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Outcomes of Multidisciplinary Care at a Chronic Thromboembolic Pulmonary Hypertension Center

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ABSTRACT

Recent international guidelines recommend a multidisciplinary evaluation and care model for patients with chronic thromboembolic pulmonary hypertension (CTEPH), but there is a paucity of supporting data. The aim of this study was to describe the outcomes of a multidisciplinary team approach to the comprehensive care of CTEPH patients. This single-center cohort study enrolled 166 consecutive adult patients undergoing CTEPH treatment evaluation from 2016 to 2022 at a tertiary care, academic regional referral and comprehensive CTEPH center with pulmonary thromboendarterectomy (PTE) and balloon pulmonary angioplasty (BPA) capabilities. Patients underwent PTE, BPA, or medical management after consensus evaluation by a multidisciplinary team including pulmonary hypertension physicians, surgeons, interventional cardiologists, and radiologists. 86% (142/166) of patients underwent interventional therapies; 100 (60%) underwent PTE and 42 (25%) BPA. Of the 24 (14%) medically treated patients, 13 patients were offered but deferred intervention; 11 patients had non-intervenable disease. 30-day mortality in both PTE and BPA was 0%. 1- and 3-year survival was 99% and 96% for PTE, 100% and 93% for BPA, 79% and 79% for medical management. Patients who underwent PTE had the best hemodynamic response (ΔPVR: PTE -278.8 ± 366.9 dyne/sec/cm^5; BPA -15.9 ± 171.8 dyne/sec/cm^5; medical -60.2 ± 233.1 dyne/sec/cm^5; $p = 0.001$), largest improvement in Borg Dyspnea Scale; [PTE −1.0 (−2.8 to 0.0), BPA + 0.5 (−0.8 to 5.0), medical +1.0 (0.75 to 3.0), $p = 0.01$], and most improvement in NYHA functional class [% improving at least 1 functional class: PTE 64% (47/73), BPA 18% (5/28), medical 21% (4/19), $p = 0.0004$].

1 | Background

Recovery from acute pulmonary embolism is often incomplete with up to 50% of patients reporting ongoing exercise limitation at 1 year despite appropriate anticoagulation [1]. Although several mechanisms underlie post-PE exercise limitation, 2%–9% of patients develop CTEPH following acute pulmonary embolism [2–4]. The high annual incidence of acute pulmonary embolism in the United States (US) along with the relatively low rates of definitive interventions for CTEPH—approximately 500 pulmonary thromboendarterectomy (PTE) surgeries and 300 balloon pulmonary angioplasties (BPA) per year—suggest a significant under-recognition and under-treatment of this highly morbid condition [5–9]. Traditionally, referral for and access to advanced CTEPH interventions have been limited by distance from a comprehensive CTEPH center [10, 11]. This

may partly account for undertreatment and highlights the need for data demonstrating specialized CTEPH interventions can be deployed at a regional level while not compromising patient outcomes.

The 7th World Symposium for Pulmonary Hypertension (WSPH) emphasizes mechanical intervention as the cornerstone of modern therapy for CTEPH [12]. Adoption of contemporary techniques for invasive treatments has been underreported and the results of pioneering centers have been reproduced in only a few international centers [13–16]. While PTE remains the gold standard, BPA is increasingly utilized. The highest volume CTEPH centers globally have the advantage of decades of surgical experience, while BPA has been slowly adopted over the past decade [9]. BPA indications, techniques, session frequency and lesion treatment feasibility are all areas of active investigation. Few centers around the world have expertise in both PTE and BPA, as this field rapidly evolves it is clear PTE and BPA represent complimentary pathways leading to optimal patient outcomes, rather than mutually exclusive treatment modalities.

Importantly, in this increasingly complex treatment space, the 7th WSPH statement on CTEPH emphasizes the importance of a multidisciplinary team in navigating the decisions around multimodal therapies [12]. The team should be comprised of experienced PTE surgeons, BPA interventionalists, pulmonary vascular medicine specialists, and cardiovascular radiologists. Regular multi-disciplinary case reviews combined with structured long-term follow-up facilitates optimal individualized therapeutic plans. Recognizing and providing access to the interplay between PTE, BPA, and medical therapy is critical to making therapeutic decisions that may unfold over the patient's lifetime. Here, we describe our initial experience establishing a regional comprehensive CTEPH center with a multidisciplinary team-based approach to evaluation and management.

2 | Methods

2.1 | Study Population

This study was approved by the Northwestern University Institutional Review Board (IRB#STU00219967, approved 9/25/2023). From 2016 to 2022, 166 consecutive CTEPH patients referred to a single university-based tertiary care center for management were evaluated by multidisciplinary CTEPH team and assigned to treatment with singular PTE, BPA or medical management. The multidisciplinary CTEPH team evaluating patients included a cardiac surgeon (SCM) who performed PTE, an interventional cardiologist (DS) who performed BPA, and a pulmonologist (MC) who heads the Pulmonary Vascular Disease (PVD) Program and cardiovascular radiologist (RA). Patients were seen by a pulmonologist or cardiologist with an expertise in pulmonary hypertension (PH) with evaluation of relevant imaging including echocardiography, V/Q scan, CT angiogram, pulmonary angiography, and right-heart catheterization. Subsequently, all cases were reviewed in a multidisciplinary conference, including specialists mentioned above, a radiologist specializing in cardiovascular imaging (RA), nurse coordinator, and advanced practice providers. If intervention was recommended patients were seen by a surgeon for PTE or interventional cardiologist for BPA. Echocardiogram and CT angiography were performed after PTE before discharge. Routine pulmonary angiography and right-heart catheterization was performed 3 months after PTE and last BPA session. A follow-up echocardiogram, 6-min walk test and CT angiogram were performed at 6 months post intervention. Patients were maintained on anticoagulation indefinitely. The general diagnostic and treatment workflow is shown in Figure 1A.

Endpoints included survival, improvement in pulmonary hemodynamics, and symptom improvement. Pulmonary hypertension was assessed using mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) during right-heart catheterization. Symptom improvement was evaluated using World Health Organization functional class and 6-min walk test.

Data analysis was performed by using the R Studio Version 4.3.1. Descriptive statistics (median and interquartile range or percentage and standard deviation) were provided for the selected covariates. χ^2 analyses for categorical values and Kruskal–Wallis analyses for continuous variables were utilized. Survival probability was estimated using the Kaplan–Meier method and analyzed by the log-rank test to compare invasively-treated and medically-treated patients.

3 | Results

Of 166 consecutive CTEPH patients who underwent formal review by our CTEPH multidisciplinary team, 142 patients (86%) underwent invasive treatment: 100 (60%) PTE and 42 (25%) BPA; 24 (15%) patients received medical therapy alone (Figure 1B). Of the 42 patients treated with BPA, 12 (29%) were deemed operable but chose not to undergo surgery (Figure 1C). The remaining 30 (71%) were deemed technically non-operable (distal disease) or prohibitive surgical risk given comorbidity burden. Of the 24 patients treated with medical therapy, 13 (54%) were candidates for intervention but opted against intervention or were operable candidates but either did not survive to surgery or were lost to follow-up. The remaining 11 (46%) were deemed to be non-operable and not eligible for BPA due to anatomy or comorbidity burden (Figure 1D). Ultimately, 155 (93%) were deemed eligible for either BPA or PTE intervention by the multi-disciplinary team.

Baseline characteristics for each group stratified by treatment strategy are shown in Table 1. Patients treated with PTE were younger with a median age of 54 (IQR 43–63) years, vs. those treated with BPA or medical management (BPA 67 years, IQR 63–78; medical therapy 71 years; IQR 58–79). Most patients who underwent PTE or BPA were on PH-directed medical therapy (PTE 54%, $n = 54$; BPA 55%, $n = 23$) at the time of their intervention. Patients were primarily treated with DOAC (PTE 61%, $n = 61$; BPA 74%, $n = 31$; medical therapy 65%, $n = 15$). PTE patients had a higher incidence of severe RV dysfunction (PTE 27%, $n = 27$; BPA 12%, $n = 5$; medical therapy 13%, $n = 3$, $p = 0.07$) and higher PVR (PTE 619.2 ± 357.9 dynes; BPA 455.5 ± 356.9 dynes; medical therapy 443.9 ± 159.8 dynes, $p = 0.002$).

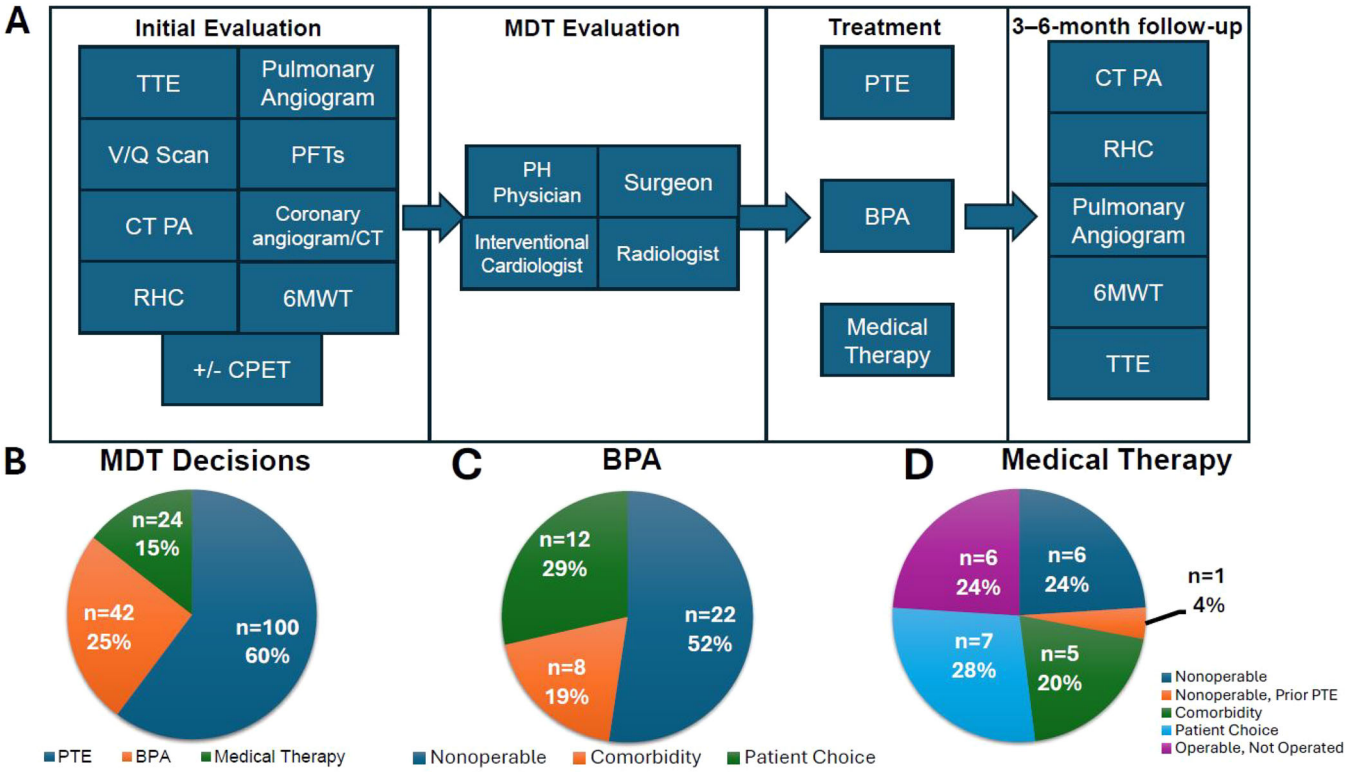

FIGURE 1 | (A) Diagnostic and treatment workflow for patient undergoing evaluation for CTEPH.(B–D) Outcomes of MDT treatment pathways. TTE = transthoracic echocardiogram, V/Q = ventilation/perfusion, PFTs = pulmonary function tests, CT = computed tomography, PA = pulmonary angiography, RHC = right heart catheterization, 6MWT = 6-min walk test, CPET = cardiopulmonary exercise testing. MDT = multidisciplinary team, PH = pulmonary hypertension, PTE = pulmonary thromboendarterectomy, BPA = balloon pulmonary angioplasty.

Thirty-day post-intervention mortality in both PTE and BPA groups was 0%. 1- and 3-year survival in the PTE cohort was 99% and 96%, respectively. Subsequently, 16%, $n = 16$ of PTE patients had BPA for either residual pulmonary hypertension or residual symptomatic limitation; of these 69% ($n = 11$) were free from PH-directed medical therapy on last follow-up. Of the 84 patients who did not undergo BPA after PTE, 87% ($n = 73$) were free from PH-directed medical therapy on last follow-up (Figure 2A). In patients who underwent BPA, 1- and 3-year survival was 100% and 93%. Of the 23 (55%) of patients on PH directed medical therapy undergoing BPA, none came off therapy at the end of study period. 1- and 3-year survival was 79% and 79% for patients treated with medical therapy. Kaplan–Meier survival estimates for 3-year survival are shown in Figure 3).

Hemodynamic and functional outcomes at 3- to 6-month follow-up are shown in Table 2. 73% ($n = 73$) of PTE patients completed their follow-up invasive investigations as compared to 18 of 42 (43%) of BPA and 10 of 24 (42%) medical management patients. Among the PTE, BPA and medical management groups, the average reduction in mPAP was 12.2 ± 15.6, 0.8 ± 10.4, and 1.2 ± 11.8 mmHg ($p = 0.15$); reduction in PVR was 278.8 ± 366.9, 15.9 ± 171.8, 60.2 ± 233.1 dynes/sec/cm^5 ($p = 0.001$), respectively. Similarly, in the PTE and BPA groups the 6-min walk test distance improved by an average of 128.9 ± 164.5 and 85.5 ± 127.1 m, respectively, but declined by 38.9 ± 105.9 in the medical management group ($p = 0.18$).

4 | Discussion

In this study we report the outcomes at a newly established regional comprehensive CTEPH center with both PTE and BPA capabilities. This study highlights a US center reporting outcomes driven by a multidisciplinary, multimodal approach to the management of CTEPH. Our main findings were: (1) Our multidisciplinary evaluation concluded that 93% of new CTEPH referrals were eligible for advanced mechanical interventions and 85% of referrals received either PTE or BPA; (2) Outcomes for advanced interventions were safe (30-day mortality 0%) and effective (improved hemodynamics and functional outcomes). (3) Similar to US and international registry data, survival was good in patients undergoing PTE (1-year 99%, 3-year 96%) and BPA (1-year 100%, 3-year 93%), but worse in patients undergoing medical therapy alone (1-year 73%, 3-year 73%) [17–20].

Several other findings were also of interest, especially in the context of recent international and US registry studies. First, most patients had been prescribed PH-directed therapy with 60% ($n = 99$) of the entire cohort on PH medication at initial evaluation. This represents a greater proportion of patients than reported in both the US CTEPH registry report with 44% on PH therapy, and in the second international CTEPH registry report with 33% of patients on PH therapy [19, 20]. Of note, we were not a participating center in the first US CTEPH registry report nor was there a PTE or BPA center in the Chicago metropolitan area at the time of registry initiation in 2015.

TABLE 1 | Preoperative patient characteristics.

Variable	PTE ($n = 100$)	BPA ($n = 42$)	Medical ($n = 24$)	p-value
Age, years	54 (43–63)	67 (53–78)	71 (58–79)	< 0.001
Female sex	61 (61)	30 (70)	15 (63)	0.44
Body mass index	32 (27–41)	31 (26–38)	31 (25–34)	0.48
NYHA functional class				
I	2 (2)	0 (0)	0	
II	19 (19)	9 (21)	6 (25)	
III	71 (71)	27 (64)	18 (75)	
IV	5 (5)	3 (7)	0	
Previous venous thromboembolism				
Deep vein thrombosis	56 (56)	22 (52)	16 (67)	
Pulmonary embolism	76 (76)	30 (71)	21 (88)	
Permanent central venous catheter	4 (4)	1 (2)	1 (4)	
Splenectomy	4 (4)	5 (12)	1 (4)	
Thyroid disease				
Hypothyroid history	7 (7)	10 (24)	4 (17)	
Hyperthyroid history	1 (1)	3 (7)	0 (0)	
Thrombophilia	16 (16)	8 (19)	3 (13)	
Cancer	6 (6)	5 (12)	6 (25)	
Inflammatory bowel disease	1 (1)	2 (5)	1 (4)	
Home oxygen	20 (20)	13 (31)	9 (38)	
Pulmonary hypertension-targeted therapy	54 (54)	23 (55)	22 (92)	
Riociguat mono	31 (31)	13 (31)	16 (66)	
Rio + ERA	5 (5)	4 (10)	2 (8)	
Rio + prostacyclin	2 (2)	1 (2)	1 (4)	
Rio + ERA + Prostacylin	1 (1)	—	—	
PDE5i mono	9 (9)	5 (12)	2 (8)	
PDE5i + ERA	2 (2)	1 (2)	1 (4)	
PDE5i + prostacyclin	3 (3)	1 (2)	—	
PDE5i + ERA + prostacyclin	1 (1)	1 (2)		
Anticoagulation				
Warfarin	30 (30)	9 (21)	8 (35)	
Direct anticoagulant	61 (61)	31 (74)	15 (65)	
Low molecular weight heparin	7 (7)	2 (5)	—	
Heparin	2 (2)		—	
6-Meter walk test (meters)	313.5 ± 148.3	306.9 ± 134	260.1 ± 128.0	0.14
Echo –Tricuspid regurgitation grade				0.317
0 (none)	1 (1)	1 (2)	0 (0)	
1 (trivial)	32 (32)	9 (21)	4 (17)	
2 (mild)	27 (27)	6 (14)	9 (38)	
3 (moderate)	26 (26)	12 (29)	9 (38)	
4 (severe)	13 (13)	2 (5)	2 (8)	
Missing data	1 (1)	12 (29)	—	
Missing data	1 (1)	12 (29)	—	

(Continues)

TABLE 1 | (Continued)

Variable	PTE ($n = 100$)	BPA ($n = 42$)	Medical ($n = 24$)	p-value
Echo—Right ventricular function				0.07
Normal	29 (29)	16 (38)	8 (33)	
Mild decrease	12 (12)	6 (14)	4 (17)	
Moderate decrease	30 (30)	4 (10)	9 (38)	
Severe decrease	27 (27)	5 (12)	3 (13)	
Missing data	2 (2)	11 (29)	—	
Echo—Right ventricular dilation				0.28
Normal	14 (14)	11 (26)	3 (13)	
Mild	10 (10)	6 (14)	4 (17)	
Moderate	28 (28)	4 (10)	7 (29)	
Severe	34 (34)	9 (21)	6 (25)	
Missing data	14 (14)	13 (31)	1 (4)	
Echo—Left ventricular ejection fraction	63 ± 7	64 ± 8	63 ± 6	0.69
Right heart catheterization				
Right atrial pressure	9.6 ± 5.7	8.8 ± 4.4	9.0 ± 5.8	0.81
Mean pulmonary artery pressure	45.0 ± 12.4	37.8 ± 12.6	41.3 ± 8.4	0.01
Pulmonary capillary wedge pressure	11.9 ± 5.0	12.5 ± 5.7	13.8 ± 5.3	0.26
Cardiac output	4.9 ± 1.4	5.2 ± 1.7	5.2 ± 1.2	0.18
Cardiac index	2.4 ± 0.7	2.7 ± 0.8	2.6 ± 0.6	0.04
Pulmonary vascular resistance	619.2 ± 357.9	455.5 ± 356.9	443.9 ± 159.8	0.002

Note: Values are mean ± SD, mean (IQR) or n (%).
Abbreviations: ERA, endothelin receptor antagonists; NYHA, New York Heart Association; PDE5i, phosphodiesterase type 5 inhibitor; Rio, Riociguat.

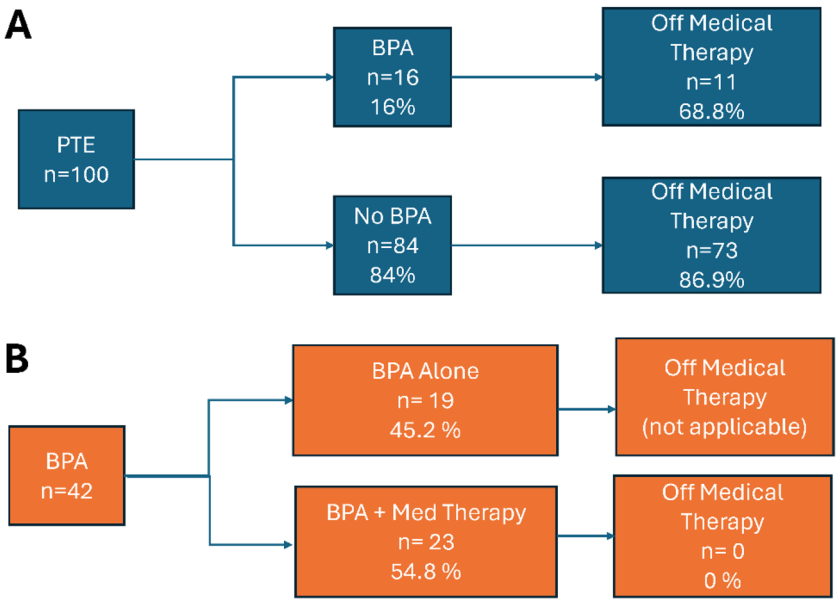

FIGURE 2 | Multimodal intervention pathways for chronic thromboembolic pulmonary hypertension (A, B). BPA = balloon pulmonary angioplasty, PTE = pulmonary thromboendarterectomy.

These findings likely represent prescribing practices in treatment "deserts" that lack local access to mechanical therapy options for CTEPH in the US. Although some data supports the use of medical therapy before BPA for certain subsets of patients with inoperable CTEPH to mitigate complication risk, data supporting this practice in patients awaiting PTE is lacking [21, 22]. Exploring the potential impact of initiation of PH medication on delayed referral for definitive mechanical intervention and outcomes of procedures is an important question that needs to be answered.

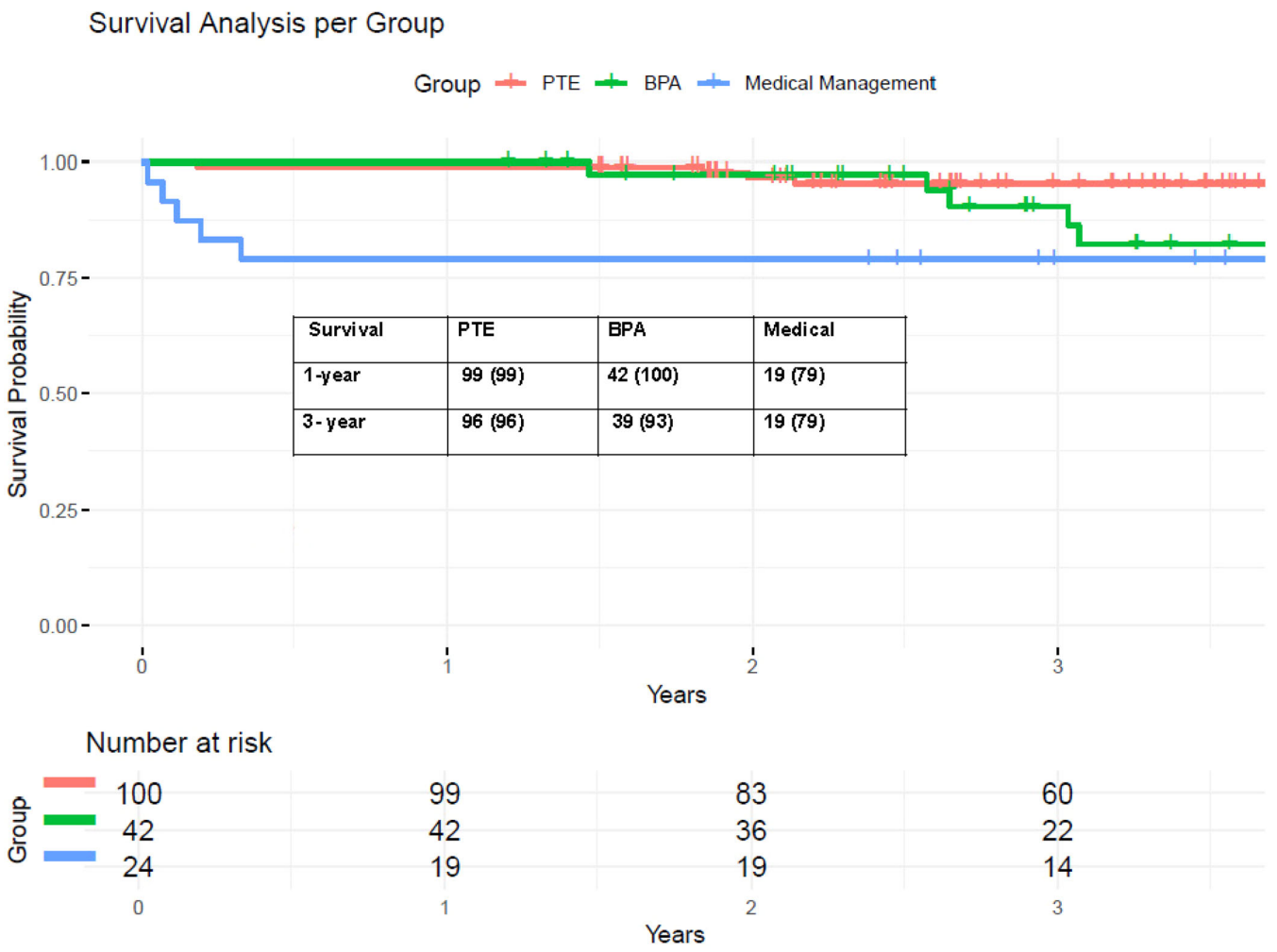

FIGURE 3 | Three-year Kaplan–Meier survival estimates per treatment group. BPA = balloon pulmonary angioplasty, PTE = pulmonary thromboendarterectomy.

Second, mechanical therapy selection at our center closely mirrored the second international CTEPH registry treatment modality distribution. In that report, 60% of patients underwent PTE and 18% underwent BPA compared to 60% undergoing PTE and 25% BPA in our series [19]. In contrast, in the US CTEPH registry, 76% of patients underwent surgery [20]. This treatment differential is likely attributable to equipoise in segmental level disease management (PTE vs. BPA) based on multidisciplinary evaluation including both a surgeon and interventionalist during the early procedural learning curve. Given overall good midterm survival outcomes in our study, in keeping with the recent international CTEPH registry data, this report likely supports BPA as an appropriate therapy for segmental level disease in terms of providing similar survival benefit [19].

Third, despite systematic follow-up, there were differences in available invasive hemodynamic data in the post-PTE, post-BPA, and medical therapy groups. We captured a high percentage (73%) of post-PTE patient's hemodynamic outcomes with right heart catheterization (RHC). Previously published functional and hemodynamic benefits of PTE from high volume single center series were re-demonstrated in this early surgeon experience series. However, capturing invasive hemodynamic data in the post-BPA and post-medical therapy patients was challenging. In the post-BPA group, noninvasive outcomes data was available in 45%–67%; however, only 43% had invasive hemodynamic data. Our group does not routinely capture complete invasive hemodynamic data at the time of BPA intervention, rather we attempt to obtain this data 3 months after the final BPA session. Travel distance to our center for follow up hemodynamics assessments after multiple therapeutic BPA sessions led to higher than anticipated rates of RHC refusal. We hypothesize the attenuated hemodynamic response to BPA in our cohort likely represents selection bias of patients who remain symptomatic with the least hemodynamic improvement agreeing to follow up RHC testing, especially since the functional outcome improvement in 6MWD and survival in the BPA group remained excellent and closer to international registry data. In the medical therapy group 83%–87% had noninvasive follow-up data while only 42% had invasive RHC data which tracks with our groups practice of foregoing routine hemodynamic testing in all patients on medical therapy.

This study has several important limitations. First, it is single-center registry data, with medical management and interventional outcomes not necessarily reproducible at all new centers.

TABLE 2 | Hemodynamic and physiologic outcomes.

	PTE ($n = 73$[a])	BPA ($n = 18$[a])	Medical ($n = 10$[a])	*p*-value
Follow-up time (d)	112.7 ± 57	416 ± 366.9	725.2 ± 599.4	
mPulmonary Atery Pressure—baseline	45.0 ± 12.4	37.8 ± 12.6	41.3 ± 8.4	
mPAP—follow up	29.9 ± 11.9	39.3 ± 11.0	40.5 ± 12.3	
Δ mPAP	−12.2 ± 15.6	−0.8 ± 10.4	−1.2 ± 11.8	0.15
PVR—baseline	619.2 ± 357.9	455.5 ± 356.9	443.9 ± 159.8	
PVR— follow up	279.1 ± 166.0.	378.3 ± 183.3	362.2 ± 226.0	
Δ PVR	−278.8 ± 366.9	−15.9 ± 171.8	−60.2 ± 233.1	0.001
	$N = 61$	$N = 19$	$N = 20$	
Follow-up time (d)	277 ± 154.3	665.2 ± 559.7	722.3 ± 610.4	
6-min Walk Test (min)—baseline	306.2 ± 149.8	306.9 ± 134	260.1 ± 128.0	
6-min Walk Test (min)—follow-up	373.4 ± 99.1	327.4 ± 111.3	260.0 ± 142.1*	
Δ 6-min Walk Test	+128.9 ± 164.5	+85.5 ± 127.1	−38.9 ± 105.9	0.18
Borg Dyspnea Scale—baseline	4.0 (2.0–5.0)	4.0 (3.0–6.8)	3 (1.8–4.3)	
Borg Dyspnea Scale—follow-up	1.0 (0.0-3.0)	3 (0.8–5)	3.5 (1.8–5)	
Δ Borg Dyspnea Scale	−1.0 (−2.8-0.0)	+0.5 (0.8-5.0)	+1 (0.75–3)	0.01
	$N = 73$	$N = 28$	$N = 21$	
Follow-up time (d)	146.6 ± 127.7	119 ± 94.5	240 ± 230.4	
NYHA Class—baseline—(median, IQR)	3 (3–3)	3 (3–3)	3 (2.75–3)	
NYHA Class—follow-up—(median, IQR)	2 (1.25–2)	3 (2–3)	3 (2–3)	
ΔNYHA functional classification	−1 (−1–0)	0 (0–0)	0 (0–0)	0.0004

Abbreviations: mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PVR, mean pulmonary vascular resistance.
[a]Number of subjects available with follow-up data.

While the practice group was in their initial procedural learning curve, the PH physician (MC) was experienced in the diagnosis of CTEPH and the surgeon (SCM) and interventionalist (DS) in this study were each highly experienced in thoracic aortic surgery (> 10 years) and percutaneous interventions for chronic thrombotic occlusions of the coronary arteries (> 7 years). Second, the follow-up adherence represents real-world data. Our ability to draw conclusions about the hemodynamic effects of BPA are limited, but functional and survival outcomes are similar to previous reports. Lastly, this study was not designed to compare procedural outcomes and thus is not powered to do so.

Overall, this study supports the notion that regional access to comprehensive CTEPH care, including both PTE and BPA, can lead to excellent hemodynamic and functional outcomes comparable to that reported at larger historic national centers. This is potentially a significant advance toward addressing under-recognition and under-treatment of the CTEPH population. As more centers adopt contemporary techniques and gain expertise in advanced interventions, the prospects for improved patient care and outcomes in CTEPH continue to progress.

5 | Conclusion

The findings of this study add to the growing body of evidence supporting a multidisciplinary approach to multimodal treatments in the framework of an academic CTEPH program.

Author Contributions

All authors contributed to the concept of the project and analysis and interpretation of data to draft and revise the manuscript. All authors approved the submitted manuscript.

Acknowledgments

The authors have nothing to report. All authors had access to study data for purposes of completing this manuscript.

Ethics Statement

This study was approved by the Northwestern University Institutional Review Board (IRB# STU00219967, approved 9/25/2023).

Conflicts of Interest

The authors declare no conflicts of interest.

Guarantor

S. Chris Malaisrie.

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