**SUPPLEMENTARY METHODS**

**Hemodynamic measurements of MCT rats**

Rats were intubated with a 16-gauge intravenous cannula for mechanical ventilation after anesthetized with Zoletil® 50 (Virbac, Colombia, IN, USA). The right ventricular systolic pressure (RVSP) and left ventricular systolic pressure were measured to evaluate pulmonary artery pressure.[1]After hemodynamic measurements, the animals were sacrificed, and lung tissue was collected for histological and molecular profiling. The ratio of RV weight to left ventricular (LV) plus septal weight (RV/LV+S) was calculated to obtain Fulton’s index measurements.[2]

**Histology and immunohistochemical analysis of pulmonary arteries**

Lung specimens were managed using PBS washing through the pulmonary artery, fixed in 4% formalin, and embedded in paraffin. Tissue sections with 4 µM in each slice were stained with Elastica van Gieson (EVG) for morphometric analysis. Lung sections were stained using alpha-smooth muscle actin (α-SMA) for immunofluorescence. Lung sections were mounted with the antifade reagent in the presence of 4′,6-diamidino-2-phenylindole (DAPI) (Invitrogen, Waltham, MA, USA). Images were quantified using an image analyzer (LEICA Q550 IWB).

**Blood tests assay for human**

The blood sample was collected from PAH patients after they signed the informed consent documents. The blood samples were centrifuged at 3000rpm for 10 minutes into serum or plasma under 4℃ centrifugal immediately. After centrifuged, the blood samples were de-identified and stored in -80℃ refrigerator, preserved in biobank research database. The study then applied to the biobank to get the permission of using the de-identified blood samples for study. The average time these blood sample were stored depends on the interval between application and permission. Blood sample of the present study were stored for the average of 2 weeks to 1 month. Hematology tests included white blood cells, red blood cells, hemoglobin, hematocrit, red blood cell volume distribution, platelets, neutrophils, lymphocytes, prothrombin time, international normalized ratio, and partial thromboplastin time; the biochemistry panel consisted of sodium, blood urea nitrogen (BUN), serum creatinine (Cr), estimated glomerular filtration rate (eGFR), fasting plasma glucose level, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, and lactate dehydrogenase. Moreover, lipid profile was measured by analyzing total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels; circulating biomarkers including NT-proBNP, homocysteine, von Willebrand factor, uric acid (UA), d-dimer, and C-reactive protein (CRP) were analyzed. Furthermore, angiopoietin-2, bone morphogenetic protein (BMP)-2, BMP4, cluster of differentiation 40 (CD40), endoglin, interlukin-6, myeloperoxidase (MPO), osteopontin (OPN), and vascular endothelial growth factor (VEGFR) were analyzed using multiplex immunoassays.

**Multiplex immunoassay of human blood**

Anticoagulated blood samples were centrifuged to separate plasma. Plasma aliquots were stored at -80°C until use. A magnetic bead-based multiplex assay was used to quantify interlukin-6, endoglin, angiopoietin-2, myeloperoxidase (MPO), Osteopontin (OPN), vascular endothelial growth factor (VEGF), bone morphogenetic protein (BMP)-2, BMP-4, and cluster of differentiation 40 (CD40), using a 9-plex assay in a 96-well plate (R & D Systems, Minneapolis, MN, USA). The sample dilutions, reagents, and standards were prepared according to the manufacturer’s instructions. Each sample was analyzed in duplicate using the LUMINEX 200 system (Luminex Corp., Austin, TX, USA) and reported as the median fluorescence intensity. Data were analyzed using a 4-parameter logistic regression equation to interpolate standard curves with xPONENT 4.2 software (Luminex) and expressed as pg/mL.[3]

**Haemodynamics and cardiopulmonary function tests of human**

The World Health Organization (WHO) functional class (Fc), six-minute walking distance (6MWD), peak oxygen consumption, ventilatory equivalents for carbon dioxide (VE/VCO2), N-terminal prohormone of BNP (NT-proBNP), heart rate, right atrial pressure, cardiac output (CO), cardiac index (CI), pulmonary artery saturation, superior vena cava (SVC) saturation, inferior vena cava (IVC) saturation, mean arterial pressure, mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), pulmonary vascular resistance (PVR), LV ejection fraction, peak tricuspid regurgitation peak gradient, total lung capacity, forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO) were analyzed using hemodynamic and cardiopulmonary function tests.

**Risk level assessment**

Each parameter was graded between 1–3 points according to cut-off values proposed in the ESC/ERS model.[4] The sum of all grades, including WHO Fc, 6MWD, peak oxygen consumption, VE/VCO2, NT-proBNP, heart rate, right atrial pressure, CO, CI, and pulmonary artery saturation were divided by the number of available variables and rounded to the next integer to define the risk group.

**REFERENCES**

[1] Huang WC, Ke MW, Cheng CC, Chiou SH, Wann SR, Shu CW, et al. Therapeutic Benefits of Induced Pluripotent Stem Cells in Monocrotaline-Induced Pulmonary Arterial Hypertension. PLoS One. 2016;11:e0142476.

[2] Chi PL, Cheng CC, Hung CC, Wang MT, Liu HY, Ke MW, et al. MMP-10 from M1 macrophages promotes pulmonary vascular remodeling and pulmonary arterial hypertension. Int J Biol Sci. 2022;18:331-48.

[3] Fraser DD, Cepinskas G, Slessarev M, Martin C, Daley M, Miller MR, et al. Inflammation Profiling of Critically Ill Coronavirus Disease 2019 Patients. Critical Care Explorations. 2020;2.

[4] Damås JK, Otterdal K, Yndestad A, Aass H, Solum NO, Frøland SS, et al. Soluble CD40 ligand in pulmonary arterial hypertension: possible pathogenic role of the interaction between platelets and endothelial cells. Circulation. 2004;110:999-1005.