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Original Article

Improved cardiac function and quality of life with initial macitentan-tadalafil combination therapy compared to tadalafil alone in pulmonary arterial hypertension

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Abstract: Objectives: Pulmonary arterial hypertension (PAH) is a progressive disease leading to right ventricular failure. The purpose of this study was to evaluate the effects of macitentan combined with tadalafil versus tadalafil monotherapy on cardiac function and quality of life (QOL) in PAH patients. Methods: This retrospective analysis involved patients identified with PAH who commenced regular therapy between April 2024 and April 2025. Participants were divided into two groups according to their treatment regimen: tadalafil monotherapy (TM) and macitentan combined with tadalafil (MCT). Hemodynamic values, laboratory biomarkers, exercise capacity, and patient-reported outcomes were assessed at baseline and after 6 months of treatment. Results: In total, 217 patients were analyzed (TM group: 114; MCT group: 103). After 6 months, the MCT group demonstrated significantly greater improvements in mean pulmonary arterial pressure (38.73 vs. 40.31 mmHg, P=0.029), cardiac index (2.93 vs. 2.61 L/min/m^2, P<0.001), N-terminal pro-B-type natriuretic peptide (997.14 vs. 1058.20 fmol·ml^{-1}, P=0.034) and pulmonary vascular resistance (685.35 vs. 736.83 dyn·sec/cm^5, P=0.001) compared to the TM group. The MCT group also showed a longer 6-minute walk distance (422.27 vs. 387.94 m, P=0.013) and lower Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire symptom scores (0.84 vs. 0.95, P<0.001). Safety profiles were similar between groups (all P>0.05). Conclusions: Initial combination therapy with macitentan and tadalafil provides superior hemodynamic, functional, and QOL benefits compared to tadalafil monotherapy in patients with PAH.

Keywords: Pulmonary arterial hypertension, macitentan, tadalafil, cardiac function, quality of life

Introduction

Pulmonary arterial hypertension (PAH) is a serious progressive vascular disease marked by increased pulmonary artery pressure and pulmonary vascular resistance, resulting in right heart failure and elevated mortality [1, 2]. Clinically, it manifests as exertional dyspnea, fatigue, and activity limitation, severely impairing patients' quality of life (QOL) [3, 4]. Current treatments primarily target three pathways: the endothelin pathway, the nitric oxide-cyclic guanosine monophosphate (cGMP) pathway, and the prostacyclin pathway, which have improved prognoses [5]. However, a proportion of patients respond inadequately to monotherapy, highlighting the need for more effective strategies [6]. Initial combination therapy is increasingly recognized as a promising approach to simultaneously address multiple pathologic pathways [7]. Current guidelines recommend initial endothelin receptor antagonist- phosphodiesterase-5 inhibitor (ERA-PDE5i) combination therapy for intermediate- or high-risk PAH. However, in real-world practice, PDE5i monotherapy remains a first-line option for selected patients (e.g., milder disease, reimbursement constraints). However, evidence for the specific combination of macitentan and tadalafil versus tadalafil alone remains limited, particularly regarding comprehensive patient-reported outcomes and QOL. This study was designed to address this gap by evaluating the effects of macitentan-tadalafil combination versus tadalafil monotherapy on cardiac function, exercise capacity, and patient-centered quality of life in a real-world PAH cohort.

The pathogenesis of PAH is multifactorial, involving endothelial dysfunction, vasoconstric-

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tion, and vascular remodeling [8, 9]. Recent studies have emphasized the potential benefits of combination therapy for PAH, particularly the synergistic effects of ERA and PDE5i [10]. The endothelin (ET) system plays a key role, with ET-1 promoting vasoconstriction, smooth muscle cell proliferation, and fibrosis via endothelin A receptor (ETA) and endothelin B receptor (ETB) [11]. ERAs like macitentan block this pathway. The cGMP pathway is a crucial vasodilatory system that has been shown to interact at the molecular level, suggesting that simultaneous inhibition of endothelin signaling and enhancement of cGMP signaling may produce additive or even synergistic therapeutic effects [12, 13]. However, specific clinical data comparing macitentan combined with tadalafil versus tadalafil monotherapy remain limited, particularly in terms of long-term outcome and improvement in QOL.

Materials and methods

Ethical statement

This study was a retrospective study, using all data that have been anonymized and de-identified, without any effect on the treatment process or follow-up of the involved patients. The design and implementation of the study adhered to the ethical principles of the Declaration of Helsinki and have been approved by the Ethics Review Committee of Guangzhou Red Cross Hospital. Given that the study only involved the analysis of historical anonymous records and did not involve direct contact or intervention with patients, the ethics committee agreed to waive patient informed consent.

Study design

This was a retrospective cohort study. Through the hospital's electronic medical record system, patients with PAH who started regular treatment at our center between April 2024 and April 2025 and had at least 6 months of complete follow-up data were screened and included. All patients were definitively diagnosed with PAH by right heart catheterization (RHC). The study aims to assess the clinical advantages of combination therapy versus monotherapy by retrospectively analyzing the initial characteristics of the two patient groups, as well as their follow-up data at 6 months after the start of treatment.

As this was a retrospective analysis based on existing medical records, the treatment allocation was not randomized. Patients were grouped according to the regimen they had actually received during the study observation period, which was determined by their treating physicians based on individual clinical considerations, local practices, and patient factors prior to the study start.

Patients inclusion and grouping

Inclusion criteria included: (1) Aged 18 to 75 years; (2) Definitively diagnosed with PAH via right heart catheterization [14]; (3) Complete baseline clinical data and regular follow-up data for 6 months after the initiation of treatment.

Exclusion criteria were: (1) Other types of pulmonary arterial hypertension (such as those caused by left heart disease, pulmonary diseases); (2) Coexisting severe hepatic or renal insufficiency, active infection, or malignant tumors that could affect the evaluation; (3) Pregnant or lactating women; (4) Incomplete follow-up data.

According to the actual treatment regimen received by patients during the observation period, participants were categorized into two groups: the tadalafil monotherapy group (114 cases) and the macitentan combined with tadalafil group (103 cases).

Patients in the tadalafil monotherapy (TM) group took a fixed dose of oral tadalafil (5 mg, twice daily) continuously for 6 months. Patients in the macitentan combined with tadalafil (MCT) group took oral tadalafil (5 mg, twice daily) and additionally took oral macitentan (10 mg, once daily), with both drugs being used concurrently throughout the 6-month observation period.

Data collection

Baseline data: Initial data were retrieved from the hospital's electronic medical record system using a standardized procedure. Demographic basic information was recorded in a structured format within the system. The etiological clinical classification of PAH strictly followed the patient admission records, examination reports, and medical history, and was deter-

mined based on the classification standards of the World Symposium on Pulmonary Hypertension. Idiopathic PAH required exclusion of all known secondary factors; connective tissue disease-associated PAH needed clear diagnostic evidence of rheumatic and autoimmune diseases and confirmation by a specialist physician; congenital heart disease-associated PAH required confirmation of cardiac structural abnormalities via echocardiography or cardiac catheterization. The World Health Organization functional class (WHO FC) was retrospectively assessed according to the descriptive records of the patient's symptoms and activity capacity by the attending physician in the medical records, with the criteria being: Class I (no limitation of physical activity), Class II (slight limitation of physical activity, no symptoms at rest), Class III (notable restriction of physical activity, symptoms occur with minimal exertion), Class IV (symptoms at rest, unable to perform any physical activity) [14].

Hemodynamic and laboratory values: Pulmonary circulation pressure indicators were obtained through RHC. Right heart function and oxygenation parameters were simultaneously acquired during the RHC procedure. These procedures were performed by experienced cardiovascular physicians under sterile conditions in the catheterization laboratory. During the examination, a Swan-Ganz pulmonary artery catheter (774F75, Edwards Lifesciences, USA) was inserted via either the internal jugular vein or femoral vein route and advanced under fluoroscopic guidance to sequentially reach the right atrium, right ventricle, and ultimately be wedged into a branch of the pulmonary artery. Pulmonary artery pressure (PAP), mean pulmonary artery pressure (mPAP), right atrial pressure (RAP), and mean right atrial pressure (mRAP) were read and recorded in real-time via a pressure sensor (IntelliVue MX750, Philips, Netherlands) connected to the tip of the catheter. Pulmonary artery wedge pressure (PAWP) was measured after the catheter was wedged, by recording the downstream retrograde transmission of the pulmonary venous-left atrial pressure waveform through the sensor. All pressure waveform data were synchronously collected and stored using a dedicated physiological recording system (LabChart Pro, ADInstruments, Australia) in the catheterization laboratory. The average value of three consecutive, stable cardiac cycles was calculated to ensure data accuracy. Cardiac index was determined using the thermodilution method. A rapid injection of 10 ml of cold saline solution through the right atrial port of the catheter allowed for the measurement of temperature changes in the pulmonary arterial blood by a thermistor at the catheter tip, from which the cardiac output was automatically calculated by an internal computation module in the monitor and then divided by the patient's body surface area.

Mixed venous oxygen saturation (SvO_2) was measured by drawing a mixed venous blood sample from the pulmonary artery port of the catheter and immediately analyzing it using a bedside blood gas analyzer (ABL90 FLEX, Radiometer, Denmark).

Pulmonary vascular resistance (PVR) was calculated using the standard formula [(mean pulmonary artery pressure - pulmonary artery wedge pressure)/cardiac output], while total pulmonary resistance (TPR) was calculated as [mean pulmonary artery pressure/cardiac output]. The data for pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac output used in these calculations were sourced from the aforementioned right heart catheterization. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels reflecting cardiac involvement were quantitatively detected using a fully automated electrochemiluminescence immunoassay analyzer (Cobas e 801, Roche Diagnostics, Switzerland) and accompanying reagent kits, by collecting fasting venous blood samples from patients in the morning, allowing them to stand, and then centrifuging to obtain serum.

Exercise capacity and clinical outcomes: Exercise capacity was evaluated using the 6-minute walk distance (6MWD). The measurement of the 6MWD strictly followed the guidelines of the American Thoracic Society, conducted on a flat, straight corridor indoors that is 30 meters long [15]. The test was operated and recorded by researchers who had received unified training. Before the test, researchers explained the procedure to the patients. During the test, standardized encouragement phrases were used, and clear markers were placed at the starting point and the turnaround point. At the end of six minutes, the total walking distance

(in meters) was accurately recorded. Based on the actual measured values of 6MWD before and after treatment for each patient, the proportion with a decline of more than 15% from baseline was calculated.

The recording of adverse events during the treatment period was completed by reviewing the patient's medical records. All adverse event information was sourced from outpatient or inpatient medical records within the 6-month follow-up period, which included doctors' proactive inquiries, physical examination records, and corresponding diagnoses. Symptoms such as headache and cough relied on patient-reported descriptions. Signs like peripheral edema were based on descriptions in the physical examination sections of the medical records. Diagnoses of upper respiratory tract infections, nasopharyngitis, bronchitis, etc., required corresponding clinical symptoms (such as sore throat, runny nose, sputum production) and clear diagnostic records by the doctor as evidence.

Patient-reported quality of life: The Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire (PAH-SYMPACT) is a disease-specific tool used to quantify the symptom burden associated with PAH and its impact on patients' lives [16]. The questionnaire includes 16 symptom items (covering dyspnea, fatigue, chest pain, etc.) and 25 impact items (assessing the impact on daily activities, social interactions, and emotions), scored using a 5-point Likert scale (0 = never/no impact, 4 = always/extreme impact). The average score of all items in each dimension was calculated, with higher scores indicating more severe symptoms or greater disease effect.

The 36-Item Short Form Health Survey (SF-36) was used to assess overall health status [17]. The questionnaire covers eight health domains, which are converted into a Physical Component Summary (PCS) and a Mental Component Summary (MCS) using standard algorithms. Both summary scores are standardized, with a scoring range of 0-100 points; higher scores suggest better health-related QOL.

Statistical analysis

All statistical evaluations were conducted utilizing R software (version 4.4.3; R Foundation for Statistical Computing, Austria). Continuous variables were first assessed for normal distribution utilizing the Shapiro-Wilk test. All continuous data in this study conformed to a normal distribution and were described as mean ± standard deviation (Mean ± SD). Between-group comparisons of continuous variables were conducted using independent samples t-tests. Categorical variables were described as frequencies and percentages [n (%)], with between-group comparisons performed using chi-square tests. All tests were two-sided, with $P<0.05$ considered indicative of statistical significance.

Results

Baseline clinical characteristic

Table 1 shows the baseline demographic and clinical characteristics of the study population. There were no significant differences between the TM group and the MCT group in terms of gender, age, body mass index (BMI), education level, time since PAH diagnosis, and PAH classification (all $P>0.05$). Additionally, the distribution of WHO functional class showed no significant variation ($P=0.959$). These results indicated that two groups are comparable concerning demographic and baseline clinical characteristics in this study.

Hemodynamic and laboratory values

Pulmonary circulation pressure results showed that at baseline, there were no notable differences in PAP, mPAP, and PAWP across the two groups (all $P>0.05$). After treatment, although PAP and PAWP did not show significant differences between the two groups ($P>0.05$), the mPAP in the MCT group was significantly lower than that in the TM group ($P=0.029$), indicating that after treatment, the MCT group was more effective than the TM group in reducing mean pulmonary artery pressure (**Figure 1**).

At baseline, RAP, mRAP, cardiac index, and SvO_2 did not show significant differences between the two groups (all $P>0.05$). After treatment, although the differences in RAP and mRAP did not reach statistical significance ($P>0.05$), the cardiac index in the MCT group was significantly higher compared to the TM group ($P<0.001$), indicating that the MCT group was more effective in improving cardiac pump-

Table 1. Basic demographic and clinical characteristics of the study participants

Marker	TM group (N=114)	MCT group (N=103)	t/χ^2	P
Gender (Female/Male)	80 (70.18%)/34 (29.82%)	78 (75.73%)/25 (24.27%)	0.843	0.359
Age	47.39 ± 5.17	46.88 ± 4.91	0.747	0.456
BMI	23.78 ± 2.63	23.47 ± 2.78	0.840	0.402
Highest Education Attained			0.974	0.614
Middle School or Below	23 (20.18%)	25 (24.27%)		
High School	49 (42.98%)	46 (44.66%)		
Higher than High School	42 (36.84%)	32 (31.07%)		
Time from diagnosis of PAH (years)	4.89 ± 1.52	4.81 ± 1.36	0.415	0.679
PAH classification			None	0.956
Idiopathic PAH	61 (53.51%)	58 (56.31%)		
Heritable PAH	4 (3.51%)	2 (1.94%)		
Associated with connective tissue disease	35 (30.70%)	33 (32.04%)		
Associated with congenital heart disease	9 (7.89%)	7 (6.80%)		
Associated with HIV	1 (0.88%)	1 (0.97%)		
Drug or toxin induced	4 (3.51%)	2 (1.94%)		
WHO FC			0.307	0.959
I	6 (5.26%)	4 (3.88%)		
II	52 (45.61%)	48 (46.60%)		
III	45 (39.47%)	42 (40.78%)		
IV	11 (9.65%)	9 (8.74%)		

TM: tadalafil monotherapy; MCT: macitentan combined with tadalafil; BMI: body mass index; PAH: pulmonary arterial hypertension; HIV: human immunodeficiency virus; WHO FC: World Health Organization functional classification.

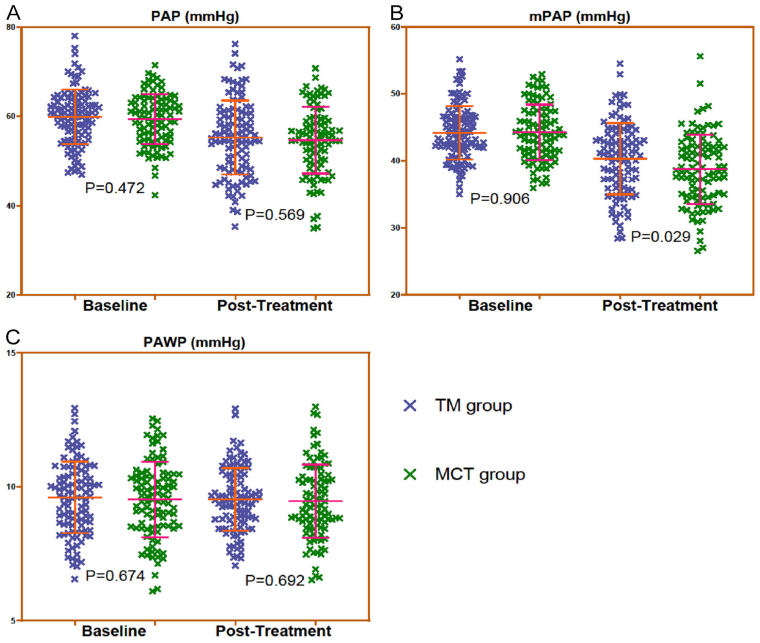

Figure 1. Pulmonary circulatory pressure measurements. A. PAP (mmHg); B. mPAP (mmHg); C. PAWP (mmHg). TM: tadalafil monotherapy; MCT: macitentan combined with tadalafil; PAP: pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure.

ing function. Additionally, the SvO_2 in the MCT group was also significantly higher than that in the TM group after treatment (P=0.044), suggesting that the MCT group may be more effective in improving blood oxygenation levels. These results suggest that compared to TM, MCT treatment may have a more positive impact on enhancing patients' cardiac function and blood oxygenation status (**Table 2**).

At baseline, PVR, NT-proBNP, and TPR did not show significant differences among the two groups (all P>0.05). After treatment, the PVR in the MCT group was significantly reduced compared to the TM group (P=0.001), indicating that MCT was more effective in reducing pulmonary vascular resistance. Additionally, the NT-proBNP levels in the MCT group were also significantly lower than those of the TM group (P=0.034), suggesting that MCT may have a more positive effect on cardiac function.

Table 2. Right heart function and oxygenation values

Marker	TM group (N=114)	MCT group (N=103)	t	P
Baseline				
RAP (mmHg)	9.02 ± 1.69	9.07 ± 1.79	0.192	0.848
mRAP (mmHg)	8.08 ± 2.43	8.12 ± 2.41	0.122	0.903
Cardiac index (L/min/m^2)	2.42 ± 0.34	2.39 ± 0.28	0.566	0.572
SvO_2 (%)	65.22 ± 5.71	64.74 ± 5.59	0.627	0.531
Post-Treatment				
RAP (mmHg)	8.12 ± 1.75	7.78 ± 1.55	1.541	0.125
mRAP (mmHg)	6.65 ± 1.34	6.53 ± 1.41	0.659	0.510
Cardiac index (L/min/m^2)	2.61 ± 0.67	2.93 ± 0.53	3.900	<0.001
SvO_2 (%)	64.80 ± 4.69	66.11 ± 4.82	2.028	0.044

RAP: right atrial pressure; mRAP: mean right atrial pressure; SvO_2: central venous oxygen saturation.

Table 3. Pulmonary vascular resistance and cardiac involvement biomarkers

Marker	TM group (N=114)	MCT group (N=103)	t	P
Baseline				
PVR (dyn·sec/cm^5)	976.12 ± 396.70	954.65 ± 331.55	0.430	0.668
NT-proBNP (fmol/ml)	1070.31 ± 208.44	1052.54 ± 184.30	0.662	0.509
TPR (WU)	14.54 ± 1.86	14.62 ± 1.94	0.329	0.742
Post-Treatment				
PVR (dyn·sec/cm^5)	736.83 ± 114.34	685.35 ± 120.97	3.222	0.001
NT-proBNP (fmol/ml)	1058.20 ± 216.68	997.14 ± 203.16	2.135	0.034
TPR (WU)	8.24 ± 1.49	7.81 ± 1.32	2.256	0.025

PVR: pulmonary vascular resistance; NT-pro BNP: N-terminal pro-B-type natriuretic peptide; TPR: total pulmonary resistance.

Table 4. Change in 6-minute walk distance

Marker	TM group (N=114)	MCT group (N=103)	t/χ^2	P
Baseline	334.55 ± 116.52	338.42 ± 112.94	0.248	0.804
Post-Treatment	387.94 ± 104.51	422.27 ± 96.82	2.502	0.013
Decrease of More Than 15% from Baseline	17 (14.91%)	6 (5.83%)	4.715	0.030

Furthermore, the TPR in the MCT group showed a significant decrease relative to the TM group after treatment (P=0.025), showing that MCT is more effective in reducing total peripheral resistance. These results suggest that compared to TM, MCT treatment may have more significant effects in improving pulmonary vascular resistance, cardiac function, and reducing total peripheral resistance (**Table 3**).

Exercise capacity and clinical outcome

At baseline, there was no notable difference in the 6MWD between the two groups (P=0.804). After treatment, the 6MWD in the MCT group showed a significant increase compared to the TM group (P=0.013), pointing to the MCT group was more effective in improving patients' activity capacity. The proportion of patients with a decline of more than 15% from baseline also exhibited a significant distinction between the two groups (P=0.030), with fewer patients in the MCT group experiencing a decline in walk distance of more than 15%, suggesting that MCT may be more effective than TM in maintaining or improving patients' exercise endurance (**Table 4**).

For adverse events such as upper respiratory tract infections, peripheral edema, nasopharyngitis, bronchitis, and cough, there was no significant variation between the two groups (all P>0.05). The incidence of headache app-

Table 5. Treatment-emergent adverse events

Marker	TM group (N=114)	MCT group (N=103)	χ^2	P
Upper Respiratory Tract Infection	13 (11.40%)	11 (10.68%)	0.029	0.865
Peripheral Edema	14 (12.28%)	8 (7.77%)	1.210	0.271
Nasopharyngitis	11 (9.65%)	10 (9.71%)	0.000	0.988
Bronchitis	6 (5.26%)	7 (6.80%)	0.226	0.635
Cough	16 (14.04%)	13 (12.62%)	0.093	0.760
Headache	11 (9.65%)	19 (18.45%)	3.515	0.061

Table 6. PAH-SYMPACT questionnaire scores

Marker	TM group (N=114)	MCT group (N=103)	t	P
Baseline				
Symptom	1.50 ± 0.26	1.47 ± 0.27	0.921	0.358
Impact	1.63 ± 0.31	1.59 ± 0.29	0.988	0.324
Post-Treatment				
Symptom	0.95 ± 0.25	0.84 ± 0.21	3.644	<0.001
Impact	1.19 ± 0.33	1.13 ± 0.35	1.228	0.221

PAH-SYMPACT: Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire.

roached significance among the two groups (P=0.061), with more patients reporting headaches in the MCT group compared to the TM group, although this discrepancy did not attain statistical significance. These data implies that TM and MCT had similar safety profiles (**Table 5**).

Patient-reported QOL

At baseline, the PAH-SYMPACT questionnaire scores for both Symptom and Impact did not show significant differences between the two groups (all P>0.05). After treatment, the symptom score in the MCT group showed a significantly lower value compared to the TM group (P<0.001), indicating that MCT is more effective than TM in alleviating patient symptoms. Although the impact scores did not reveal a significant distinction between two groups after treatment (P=0.221), the MCT group showed a trend of slightly lower scores. These results suggest that compared to TM, MCT may be more effective in relieving patient symptoms and have a greater impact on improving patients' QOL (**Table 6**).

No significant differences were found in the physical and mental scores between the two groups (all P>0.05) at baseline. After treatment, the physical health score in the MCT group was significantly greater compared to in the TM group (P=0.006), demonstrating that MCT is more effective than TM in improving patients' physical health. Regarding mental health scores, although the MCT group had slightly higher scores than the TM group, this difference was not statistically significant (P=0.055). These results suggest that MCT shows a significant advantage in enhancing the QOL for PAH patients, particularly in terms of physical health (**Figure 2**).

Discussion

This retrospective analysis offers evidence that initial combination therapy with macitentan and tadalafil offers superior clinical benefits compared to tadalafil monotherapy in PAH patients. Over a six-month period, the dual-targeted approach was more effective in improving hemodynamic abnormalities, enhancing cardiac performance, increasing exercise tolerance, and reducing symptom burden.

One of the most significant findings of this study was the observed reduction in mPAP in the combination therapy group. Macitentan, as a dual endothelin receptor antagonist, mitigates the potent vasoconstrictive and proliferative effects of endothelin-1 by blocking both ETA and ETB receptors, thereby reducing vascular tone and remodeling [18]. Tadalafil enhances vasodilation and inhibits smooth muscle proliferation by augmenting the nitric oxide-cGMP pathway [19, 20]. The greater reduction in mPAP seen with combination therapy suggests additive or synergistic effects on pulmonary vasodilation, a hypothesis supported by previous randomized controlled trials such as AMBITION, which demonstrated that ambrisentan-tadalafil combination therapy was superior

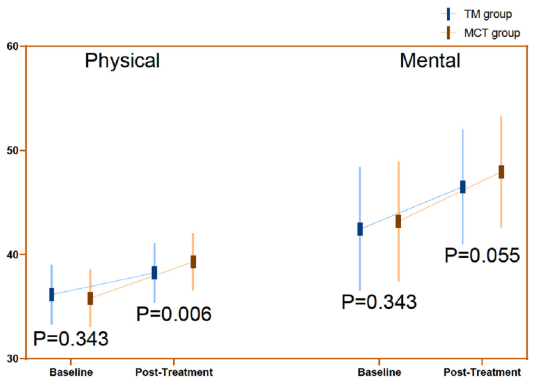

Figure 2. SF-36 health survey score. SF-36: 36-Item Short Form Health Survey.

to monotherapy in reducing clinical failure events, partly due to improved hemodynamics [21].

Accompanied by a reduction in afterload, the cardiac index improved in the combination therapy group. This is a crucial finding as it reflects an increase in right ventricular output and pumping efficiency, going beyond mere decompression to achieve functional improvement [22, 23]. The improvement in cardiac index may be due to the combined effects of reduced pulmonary vascular resistance, improved myocardial perfusion, and decreased wall stress, potentially mediated by a direct positive inotropic effect [24]. The sensitivity of right ventricular function to pharmacologic interventions has been demonstrated in other clinical contexts, where different anesthetics were shown to exert differential effects on right ventricular performance [25]. The concurrent increase in SvO_2 further underscores the enhancement in cardio-pulmonary efficiency. Higher SvO_2 indicates a better balance of tissue oxygen extraction, which could be attributed to increased cardiac output delivering more oxygenated blood, improved ventilation-perfusion matching due to pulmonary vasodilation, and reduced peripheral oxygen demand due to decreased cardiac workload [26]. This aligns with prior research indicating that reductions in PVR and mPAP are linked to improvements in right ventricular efficiency and physical activity capacity [27].

PVR is a more specific measure of precapillary vascular obstruction, while TPR reflects the total impedance faced by the right ventricle. The decline in PVR following combination therapy suggests a more effective reversal or improvement of the pathological vascular remodeling and vasoconstriction characteristic of PAH [28]. This is consistent with the known antiproliferative properties of both classes of drugs. The parallel reduction in NT-proBNP levels, a sensitive biomarker of right ventricular wall stress and dysfunction, provides biochemical evidence of hemodynamic improvement [29]. Lower NT-proBNP levels in the combination group indicate less cardiac strain, which may have favorable effects on right ventricular remodeling. These findings are consistent with earlier studies on ERA/PDE5i combinations, which demonstrated that compared to monotherapy, reductions in PVR and NT-proBNP reinforce the mechanistic basis for dual-pathway inhibition to target the multifaceted drivers of increased vascular resistance and ventricular pressure [30].

The improvement in exercise tolerance demonstrates that these hemodynamic and biochemical advantages translate into tangible clinical benefits. Patients receiving combination therapy showed an increase in the 6MWD and a lower incidence of clinically meaningful declines compared to baseline. This improvement may stem from the increased cardiac output, reduced pulmonary pressure, and enhanced systemic oxygen delivery discussed earlier, allowing patients to engage in physical activities with less breathlessness and fatigue [31]. Additionally, the lower proportion of patients showing a decline in 6MWD suggests that combination therapy may more effectively maintain functional status. This outcome echoes the functional benefits seen in major combination trials and underscores that improvements in hemodynamics can successfully translate into enhanced patient activity and endurance [32].

The safety profile observed in this study is reassuring. The frequency of common adverse events was similar between the groups. Although the trend toward a higher incidence of headaches in the combination therapy group failed to reach statistical significance, it is biologically plausible. Both classes of drugs are vasodilators, and headache is a known side effect believed to be related to cerebral vasodilation [33]. This observation indicates that the combination of macitentan and tadalafil is generally well-tolerated in clinical practice, con-

sistent with the established safety profiles of their respective monotherapies and in combination registration trials [34]. Similar findings have been reported in the hypertension literature: a meta-analysis comparing amlodipine/ACEI combination therapy versus amlodipine monotherapy found that the combination group had a significantly lower overall rate of adverse events (RR: 0.86) and a markedly reduced incidence of edema (RR: 0.40), although cough was more frequent (RR: 3.28), demonstrating that combination therapy can improve tolerability by reducing dose-dependent side effects of individual agents [35].

The improvements in PAH-SYMPACT and SF-36 scores in the combination therapy group highlight the patient-centered benefits of this treatment strategy. The symptom burden of PAH is closely related to hemodynamic status, so the observed reductions in mPAP and PVR may translate into decreased dyspnea, fatigue, and chest discomfort, all reflected in lower symptom scores [36]. The improvement in the physical component of SF-36 further emphasizes that patients experienced tangible benefits in their daily functioning. Although not reaching statistical significance, the trend toward improved impact and mental scores suggested potential benefits for daily activities and emotional well-being. Our findings help bridge this gap for the macitentan-tadalafil combination, indicating that its comprehensive physiologic benefits are indeed perceptible and meaningful to patients, addressing critical therapeutic goals beyond extending survival.

Several constraints in this study must be considered. Firstly, the retrospective design introduced inherent selection bias, as treatment allocation was not randomized and confounding variables may influence the results. The single-center nature of the study limits the extendability of the findings to a broader audience, more diverse patient population, especially considering potential differences in disease severity and comorbidities across different healthcare settings. Secondly, the follow-up period was limited to six months. While this duration was sufficient to observe initial hemodynamic and functional responses, the long-term sustainability of these benefits, their effect on long-term morbidity, and effects on mortality remain unknown and require investigation over a longer period.

Subsequent research should seek to confirm these findings through prospective through prospective, multicenter randomized controlled trials and extend the follow-up period to assess the durability of benefits and their impact on survival. Research into the molecular mechanisms underlying the observed synergistic effects can illuminate additional therapeutic targets and inform personalized treatment strategies.

Conclusion

This study suggests that starting combination therapy with macitentan and tadalafil is linked to better outcomes in hemodynamics, exercise capacity, and patient-reported symptoms compared to tadalafil monotherapy. These insights advocate for the inclusion of tadalafil as part of a preferred treatment strategy for patients with pulmonary arterial hypertension.

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Disclosure of conflict of interest

None.

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