.9)	4 (10.8)	.20
History of splenectomy, n (%)	3 (1.9)	3 (2.5)	0	.76
Thrombophilia or blood disorder, n (%)	23 (14.5)	20 (16.4)	3 (8.1)	.21
Chronic inflammatory systemic disease, n (%)‡	3 (1.9)	3 (2.5)	0	.76
Active or recent (<3 y) smoker, n (%)	12 (7.5)	9 (7.4)	3 (8.1)	.89
New York Heart Association functional class, n (%)				
II	32 (20.1)	25 (20.5)	7 (18.9)	
III	105 (66.0)	84 (68.9)	21 (56.8)	.11
IV	22 (13.8)	13 (10.7)	9 (24.3)	
Hemoptysis on admission, n (%)	5 (3.1)	4 (3.3)	1 (2.7)	.86
Six-minute walk test distance, median [IQR], m	(n = 86) 400.0 [305.5-462.0]	(n = 65) 404.0 [342.5-480.0]	(n = 21) 346.0 [251.0-442.0]	.08
Therapies				
Treatment naïve, n (%)	128 (80.5)	97 (79.5)	31 (83.8)	.56
Double therapy, n (%)	12 (7.5)	10 (8.2)	2 (5.4)	.78
Prostanoid therapy, n (%)	1 (0.6)	1 (0.8)	0	.55
Phosphodiesterase inhibitors, n (%)	19 (11.9)	14 (11.5)	5 (13.5)	.95
Endothelin receptor blockers, n (%)	23 (14.5)	20 (16.4)	3 (8.1)	.28
Statins, n (%)	21 (13.2)	20 (16.4)	1 (2.7)	.05
Hemodynamics				
RAP, median [IQR], mm Hg	7.0 [4.0-10.0]	7.0 [4.0-10.0]	8.0 [4.0-10.0]	.31
Mean PAP, median [IQR], mm Hg	45.0 [38.0-53.0]	44.0 [38.0-52.0]	50.0 [43.0-56.0]	.01
PAWP, median [IQR], mm Hg	(n = 156) 5.0 [3.0-7.0]	(n = 121) 5.0 [3.0-7.0]	(n = 35) 5.0 [3.0-8.0]	.42
Cardiac index, median [IQR], L/min/m^2	2.5 [2.1-2.9]	2.6 [2.2-2.9]	2.3 [1.9-2.8]	.02
Total pulmonary resistance, median [IQR], WU	10.1 [7.0-11.5]	9.3 [6.8-11.9]	11.6 [10.3-14.1]	<.01
Total pulmonary resistance index, median [IQR], WU/m^2	18.1 [13.4-22.8]	16.7 [12.9-21.7]	20.6 [17.4-26.4]	<.01
Pulmonary vascular resistance, median [IQR], WU	(n = 156) 8.7 [6.1-11.5]	(n = 121) 8.2 [5.9-10.2]	(n = 35) 9.8 [9.1-12.6]	<.01
Pulmonary vascular resistance index, median [IQR], WU/m^2	(n = 156) 15.5 [11.6-20.5]	(n = 121) 14.4 [11.0-19.6]	(n = 35) 18.8 [15.1-23.3]	<.01
Pulmonary functional tests				
DLCO, median [IQR], %	(n = 76) 64.9 [51.0-75.5]	(n = 62) 65.5 [51.0-75.4]	(n = 15) 64.1 [47.9-82.4]	.73
Resting paO_2, median [IQR], mm Hg	(n = 121) 64.0 [57.3-74.0]	(n = 95) 64.1 [57.8-72.8]	(n = 26) 61.9 [55.4-77.5]	.87

CRP, C-reactive protein; *IQR*, interquartile range; *RAP*, right atrial pressure; *PAP*, pulmonary arterial pressure; *PAWP*, pulmonary arterial wedge pressure; *DLCO*, diffusing capacity for carbon monoxide). *Comparison between the 2 subgroups preoperative CRP levels lower or higher than the detection threshold (10 mg/L) (using the Mann–Whitney *U* test or χ^2 test). †Including implantable port, pacemakers, ventricular-arterial derivation. ‡Three patients received immunosuppressive therapy for history of systemic inflammatory disease (1 with lupus treated by hydroxychloroquine, 1 with Crohn disease treated by methotrexate, azathioprine and corticosteroids, and 1 with Wegener treated by azathioprine and corticosteroids); their CRP level was below 10 mg/L.

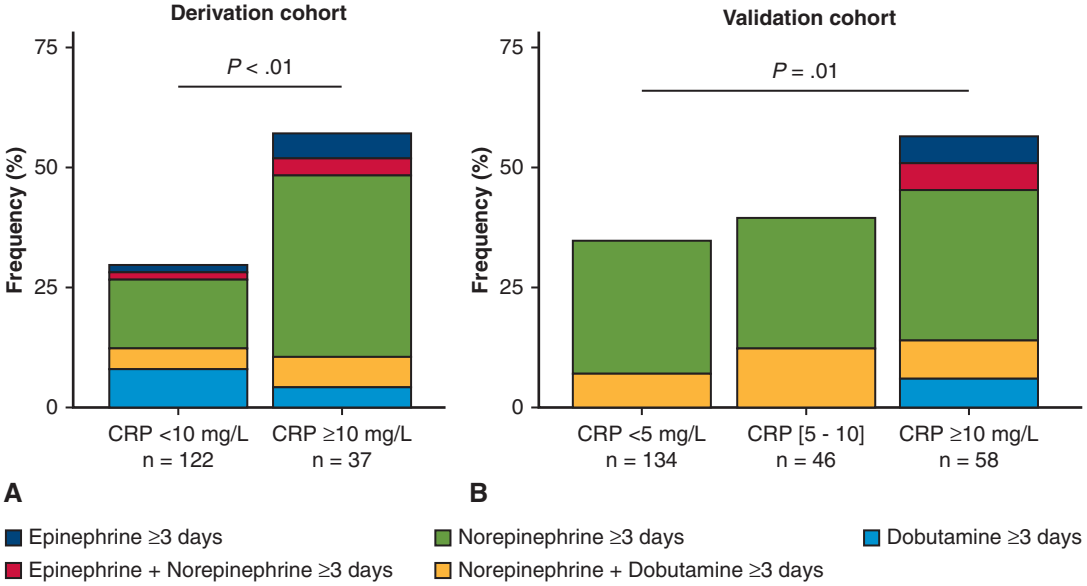


FIGURE 2. Frequency and type of inotropic (dobutamine) or catecholamine (norepinephrine and epinephrine) support ≥3 days postendarterectomy in the derivation (A) and validation cohorts (B), according to the preoperative plasma level of CRP. *P* value for comparison between CRP groups using the χ^2 test. *CRP*, C-reactive protein.

Statistical analyses were performed using SPSS, version 23.0 (IBM Corp, Armonk, NY).

RESULTS

Derivation Cohort (n = 159)

Median age was 63 [52-73] years (Table 1). Patients with CRP ≥10 mg/L had significantly lower cardiac index, greater MPAP, and greater resistance levels than patients with low CRP. In the subgroup of patients with complete echocardiographic data (n = 59), the 18 patients with CRP ≥10 mg/L had similar pulmonary vascular resistance than the 41 patients with low CRP (9.8 [8.9-11.3] WU vs 8.2 [6.0-11.7], $P = .22$) and similar cardiac index (2.4 [2.0-2.9] L/min/m^2 vs 2.5 [2.2-3.0] respectively, $P = .77$), as presented in Table E1. The RV size and function was similar in both groups as assessed by the RV end-systolic area index (12.8 [9.8-15.2] cm^2/m^2 in patients with low CRP vs 12.0 [9.8-15.5] in those with CRP ≥10 mg/L, $P = .74$), RV fractional area change (24.8 [21.4-27.9]% vs 25.5 [18.9-30.1] respectively, $P = .74$), RV longitudinal strain (16.0 [12.7-19.7]% vs 16.4 [11.8-18.4], $P = .77$) and the tricuspid annular plane systolic excursion (15.3 [12.8-18.0] mm vs 15.0 [10.8-19.4], $P = .93$).

When comparing the biological inflammatory features of patients with high (≥10 mg/L) and low CRP in the total derivation cohort (Table E2), patients with high CRP had greater neutrophil counts (4.7 [4.0-7.0] G/L vs 4.0 [3.2-5.0]) and monocyte counts (0.6 [0.5-0.7] vs 0.5 [0.4-0.6]) than patients with low CRP (both $P < .01$). Patients with high CRP had also higher levels of plasma fibrinogen (4.8 [4.3-5.5] mg/dL vs 3.7 [3.2-4.3]), interleukin-6 (24.1 [9.2-56.6] vs 6.3 [2.4-36.7]), and D-dimers (564.0 [315.0-1135.8] vs 350.0 [224.3-596.8]) than those with low CRP (all $P < .01$). Patients with high CRP had greater conjugated bilirubin levels than those with low CRP (3.0 [2.0-5.8] μmol/L vs 2.0 [2.0-4.0], $P < .01$); no patient had high CRP but normal other inflammatory markers because of liver failure (Table E2). Figure E1 illustrates the correlation heatmap of immune markers, highlighting the significant moderate correlation between CRP levels and fibrinogen ($r = 0.47$), interleukin-6 ($r = 0.38$), neutrophils ($r = 0.28$), and monocyte count ($r = 0.28$), all $P < .01$. CRP levels were also significantly correlated with D-dimer levels ($r = 0.27$, $P < .01$), but not with resistance or cardiac index. The Jamieson classification did not significantly differ between patients with high or low CRP levels ($P = .11$). There was no significant difference between the groups in term of cardiopulmonary bypass, aortic clamping, or circulatory arrest duration (all $P > .68$, Table E3).

At 30 days, 8 patients had died (Figure 1, *A*). Causes of death included persistent pulmonary hypertension associated with refractory right heart failure (n = 3), sepsis related to pneumonia (n = 3), and severe hemorrhage (n = 2). Median duration of intensive care unit stay was 8.0 [5.0-15.0] days, and median in-hospital stay duration was 18.0 [11.0-46.3] days. The primary composite endpoint was reached in 60 of 159 (37.7%) patients, most frequently in patients with preoperative high CRP (56.8% vs 32.0%, $P < .01$). Patients

TABLE 2. Univariate analysis of correlates of the primary endpoint (early death or heart-lung transplant or ECMO need or prolonged inotropic/catecholamine support) in the derivation cohort (n = 159)

Variables	Odds ratio* (95% confidence interval)	*P* value
Age, y	1.33 (0.98-1.75)	.20
Female sex	1.04 (0.55-1.97)	.92
History of splenectomy	3.38 (0.30-38.09)	.33
History of endovascular device	1.11 (0.30-4.10)	.88
Active or <3 y smoking	0.81 (0.23-2.86)	.74
NYHA class (reference class = II)		.02
III	1.18 (0.51-2.75)	.70
IV	4.38 (1.67-11.50)	<.01
6-min walk test distance, m	0.60 (0.40-1.00)	.04
Preoperative right heart catheterization (n = 159)		
Heart rate, bpm	1.75 (0.69-4.42)	.24
Right atrial pressure, mm Hg	1.39 (1.05-1.96)	.04
Mean pulmonary arterial pressure, mm Hg	1.30 (0.93-1.69)	.15
Cardiac index, mm Hg	0.97 (0.69-1.33)	.82
Total pulmonary resistance, WU	1.06 (0.78-1.43)	.71
Pulmonary vascular resistance, WU	1.10 (0.79-1.50)	.56
Preoperative laboratory data (n = 159)		
CRP ≥10 mg/L	2.79 (1.32-5.93)	<.01
LogCRP	1.42 (1.02-1.97)	.04
Fibrinogen, mg/dL	0.84 (0.71-1.40)	.96
Interleukin-1, ng/mL (n = 72)	0.61 (0.28-1.39)	.24
Interleukin-6, ng/mL (n = 78)	1.94 (1.25-3.70)	.01
MCP-1, ng/mL (n = 72)	1.00 (0.03-1.00)	.84
D-dimers, ng/mL	1.00 (0.99-1.79)	.93
Antithrombin III, %	1.15 (0.75-1.75)	.64
Leucocytes, G/L	1.54 (1.01-2.32)	.04
Neutrophils, G/L	1.46 (1.04-2.02)	.03
Monocytes, G/L	1.43 (1.02-2.01)	.04
Neutrophil/lymphocyte ratio	1.26 (0.81-1.96)	.31
Hemoglobin, g/dL	0.79 (0.56-1.10)	.16
Platelets, G/L	1.00 (0.41-1.00)	.83
Blood urea nitrogen, mg/dL	1.03 (0.87-1.22)	.74
Creatinine clearance <60 mL/min	2.03 (0.99-1.11)	.05
Aspartate transaminase, U/L	1.52 (0.79-2.96)	.21
Alanine transaminase, U/L	0.49 (0.24-0.98)	.04
Gamma-glutamyl transferase, U/L	0.77 (0.46-1.47)	.47
Alkaline phosphatase, U/L	1.38 (0.82-2.33)	.23
Total bilirubin, μmol/L	1.60 (0.88-2.94)	.13
Conjugated bilirubin, μmol/L	0.72 (0.33-1.56)	.41
BNP, pg/mL	1.55 (1.00-1.09)	.28
Preoperative echocardiograms (n = 59)		
RV end-diastolic area index, cm^2/m^2	2.75 (1.34-5.41)	<.01
RV end-systolic area index, cm^2/m^2	2.59 (1.32-4.89)	<.01
RV end-systolic remodeling index	3.46 (1.57-7.63)	<.01
RV fractional area change, %	0.56 (0.30-1.08)	.08
RV longitudinal strain, absolute %	0.68 (0.38-1.17)	.18
Tricuspid annular plane systolic excursion, mm	0.69 (0.40-1.24)	.23
Right atrial area index, mm Hg	2.28 (0.96-2.91)	.08
Perioperative data (n = 159)		
Jamieson classification (reference group = 1)		.01
Group 2	2.76 (0.58-13.15)	.20

(Continued)

TABLE 2. Continued

Variables	Odds ratio* (95% confidence interval)	*P* value
Group 3	6.57 (1.31-32.86)	.02
Group 4	12.00 (1.56-92.29)	.02
Associated cardiac procedure	1.72 (0.53-5.61)	.37
Cardiopulmonary bypass duration, min	2.08 (1.45-2.99)	.02
Aortic clamping duration, min	1.55 (1.25-1.93)	.01
Circulatory arrest duration, min	1.22 (0.82-1.63)	.31

NYHA, New York Heart Association; *CRP*, C-reactive protein; *MCP-1*, monocyte chemoattractant protein-1; *BNP*, B-type natriuretic peptide; *RV*, right ventricular. *Odds ratios are presented as odds ratio adjusted by the standard deviation of the continuous variable (OR^{SD}) for comparison purposes.

with CRP ≥10 mg/L required more frequently norepinephrine than those with low CRP (45.9% vs 21.3%, $P < .01$) (Figure 2, *A*). Regarding the secondary endpoints, 8 patients died or required heart-lung transplant, including 3 in the high CRP group versus 5 in the low CRP group ($P = .33$). Twelve patients reached the endpoint of "death or heart-lung transplant or ECMO need"; 4 in the high CRP group versus 8 in the low CRP group ($P = .42$). There was no difference in term of intensive care unit stay duration (9.0 [5.0-16.0] days in the high CRP group vs 8.0 [5.0-15.0] in the low CRP group) or mechanical ventilation duration (2.0 [1.0-7.0] days vs 1.0 [1.0-3.0], respectively).

Table 2 presents the univariable analyses for correlates of the primary endpoint. To minimize overfitting the multivariable model, only 5 variables were included in addition to age and sex: CRP ≥10 mg/L, New York Heart Association (NYHA) class IV and invasive RAP (both predictor of outcomes in univariate analysis and in previous cohorts with pulmonary hypertension), total pulmonary resistance (as a reflection of the disease severity; a similar model including pulmonary vascular resistance provided the same results), and aortic clamping duration (reflecting the duration of the procedure associated with the accessibility of lesions). On multivariable analysis, CRP ≥10 mg/L (odd ratio, 2.49 [1.11-5.61]; $P = .04$), NYHA class IV (4.98 [1.54-16.12], $P < .01$), and aortic clamping duration (1.55 [1.14-2.39], $P < .01$) were retained in the model for the primary endpoint ($\chi^2 = 23.7$; $P < .001$. CRP ≥10 mg/L was not associated with any of the secondary endpoints, except for prolonged inotropic or catecholamine need in univariable analysis (2.88 [1.10-7.52], $P = .03$) but was not retained in the multivariable model ($P = .09$).

Validation Cohort (n = 238)

Patients had similar demographics (median age 63.5 [50.0-70.0] years, with 46% female) and disease severity, reflected by hemodynamics and functional parameters, to those from the derivation cohort (Table E4). They were more frequently treatment-naïve than in the derivation cohort (88.7% vs 80.7%, $P = .03$). Patients with preoperative CRP ≥5 mg/L (n = 104), the limit of detection during the second study period, had significantly greater RAP (9.0 [5.0-11.0] mm Hg vs 7.5 [5.0-10.0], $P = .04$), greater MPAP levels (49.0 [40.0-55.0] mm Hg vs 43.0 [35.0-50.0], $P < .01$), and greater total pulmonary resistance levels (10.4 [8.4-13.5] WU vs 9.4 [6.8-12.6], $P = .04$) than patients with CRP <5 mg/L (n = 134), as presented in Table E4. Fifty-eight patients had CRP levels ≥10 mg/L, representing 24.4% of the total validation cohort and 55.8% of the CRP ≥5 mg/L subgroup.

At 30 days, 11 patients had died (Figure 1, *B*). Causes of death included persistent pulmonary hypertension associated with refractory right heart failure (n = 5), sepsis related to pneumonia (n = 4), severe hemorrhage (n = 1), and acute pancreatitis (n = 1). One patient underwent double-lung transplantation for refractory right heart failure within the same index hospitalization after 30 days. Median in-hospital stay was 16.0 [11.0-24.5] days and median duration of intensive care unit stay was 11.0 [4.0-18.0] days. Overall, 104 (43.7%) patients reached the primary endpoint. Using univariable analysis (Table 3), CRP ≥10 mg/L was associated with the primary endpoint, whereas CRP ≥5 mg/L did not reach significance. On multivariable analysis using the same variables as in the derivation cohort, age, CRP ≥10 mg/L and aortic clamping duration were retained in the model ($\chi^2 = 33.0$, $P < .001$, Table 3). Patients with high CRP required more frequently norepinephrine (46% if CRP ≥10, 4% if [5-10], 37% if <5 mg/L, $P < .001$) or epinephrine for ≥3 days (7%, 0% and 0% respectively, $P < .01$) than in those with low CRP (Figure 2, *B*). Regarding the secondary endpoint of death or transplantation (reached in 4.6% of patients), when testing the same variables in multivariable analysis, CRP ≥10 mg/L (6.55 [1.22-35.11], $P = .03$), aortic clamping duration (3.31 [1.63-5.25], $P < .01$), and NYHA class IV (10.18 [1.52-68.11], $P = .02$) were retained in the model ($\chi^2 = 32.5$; $P < .001$). Regarding the secondary endpoint of death or transplantation or ECMO need (reached in 10.5% of patients), when testing the same variables in multivariable analysis, CRP ≥10 mg/L (2.57 [1.02; 6.52], $P = .04$), aortic clamping duration (2.02 [1.41; 2.94], $P < .01$), and NYHA class IV (4.46 [1.64; 12.10], $P < .01$) were retained in the

TABLE 3. Logistic regression analysis of correlates of the primary endpoint (early death or heart-lung transplant or ECMO need or prolonged inotropic/catecholamine support) in the validation cohort (n = 238)

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio* (95% CI)	*P* value	Odds ratio* (95% CI)	*P* value
Age, y	1.73 (1.32-2.57)	<.01	1.73 (1.32-2.25)	<.01
Female sex	0.76 (0.45-1.27)	.29	–	–
Body mass index, kg/m^2	0.80 (0.60-1.06)	.08		
NYHA class (reference = I)		<.01		
II	0.36 (0.05-2.80)	.33		
III	0.93 (0.13-6.80)	.94		
IV	1.29 (0.16-10.30)	.81	–	–
6-min walk test distance, m	0.29 (0.28-3.46)	.16		
Right heart catheterization				
Right atrial pressure, mm Hg	1.09 (0.84-1.46)	.58	–	–
Mean pulmonary arterial pressure, mm Hg	1.97 (1.41-2.45)	<.01		
Cardiac index, mm Hg	0.65 (0.48-0.87)	<.01		
Total pulmonary resistance, WU	1.82 (1.33-2.43)	<.01	–	–
Pulmonary vascular resistance, WU)	1.66 (1.19-2.25)	<.01		
Laboratory data				
CRP ≥5 mg/L	1.58 (0.99-2.65)	.05		
CRP ≥10 mg/L	1.85 (1.02-3.36)	.03	1.89 (1.09-3.61)	.04
LogCRP	1.37 (1.05-1.92)	.02		
Creatinine clearance <60 mL/min	2.99 (1.68-5.34)	<.01		
Perioperative data				
Jamieson classification (reference group = 1)				
Group 2	0.73 (0.21-2.62)	.63		
Group 3	0.79 (0.21-2.98)	.73		
Group 4	2.00 (0.24-16.36)	.52		
Cardiopulmonary bypass duration, min	1.44 (1.09-1.84)	<.01		
Aortic clamping duration, min	2.06 (1.28-3.31)	<.01	1.63 (1.28-2.06)	<.01
Circulatory arrest duration, min	1.10 (0.85-1.43)	.47		

CI, Confidence interval; *NYHA*, New York Heart Association; *CRP*, C-reactive protein. *Odds ratios are presented as odds ratio adjusted by the standard deviation of the continuous variable (OR^{SD}) and their adjusted 95% CI for comparison purposes.

model ($\chi^2 = 25.4$; $P < .001$). CRP ≥10 mg/L was significantly associated with prolonged inotropic or catecholamine need in univariable analysis (1.32 [1.05-2.52], $P = .04$) but was not retained in the multivariable model ($P = .20$).

DISCUSSION

Our study confirms that high preoperative plasma CRP levels are associated with severe preoperative hemodynamics in patients with CTEPH referred for PEA. CRP ≥10 mg/L is associated with adverse early outcomes after PEA, independently of the pulmonary disease severity, as summarized in Figure 3 and Video 1.

CRP is a pentameric protein of hepatic origin whose plasma levels rise in response to inflammation. The main factor influencing the plasma level of CRP is its rate of production by the liver.[8] In our study, no patient had high CRP levels because of isolated liver failure without features of inflammation using other markers, confirming that high CRP levels reflects systemic inflammation in this population. The expression of CRP is predominantly under transcriptional control by the cytokine interleukin-6, and to a lesser extent interleukin-1 and tumor necrosis factor, secretion by macrophages, and T-cells.[15] The heatmap provides a visual representation of the inflammatory network in operable patients with CTEPH. As illustrated in the heatmap, CRP levels correlated with interleukin-6 level, fibrinogen level, and neutrophils and monocyte counts, confirming the activation of these proinflammatory pathways in CTEPH.

There is a strong body of evidence on the value of CRP as a prognostic biomarker in cardiovascular diseases, such as atherosclerosis,[9,16] left heart failure,[17,18] and pulmonary arterial hypertension. There have been fewer studies conducted in CTEPH.[6,19] Quarck and colleagues[6] reported elevated plasma levels of high-sensitive CRP in 79 patients with CTEPH (including 44 undergoing PEA). CRP levels, however, did not correlate with the disease severity and

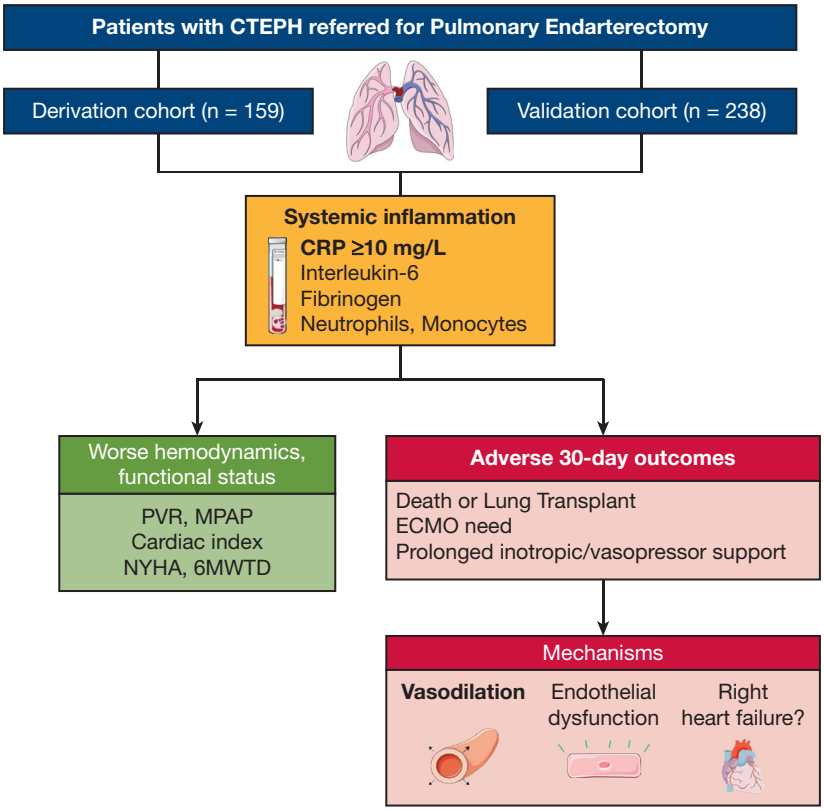
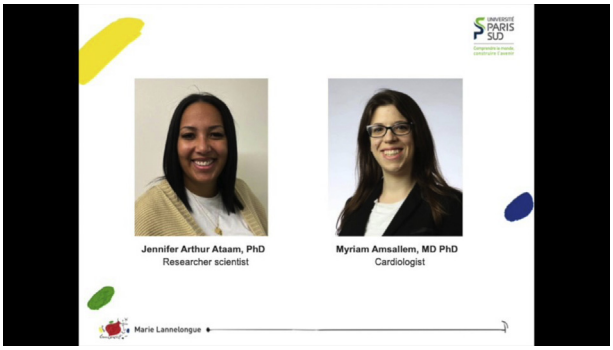


FIGURE 3. Summary of the prognostic value of preoperative CRP for early outcomes postendarterectomy in patients with operable CTEPH. Systemic inflammation (as assessed by CRP ≥10 mg/L) was associated with worse hemodynamics, functional status, and adverse 30-day outcomes. Potential mechanisms underlying these findings may include systemic inflammation-induced vasodilation and endothelial dysfunction rather than poor right ventricular adaptation to load. *CTEPH*, Chronic thromboembolic pulmonary hypertension; *CRP*, C-reactive protein; *PVR*, pulmonary vascular resistance; *MPAP*, mean pulmonary arterial pressure; *NYHA*, New York Heart Association dyspnea classification; *6MWTD*, 6-minute walk test distance; *ECMO*, extracorporeal membrane oxygenation.

were not predictive of outcomes in this study that may have been underpowered. Recently, high CRP levels has been shown to negatively correlate with the 6-minute walk test distance and RV function assessed using tricuspid annular plane systolic excursion in a large CTEPH cohort (n = 289, including 157 undergoing PEA).[19] CRP levels superior to 10 mg/L (determined by the receiver operating characteristic curve) were further associated with death or lung transplant need during the 57 [45-69] months follow-up, independently of pulmonary resistance. Our study further validates the prognostic value of CRP ≥10 mg/L for prediction of early outcomes postendarterectomy, independently of pulmonary resistance levels and duration of surgery.

In our derivation cohort, the association between high CRP levels (≥10 mg/L) and the primary endpoint was mainly driven by the ''prolonged catecholamine support'' component of the endpoint, suggesting a strong link between preoperative systemic inflammation and perioperative hemodynamic instability characterized by profound vasoplegia. This finding was confirmed in the validation cohort (with the same threshold of 10 mg/L, consistent with Skoro-Sajer and colleagues' threshold).[19] This latter, including all consecutive patients with confirmed CTEPH who underwent PEA during that era, had sufficient statistical power to further demonstrate the association between CRP ≥10 mg/L and 30-day transplant-free survival postendarterectomy. The effect of proinflammatory circulating cytokines on perioperative hemodynamic instability has been first investigated in a cohort of 14 patients undergoing PEA, reporting the positive correlation between perioperative maximum vasopressor support and peak levels of interleukin-6 that was also released during surgery (r = 0.82), suggesting cytokine-triggered vasoregulation.[5] CRP was, however, not investigated in this study. In CTEPH, the vascular effect of CRP has been mainly explored at the pulmonary arterial level. In vitro studies have shown that CRP stimulates pulmonary smooth muscle cell proliferation and induces endothelial



VIDEO 1. Co-first authors Drs Arthur Ataam and Amsallem comment the main results on the prognostic value of CRP for prediction of early postoperative outcomes after endarterectomy in CTEPH. *CRP*, C-reactive protein; *CTEPH*, chronic thromboembolic pulmonary hypertension. Video available at: https://www.jtcvs.org/article/S0022-5223(19)43490-9/fulltext.

dysfunction by increasing the expression of adhesion molecules[20-22] and after nitric oxide production, further inhibiting angiogenesis.[23]

The main clinical implication of our observational findings is to inform clinicians of the greater risk of poor early outcomes after PEA in patients with preoperative CRP $\geq$10 mg/L. In addition to perform ''the most complete'' endarterectomy achievable to decrease as much as possible the pulmonary vascular resistance, several protective approaches for both the right heart and the systemic circulation should be considered: reducing the aortic crossclamping time, the careful management of fluid infusion (to avoid RV volume overload while providing optimal systemic organ perfusion), close hemodynamic monitoring to tailor vasopressors and inotropes need, and finally the early implantation of mechanical circulatory support in case of refractory RV dysfunction and hemodynamic failure (to avoid irreversible multiorgan failure). Further interventional studies are required to explore the best timing of clinical interventions (such as mechanical circulatory support implantation) in patients with high CRP levels.

This study has several limitations that need to be acknowledged. The first limitation comes from the limited number of patients in the first period with preoperative CRP data measured, potentially exposing to a selection bias. We verified that the included cohort and the total cohort did not significantly differ in terms of preoperative demographic and hemodynamic characteristics. In addition, as CRP became routinely measured in the preoperative check-up before PEA in the second period, all patients from the validation cohort had CRP data available. The second limitation comes from the large number of multiple comparisons exposing to a type I error. The third limitation comes from the limited echocardiographic data available in a subset of patients limiting the extrapolation of RV phenotyping results. A negative correlation between CRP levels and RV function (either assessed by cardiac magnetic resonance–derived ejection fraction or by echocardiographic tricuspid annular plane systolic excursion) has been recently reported, although not adjusting for pulmonary resistance levels.[19,24] In our subgroup with echocardiographic data available, patients with high CRP had similar hemodynamics than those with low CRP, and similar RV size and function as assessed by comprehensive RV parameters, including strain. Further investigations with systematic RV phenotyping before and after PEA are needed to assess whether, after matching for afterload, patients with high CRP have different RV function or remodeling than those with low CRP, and whether preoperative inflammation is associated with worse RV adaptation to load and right heart failure after PEA. The fourth limitation derives from the absence of data on dynamic changes in CRP levels during and after surgery. Langer and colleagues[5] previously demonstrated that, in addition to preoperative increased levels of proinflammatory cytokines (such as interleukin-6), endarterectomy resulted in the release of these cytokines, particularly following deep hypothermic circulatory arrest. Finally, as data on maximal doses of vasopressors was not prospectively recorded, prolonged inotropic/vasopressor support was used to reflect hemodynamic instability.

CONCLUSIONS

Preoperative CRP levels $\geq$10 mg/L are associated with severe hemodynamics and poor early outcomes postendarterectomy in CTEPH. Patients with high CRP levels require more vasopressor support than those with low CRP, potentially secondary to inflammation-triggered systemic vasodilation.

Conflict of Interest Statement

Dr Jaïs reports grants and personal fees from Actelion, MSD, Bayer, and GlaxoSmithKline, outside the submitted work. Dr Humbert has participated to advisory boards and has given invited lectures for Actelion, Bayer, GlaxoSmithKline, and Merck. Drs Amsallem and Haddad report a research grant from Actelion. All other authors have nothing to disclose with regard to commercial support.

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Key Words: outcomes, pulmonary hypertension, endarterectomy, inflammation, chronic thromboembolic pulmonary hypertension

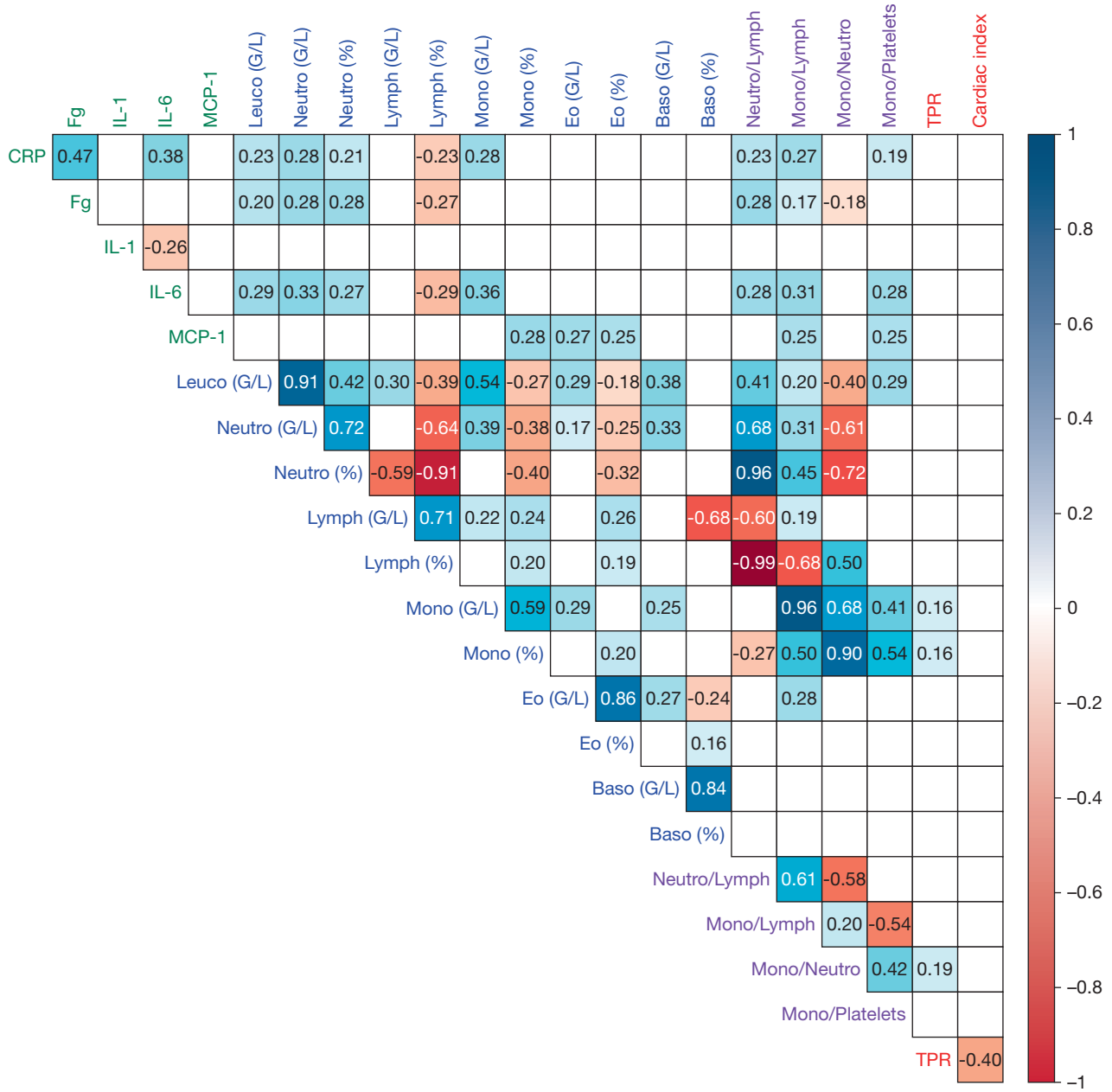

FIGURE E1. Correlation heatmap of immune markers and hemodynamics in the derivation cohort. Correlations are expressed using Spearman (rho) correlations between variables in all patients (n = 159), except for correlations with IL-1, IL-6, and MCP-1, only available in n = 72 patients. Only statistically significant correlations ($P < .05$) are shown. Correlations were similar when using pulmonary vascular resistance. *CRP*, C-reactive protein; *Fg*, fibrinogen; *IL-1*, interleukin-1; *IL-6*, interleukin-6; *MCP-1*, monocyte chemoattractant protein-1; *Leuco*, leucocytes; *Neutro*, neutrophils; *Lymph*, lymphocytes; *Mono*, monocytes; *Eo*, eosinophils; *Baso*, basophils; *TPR*, total pulmonary resistance.

TABLE E1. Comparative preoperative characteristics of the subgroup with available echocardiography data according to preoperative CRP levels

	Total cohort with echo, n = 59	CRP <10 mg/L, n = 41	CRP ≥10 mg/L, n = 18	*P* value*
Age, median [IQR], y	62.3 [50.3-72.3]	63.1 [48.4-72.3]	61.2 [48.9-73.4]	.97
Female sex, n (%)	24 (40.7)	17 (41.5)	7 (38.9)	.85
Body surface area, median [IQR], m^2	1.8 [1.6-2.0]	1.8 [1.6-2.0]	1.8 [1.7-2.0]	.90
New York Heart Association functional class, n (%)				.31
II	16 (27.1)	11 (26.8)	5 (27.8)	
III	38 (64.4)	28 (68.3)	10 (55.6)	
IV	5 (8.5)	2 (4.9)	3 (16.7)	
RAP, median [IQR], mm Hg	7.0 [4.0-10.3]	6.0 [3.5-11.0]	8.0 [5.0-10.0]	.67
Mean PAP, median [IQR], mm Hg	45.0 [35.0-53.0]	42.0 [35.0-52.5]	50.0 [44.5-55.3]	.15
Cardiac index, median [IQR], L/min/m^2	2.5 [2.1-3.0]	2.5 [2.2-3.0]	2.4 [2.0-2.9]	.77
Total pulmonary resistance, median [IQR], WU	10.4 [7.4-13.8]	10.1 [6.8-13.9]	11.2 [10.2-13.6]	.20
Pulmonary vascular resistance, median [IQR], WU	9.5 [6.6-11.2]	8.2 [6.0-11.7]	9.8 [8.9-11.3]	.22
RV end-diastolic area index, median [IQR], cm^2/m^2	17.1 [14.1-19.6]	17.3 [13.5-19.8]	16.9 [14.3-19.4]	.91
RV end-systolic area index, median [IQR], cm^2/m^2	12.4 [9.8-15.2]	12.8 [9.8-15.2]	12.0 [9.8-15.5]	.74
RV end-systolic remodeling index, median [IQR]	1.35 [1.24-1.43]	1.31 [1.23-1.43]	1.36 [1.24-1.45]	.49
RV fractional area change, median [IQR], %	24.9 [20.7-28.7]	24.8 [21.4-27.9]	25.5 [18.9-30.1]	.74
RV longitudinal strain, median [IQR], %	16.3 [12.4-19.2]	16.0 [12.7-19.7]	16.4 [11.8-18.4]	.77
Tricuspid annular plane systolic excursion, median [IQR], mm	15.0 [12.7-18.0]	15.3 [12.8-18.0]	15.0 [10.8-19.4]	.93
Right atrial area index, median [IQR], cm^2/m^2	11.6 [9.0-14.4]	12.6 [8.9-14.8]	10.0 [9.2-13.6]	.48
Severe tricuspid regurgitation, n (%)	1 (0.6)	1 (0.8)	0	.55
Estimated RAP, median [IQR], mm Hg	10.0 [10.0-15.0]	10.0 [10.0-15.0]	10.0 [10.0-17.5]	.92
Estimated RVSP, median [IQR], mm Hg†	n = 57 85.0 [66.0-99.5]	n = 40 80.5 [65.5-97.3]	n = 17 92.0 [72.5-107.5]	.23
Left ventricular ejection fraction, median [IQR], %	60.0 [60.0-65.0]	60.0 [60.0-65.0]	60.0 [60.0-65.0]	.65

CRP, C-reactive protein; *IQR*, interquartile range; *RAP*, right atrial pressure; *PAP*, pulmonary arterial pressure; *RV*, right ventricular; *RVSP*, right ventricular systolic pressure. *Comparison between the 2 subgroups preoperative CRP levels lower or higher than the detection threshold (10 mg/L) (using the Mann–Whitney *U* test or χ^2 test). †Estimated from the maximal velocity of the tricuspid regurgitation and the estimated RAP.

TABLE E2. Comparative preoperative biological characteristics of the derivation cohort according to preoperative CRP levels

	Total cohort, n = 159	CRP <10 mg/L, n = 122	CRP ≥10 mg/L, n = 37	*P* value*
Leucocytes, median [IQR], G/L	6.7 [5.6-8.1]	6.7 [5.4-7.9]	7.6 [6.0-9.6]	.03
Neutrophils, median [IQR], %	63.5 [56.4-70.9]	62.6 [55.2-69.9]	68.5 [58.3-72.9]	.04
Neutrophils, median [IQR], G/L	4.2 [3.2-5.6]	4.0 [3.2-5.0]	4.7 [4.0-7.0]	<.01
Lymphocytes, median [IQR], %	25.7 [18.1-31.7]	26.3 [20.0-31.9]	21.1 [16.7-30.3]	.03
Lymphocytes, median [IQR], G/L	1.7 [1.3-2.1]	1.8 [1.4-2.1]	1.6 [1.2-2.1]	.34
Monocytes, median [IQR], %	7.1 [5.8-9.0]	7.0 [5.6-9.0]	7.5 [6.1-9.4]	.31
Monocytes, median [IQR], G/L	0.5 [0.4-0.6]	0.5 [0.4-0.6]	0.6 [0.5-0.7]	<.01
Eosinophils, median [IQR], %	2.0 [1.4-3.1]	2.0 [1.4-3.2]	1.8 [1.3-3.1]	.34
Eosinophils, median [IQR], G/L	0.1 [0.1-0.2]	0.1 [0.1-0.2]	0.2 [0.1-0.2]	.76
Basophils, median [IQR], %	0.8 [0.6-1.0]	0.8 [0.6-1.1]	0.7 [0.5-0.9]	.23
Basophils, median [IQR], G/L	0.05 [0.04-0.07]	0.05 [0.03-0.07]	0.05 [0.04-0.07]	.99
Red blood cells, median [IQR], G/L	4.8 [4.3-5.2]	4.8 [4.3-5.2]	4.8 [4.1-5.2]	.67
Hemoglobin, median [IQR], g/dL	14.4 [13.4-15.9]	14.4 [13.3-15.9]	14.6 [13.5-16.0]	.73
Platelet count, median [IQR], G/L	244.0 [190.1-303.5]	236.0 [189.8-292.8]	265.0 [190.5-314.5]	.33
Neutrophil/lymphocyte ratio, median [IQR]	2.5 [1.9-3.9]	2.4 [1.8-3.5]	3.3 [1.9-4.4]	.03
Monocyte/lymphocyte ratio, median [IQR]	0.29 [0.22-0.41]	0.27 [0.21-0.37]	0.34 [0.28-0.51]	<.01
Monocyte/neutrophil ratio, median [IQR]	0.12 [0.09-0.15]	0.12 [0.09-0.16]	0.10 [0.09-0.15]	.64
Fibrinogen, median [IQR], mg/dL	4.0 [3.3-4.6]	3.7 [3.2-4.3]	4.8 [4.3-5.5]	<.001
Interleukin-1, median [IQR], ng/mL	n = 72 1.7 [0.6-4.3]	n = 50 1.6 [0.6-4.2]	n = 22 1.8 [0.7-4.6]	.77
Interleukin-6, median [IQR], ng/mL	n = 78 10.2 [2.9-39.9]	n = 54 6.3 [2.4-36.7]	n = 24 24.1 [9.2-56.6]	<.01
MCP-1, median [IQR], ng/mL	n = 72 399.5 [251.0-649.6]	n = 50 416.2 [227.7-671.1]	n = 22 352.6 [279.7-622.1]	.79
D-dimers, median [IQR], ng/mL	372.0 [239.8-677.3]	350.0 [224.3-596.8]	564.0 [315.0-1135.8]	<.01
Antithrombin III, median [IQR], %	103.0 [92.0-111.0]	101.5 [92.0-111.0]	104.0 [93.0-113.0]	.78
Blood urea nitrogen, median [IQR], mg/dL	7.3 [5.8-9.5]	7.0 [5.6-9.2]	8.2 [6.8-10.5]	<.01
Creatinine clearance, n (%) ≥60 mL/min 59-30 mL/min <30 mL/min	 52 (32.7) 103 (64.8) 4 (2.5)	 42 (34.4) 77 (63.1) 3 (2.5)	 10 (27.0) 26 (70.2) 1 (2.7)	 .70
Aspartate transaminase, median [IQR], U/L	28.0 [22.0-36.5]	26.0 [21.0-36.0]	31.0 [24.0-39.0]	.04
Alanine transaminase, median [IQR], U/L	25.0 [19.0-34.0]	25.0 [19.0-34.5]	24.0 [20.0-33.0]	.61
Gamma-glutamyl transferase, median [IQR], U/L	64.5 [35.0-119.5]	58.0 [33.8-105.0]	89.5 [51.3-157.5]	.04
Alkaline phosphatase, median [IQR], U/L	77.0 [61.5-100.5]	73.0 [60.0-97.0]	89.5 [65.5-105.0]	.13
Total bilirubin, median [IQR], μmol/L	14.0 [10.0-21.0]	14.0 [10.0-21.0]	14.5 [11.0-21.0]	.34
Conjugated bilirubin, median [IQR], μmol/L	3.0 [2.0-4.0]	2.0 [2.0-4.0]	3.0 [2.0-5.8]	<.01
Lactate dehydrogenase, median [IQR], U/L	247.0 [209.0-283.0]	236.0 [202.8-275.0]	264.0 [231.5-305.5]	.01
Creatine phosphokinase, median [IQR], U/L	84.0 [54.8-127.0]	78.0 [55.0-135.5]	86.0 [51.5-117.0]	.77
BNP, median [IQR], pg/mL	132.0 [39.5-393.5]	115.0 [31.8-319.5]	280.0 [101.0-626.0]	.04

CRP, C-reactive protein; *IQR*, interquartile range; *MCP-1*, monocyte chemoattractant protein-1; *BNP*, B-type natriuretic peptide. *Comparison between the 2 subgroups with preoperative CRP levels lower or higher than the detection threshold (10 mg/L) (using the Mann–Whitney *U* test or χ^2 test).

TABLE E3. Perioperative characteristics of the derivation cohort and comparison between patients with low versus high preoperative CRP levels

	Total cohort, n = 159	CRP <10 mg/L, n = 122	CRP ≥10 mg/L, n = 37	*P* value*
Jamieson classification				
Group 1, n (%)	14 (8.8)	10 (8.2)	4 (10.8)	
Group 2, n (%)	92 (57.9)	73 (59.8)	19 (51.4)	.11
Group 3, n (%)	44 (27.7)	35 (28.7)	9 (24.3)	
Group 4, n (%)	9 (5.7)	4 (3.3)	5 (13.5)	
Associated surgical procedure, n (%)†	12 (7.5)	10 (8.2)	2 (5.4)	.78
Cardiopulmonary bypass duration, median [IQR], min	222.0 [199.0-244.0]	222.0 [200.0-242.5]	222.0 [196.0-249.0]	.68
Aortic clamping duration, median [IQR], min	96.0 [85.0-112.3]	98.0 [85.5-111.5]	96.0 [83.0-119.5]	.91
Circulatory arrest duration, median [IQR], min	28.0 [23.0-35.5]	27.5 [23.0-35.0]	29.0 [22.0-36.0]	.79

CRP, C-reactive protein; *IQR*, interquartile range. *Comparison between the 2 subgroups with negative or positive preoperative CRP levels (using the Mann–Whitney *U* test or χ^2 test). †Including coronary arterial bypass graft or ascending aortic procedures.

TABLE E4. Characteristics of the validation cohort and comparison between patients with low and high preoperative CRP levels

	Total cohort, n = 238	CRP <5 mg/L, n = 134	CRP ≥5 mg/L, n = 104	*P* value*
Age, median [IQR], y	63.5 [50.0-70.0]	65.4 [51.8-71.1]	61.0 [48.6-69.0]	.11
Female sex, n (%)	110 (46.2)	59 (44.0)	51 (49.0)	.56
Body mass index, median [IQR], kg/m^2	25.8 [23.0-29.4]	26.0 [23.2-29.4]	25.5 [22.9-31.1]	.78
Presence of endovascular device, n (%)†	8 (3.4)	3 (2.2)	5 (4.8)	.27
History of splenectomy, n (%)	4 (6.7)	1 (0.7)	3 (2.9)	.19
New York Heart Association functional class, n (%)				
I	4 (6.7)	2 (1.5)	2 (1.9)	
II	60 (25.2)	38 (28.4)	22 (21.2)	.21
III	141 (59.2)	81 (60.4)	60 (57.7)	
IV	32 (13.4)	13 (9.7)	19 (18.3)	
Six-minute walk test distance, median [IQR], m	(n = 106) 384.5 [293.5-460.0]	(n = 68) 390.0 [293.3-460.8]	(n = 38) 371.5 [291.0-460.0]	.86
Hemodynamics				
RAP, median [IQR], mm Hg	8.0 [5.0-10.0]	7.5 [5.0-10.0]	9.0 [5.0-11.0]	.04
Mean PAP, median [IQR], mm Hg	45.0 [38.0-53.0]	43.0 [35.0-50.0]	49.0 [40.0-55.0]	<.01
Cardiac index, median [IQR], L/min/m^2	2.4 [2.0-2.8]	2.5 [2.1-2.8]	2.3 [2.0-2.8]	.05
Total pulmonary resistance, median [IQR], WU/index, median [IQR], WU/m^2	10.0 [7.3-13.3]/ 17.7 [13.9-24.3]	9.4 [6.8-12.6]/ 16.8 [12.8-22.8]	10.4 [8.4-13.5]/ 19.7 [14.5-27.2]	.04/ <.01
Pulmonary vascular resistance, median [IQR], WU/index, median [IQR], WU/m^2	(n = 189) 7.6 [5.0-10.8]/ 13.6 [10.1-19.7]	(n = 112) 7.3 [4.8-9.2]/ 13.1 [9.6-17.9]	(n = 77) 8.0 [5.7-11.7]/ 15.3 [10.5-22.6]	.09/ .08
Therapies				
Treatment naïve, n (%)	211 (88.7)	123 (91.8)	88 (84.6)	.08
Double therapy, n (%)	9 (3.8)	7 (5.2)	2 (1.9)	.19
Triple therapy, n (%)	2 (0.8)	0	2 (1.9)	.11
Prostanoid therapy, n (%)	9 (3.8)	0	9 (8.7)	<.01
Phosphodiesterase inhibitors, n (%)	8 (3.4)	4 (3.0)	4 (3.8)	.73
Endothelin receptor blockers, n (%)	15 (6.3)	8 (6.0)	7 (6.7)	.83
Riociguat, n (%)	8 (3.4)	2 (1.5)	6 (5.8)	.07
Statins, n (%)	29 (12.2)	14 (10.4)	15 (14.4)	.35
Laboratory data				
Creatinine clearance, n (%)				
≥60 mL/min	165 (69.3)	97 (72.4)	68 (65.4)	
59-30 mL/min	68 (28.6)	34 (25.4)	34 (32.7)	.22
<30 mL/min	0	0	0	
Jamieson classification				
Group 1, n (%)	10 (4.2)	4 (3.0)	6 (5.8)	
Group 2, n (%)	154 (64.7)	85 (63.4)	69 (66.3)	.56
Group 3, n (%)	68 (28.6)	42 (31.3)	26 (25.0)	
Group 4, n (%)	6 (2.5)	3 (2.2)	3 (2.9)	
Associated cardiac procedure, n (%)	12 (5.0)	2 (0.7)	10 (9.6)	<.01
Cardiopulmonary bypass duration, median [IQR], min	218.0 [193.5-251.0]	212.0 [194.0-250.0]	223.5 [193.3-255.3]	.35
Aortic clamping duration, median [IQR], min	97.0 [82.0-110.5]	97.0 [81.5-109.0]	98.0 [83.0-117.0]	.23
Circulatory arrest duration, median [IQR], min	30.0 [22.0-38.0]	30.5 [22.8-38.3]	28.0 [21.0-36.0]	.19

CRP, C-reactive protein; *IQR*, interquartile range; *RAP*, right atrial pressure; *PAP*, pulmonary arterial pressure. *Comparison between the 2 subgroups with preoperative CRP levels lower or higher than the detection threshold (5 mg/L) (using the Mann–Whitney *U* test or χ^2 test). †Including implantable port, pacemakers, ventricular-arterial derivation. None of the patients had chronic inflammatory disease.

THOR