Performance of DETECT PAH algorithm according to the hemodynamic definition of pulmonary arterial hypertension (PAH) in the 2022 ESC/ERS guidelines: Early detection of pulmonary arterial hypertension in systemic sclerosis patients.

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Tweet: The #DETECT pulmonary arterial hypertension (PAH) algorithm according to the 2022 ESC/ERS Guidelines hemodynamic definition remains applicable to screen for #PAH in patients with #SystemicSclerosis

ABSTRACT (240/250 words)

Objective

The evidence-based DETECT pulmonary arterial hypertension (PAH) algorithm is frequently used in systemic sclerosis (SSc) patients to help clinicians screen for PAH by using non-invasive data to recommend patient referral to echocardiography, and if applicable, for a diagnostic right heart catheterization (RHC). However, the hemodynamic definition of PAH was recently updated in the 2022 ESC/ERS guidelines. The performance of DETECT PAH in identifying patients with a high risk of PAH according to this new definition was assessed.

Methods

In this *post-hoc* analysis of DETECT, which comprised 466 SSc patients the performance of the DETECT PAH algorithm in identifying patients with a high risk of PAH as defined in the 2022 ESC/ERS guidelines (mean pulmonary arterial pressure [mPAP] >20 mmHg, pulmonary capillary wedge pressure [PCWP] ≤15 mmHg, pulmonary vascular resistance [PVR] >2 Wood Units was assessed using summary statistics and was descriptively compared to the known performance of DETECT PAH as defined in 2014 when it was developed (mPAP ≥25 mmHg and PCWP ≤15 mmHg).

Results

The sensitivity of DETECT PAH in identifying patients with a high risk of PAH according to the 2022 ESC/ERS definition was lower (88.2%) compared to the 2014 definition (95.8%). Specificity improved from 47.8% to 50.8%.

Conclusion

The performance of the DETECT algorithm to screen for PAH in SSc patients is maintained when PAH is defined according to the 2022 ESC/ERS hemodynamic definition, indicating that DETECT remains applicable to screen for PAH in SSc patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT00706082

INTRODUCTION

Systemic sclerosis (SSc) patients have a high risk of pulmonary arterial hypertension (PAH), with an estimated prevalence of 4-12% based on right heart catheterization (RHC) (1–4). Screening programs in SSc patients are recommended and can lead to prompt PAH diagnosis, early treatment and better prognosis (3, 5–7). This has recently been reflected in the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, which recommend the DETECT algorithm in adult patients with SSc of >3 years' disease duration, a forced vital capacity (FVC) ≥40%, and a pulmonary diffusing capacity for carbon monoxide (DLCO) <60%, to identify asymptomatic patients with PAH (5, 6). The DETECT study (NCT00706082) developed an evidence-based detection algorithm for PAH in SSc patients (7). DETECT uses clinical and laboratory data alongside echocardiography to recommend patient referral for RHC (10), which is required to confirm PAH diagnosis (8, 9). The DETECT algorithm is highly sensitive, minimizes false negatives and can help identify milder PAH (7).

When the DETECT algorithm was developed, pre-capillary pulmonary hypertension (PH) was hemodynamically defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg (10). the 6th World Symposium on PH (6WSPH) to update the hemodynamic definition of PH, by lowering the mPAP threshold to >20 mmHg and to include PVR ≥3 wood units (WU) as part of the hemodynamic definition of pre-capillary PH (11). Alternative PVR thresholds for pre-capillary PH were also discussed, as there is evidence that a PVR >2 WU is abnormal, and associated with reduced long-term survival (12, 13). These proposed updates have recently been confirmed in the 2022 ESC/ERS guidelines,

which updated the definition of PH to mPAP >20 mmHg, and included a PVR >2 WU in the definition of pre-capillary PH (5, 6).

The DETECT algorithm, developed based on the PH/PAH definition that prevailed at the time of its development, is established in clinical practice and widely used (14) to recommend echocardiography and diagnostic RHCs to SSc patients when applicable (7). In this analysis, we examined the performance of the DETECT algorithm in screening for PAH when PAH is hemodynamically defined according to the 2022 ESC/ERS guidelines.

PATIENTS AND METHODS

Study design

DETECT (NCT00706082) was a large, international, multicenter, real-world, cross-sectional study (7). DETECT was the first study to develop an evidence-based algorithm using non-invasive data for PAH in SSc patients. DETECT was conducted in accordance with the Declaration of Helsinki, its amendments, followed the International Conference on Harmonization Guideline for Good Clinical Practice, and was approved by local institutional review boards / ethics committees (Supplementary Appendix I). All patients provided written informed consent.

The DETECT algorithm is a two-step, internally validated process for screening of PAH in SSc patients (7). In Step 1, the patient is evaluated for non-echocardiographic variables and receives a risk score based on these variables. These include: FVC % predicted / DLCO % predicted, current / past telangiectasias, serum anticentromere antibodies, serum N-terminal probrain natriuretic peptide, serum urate, and right axis deviation (electrocardiogram). The total score of Step 1 determines whether the patient should be referred to echocardiography and thus undergo Step 2. In Step 2, two echocardiographic variables (right atrium area, tricuspid regurgitant jet velocity) are evaluated and combined with the previous risk score from Step 1. Step 1 can also directly be combined with Step 2. This overall risk score then recommends an RHC to confirm suspected PAH.

Patient population

DETECT (7) enrolled patients aged ≥18 years with a diagnosis of SSc (diagnosed according to the American College of Rheumatology criteria (15) with a duration of >3 years from first non-Raynaud's symptom and a predicted DLCO of <60% (to increase

the proportion of patients at higher risk of PAH). The exclusion criteria included confirmation of PH by RHC prior to enrollment, use of PH-specific therapy, an FVC <40% of predicted, renal insufficiency, previous evidence of clinically relevant left heart disease, or pregnancy. During DETECT, data were collected on a broad range of variables within the following four groups; (1) demographic and clinical parameters; (2) serum tests; (3) electrocardiography; (4) echocardiography. The confirmatory diagnosis by RHC was performed subsequent to this data collection to minimize bias. RHC and echocardiography were conducted according to standardized procedures. All patients who had an RHC during the DETECT study (7) were included in this *post-hoc* analysis. Patients were classified as non-PH, World Health Organization (WHO) Group 1 PH (PAH), WHO Group 2 PH, or WHO Group 3 PH. For the main analysis, patients were classified according to the updated hemodynamic definitions for PAH recommended in the 2022 ESC/ERS guidelines (5, 6) (Supplementary Table 1): **Non-PH:** mPAP ≤20 mmHg; **PH:** mPAP >20 mmHg; **PAH:** mPAP >20 mmHg, PCWP ≤15 mmHg, PVR >2 WU and (FVC >70% or [FVC 60-70% plus high resolution computed tomography (HRCT) showing mild-moderate or no parenchymal lung disease]); **WHO Group 2 PH** (PH due to left heart disease): mPAP >20 mmHg, PCWP >15 mmHg; **WHO Group 3 PH** (PH due to lung disease / hypoxia): mPAP >20 mmHg, PCWP ≤15 mmHg, PVR >2 WU and (FVC <60% or [FVC 60-70% plus HRCT not available or showing moderate-severe parenchymal lung disease]). In an additional analysis, patients were classified as above, but the PVR threshold ≥3 WU that was proposed at the 6WSPH was used to define PAH (6WSPH definition; Supplementary Table 1) (11).

Analysis and statistical methodology

In this post-hoc study, the published algorithm, a CE (Conformité Européenne)-marked product, was evaluated without further development. The reported performance evaluation is research based only and does not apply to the claimed performance of the CE-marked product. The DETECT algorithm was applied to all patients as in the original publication (7); missing values were not replaced or imputed when calculating the Step 1 and Step 2 scores of the non-PH and PAH patients. If one of the six non-echocardiographic variables was missing, the total score of Step 1 could not be calculated and the patient could not be classified. If the total score of Step 1 could be calculated with a result leading the patient to be referred to echocardiography but one of the two echocardiographic variables was missing, the total score of Step 2 could not be calculated and the patient could not be classified. Performance summary statistics (Supplementary Appendix II) were then calculated from the observed algorithm decisions compared to diagnoses based on RHC. For comparison, results for patients classified using the hemodynamic definition in the prevailing guidelines (10, 16, 17) at the time of the DETECT publication (2014 definition; Supplementary Table 1) are also shown.

RESULTS

The 466 SSc patients with RHC data who enrolled in DETECT were included in this analysis. Patient characteristics of the non-PH and PAH populations according to the 2022 ESC/ERS, 6WSPH and 2014 definitions are shown in Supplementary Table 2. Patient classification using the 2022 ESC/ERS definition is summarized in Figure 1 alongside the distribution using the 2014 definition. The number of non-PH patients decreased from 321 (2014 definition) to 242. Of the 79 patients who were re-classified from non-PH to PH by the 2022 ESC/ERS definition, 32 had an mPAP of 21 – 24 mmHg and a PVR >2 WU and were classified as PAH (Supplementary Table 3). Of the 87 patients originally classified as PAH by the 2014 definition, 82 remained classified as PAH. Using a PVR threshold of >2 WU resulted in five patients classified as PAH using the 2014 definition now being grouped under non-classified PH. The distribution of patients with mPAP 21 – 24 mmHg stratified by PVR is summarized in Supplementary Figure 1. Altogether, classifying patients according to the 2022 ESC/ERS definition led to an increase in the number of patients classified as PAH from 87 to 114 patients.

Performance of DETECT

The sensitivity of the DETECT algorithm decreased from 95.8% to 88.2% (i.e., an increase in the false negative rate from 4.2% to 11.8%), while specificity improved from 47.8% to 50.8%, when PH/PAH was defined according to the 2022 ESC/ERS definition compared to the 2014 definition (Table 1, Figure 2). The positive predictive value (PPV) improved from 34.8% to 46.9% and the negative predictive value (NPV) deteriorated from 97.5% to 89.7%. The referral rate for RHC was 62.1%, consistent with that for the 2014 definition.

An additional analysis was performed using the 6WSPH definition, which used a PVR cut-off of ≥3 WU (6WSPH definition; Supplementary Appendix III). In this analysis, the sensitivity of DETECT slightly decreased from 95.8% to 92.7% (i.e., an increase in the false negative rate from 4.2% to 7.3%) and the specificity slightly improved from 47.8% to 50.8% (Table 1, Supplementary Figure 2). There was a slight improvement in the PPV from 34.8% to 35.4%, and a decrease in the NPV from 97.5% to 96.0%. The referral rate for RHC was 59.0% when PH/PAH was defined according to the 6WSPH definition, versus 62.1% when defined according to the 2014 definition. For the 82 patients screened as true PAH positive using the DETECT algorithm with the 2022 ESC/ERS definition (Figure 2), the mean (SD) mPAP was 31.1 (8.5) mmHg and the mean (SD) PVR was 4.5 (2.6) WU. For the 69 patients screened as true PAH positive using the DETECT algorithm with the 2014 definition (Figure 2), the mean (SD) mPAP was 33.0 (8.0) mmHg and mean (SD) PVR was 4.8 (2.6) WU. For the 51 patients screened as true PAH positive using the DETECT algorithm with the 6WSPH definition (Supplementary Figure 2), the mean (SD) mPAP was 35.0 (8.3) mmHg and mean (SD) PVR was 5.7 (2.6) WU. The hemodynamics for the 11 false negative PAH patients using the DETECT algorithm with the 2022 ESC/ERS definition are presented in Supplementary Table 4.

DISCUSSION

Screening for PAH in SSc patients improves early detection of PAH and is associated with better outcomes (3, 18). The DETECT algorithm is one of the most commonly used composite screening modalities for PAH in SSc patients (14). The hemodynamic definition of PAH has recently been updated in the 2022 ESC/ERS guidelines to include a lower mPAP threshold (mPAP >20 mmHg versus mPAP ≥25 mmHg) and a PVR cut-off (≥2 WU) (5, 6, 11). In support of this new definition, a recent study showed that a mPAP 21 – 24 mmHg and PVR >2 – ≤3 WU was associated with poorer survival in a PH referral population (19). It is therefore important to understand how the DETECT algorithm performs in this new context. In this study, we took advantage of the large DETECT study dataset, which is unique as RHC, the gold standard diagnostic procedure for PAH, was performed in all patients after application of the DETECT algorithm, and therefore allows testing of the false negative rate.

DETECT algorithm performed well at identifying patients with PAH as defined in the 2022 ESC/ERS guidelines, which includes a PVR >2 WU. The specificity was comparable to that observed when PAH was defined according to the prevailing guidelines at the time of publication of DETECT (7) (50.8% versus 47.8%), although sensitivity was slightly lower (88.2% versus 95.8%). This slight decrease in sensitivity is likely due to patients with mildly elevated mPAP (21 – 24 mmHg) and with a PVR (between 2 and 3 WU, indicative of less advanced disease, being included in the PAH group when using the 2022 ESC/ERS definition. When applying the hemodynamic definition proposed at the 6WSPH, the DETECT algorithm also performed well with a sensitivity of 92.7% and specificity of 50.8%.

The results reported here are consistent with previous studies investigating SSc patients with mPAP >20 mmHg. One retrospective study evaluated the effect of the

hemodynamic definition proposed at the 6WSPH on the PH classification of SSc patients (20). Similar to our findings, the update did not have a significant impact on the diagnosis of PH (20). Furthermore, it has been shown that SSc patients with mildly elevated mPAP (21 – 24 mmHg) often have a PVR between >2 and <3 WU, have a preserved function at rest (13, 21), and can be distinguished from patients with normal mPAP (<21 mmHg) and those with PAH (mPAP ≥25 mmHg) based on clinical parameters (22). Altogether, these results support the use of DETECT PAH as a clinical screening tool for PAH in SSc patients.

This analysis provides insights on how the 2022 ESC/ERS guidelines and 6WSPH proceedings impact the number of patients in the DETECT study who would be classified as PH, and more importantly here, as PAH. Intuitively, lowering the mPAP threshold should lead to an increase in the number of patients classified as PAH. However, as demonstrated here, this was only true when this criterion was combined with a PVR of >2 WU, (and not when a PVR threshold of ≥3 WU was used to define PAH). This shows that, at least among SSc patients, those with a low mPAP tend to also have a rather low PVR (i.e., <3 WU); as such, lowering the mPAP threshold used to define PAH only significantly impacts the number of PAH patients identified when the threshold for PVR is also lowered to >2 WU. Furthermore, although the 2022 ESC/ERS guidelines updated the definition of pre-capillary PH, they did not recommend use of a specific PAH therapy for the management of PAH patients with a PVR of 2 – 3 WU; such patients may therefore be appropriate for close follow-up in the clinic, as well as further investigation via a dedicated randomized clinical trial. Changing the hemodynamic definition of PH/PAH also led to an increase in the number of PH patients not classified, however this number was relatively modest with

the definition recommended by the 2022 ESC/ERS guidelines. Hence, the size of this population can be expected to be small in clinical practice.

It is important to note that the DETECT cohort was recruited from 2008–2011 (7), and may therefore not be fully representative of the contemporary SSc patient population. Patients with DLCO ≥60% were excluded from the DETECT study to enrich for patients at high risk of PAH, therefore the results of this study may not be representative of the general SSc population. However, patients with DLCO ≥60% carry little risk of PAH and, this low prevalence combined with the current tools, renders routine screening ineffective.

In conclusion, the DETECT algorithm maintains good performance, with high sensitivity and reduced false negative rate, in identifying patients with a high risk of PAH in SSc. The DETECT algorithm remains applicable in clinical practice as a screening tool for PAH.

Data Availability Statement

Although these data are not currently publicly available for sharing, requests for sharing can be sent to the Corresponding Author and will be evaluated on an individual basis.

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Table 1: Performance of the DETECT algorithm when applying the 2014, 6WSPH and 2022 ESC/ERS definitions

	2022 ESC/ERS definition n = 282*	2014 definition n = 319*	6WSPH definition n = 244*
Sensitivity	88.2%	95.8%	92.7%
Specificity	50.8%	47.8%	50.8%
PPV (RHC hit rate)	46.9%	34.8%	35.4%
NPV	89.7%	97.5%	96.0%
False negative rate	11.8%	4.2%	7.3%
Referral rate	62.1%	62.1%	59.0%

PAH defined as: mPAP >20 mmHg, PCWP ≤15 mmHg, PVR >2 WU (2022 ESC/ERS definition); mPAP ≥25 mmHg, PCWP ≤15 mmHg (2014 definition); mPAP >20 mmHg, PCWP ≤15 mmHg, PVR ≥3 WU (6WSPH definition); non-PH defined as: mPAP ≤20 mmHg (2022 ESC/ERS definition); mPAP <25 mmHg (2014 definition); mPAP ≤20 mmHg (6WSPH definition). *n number is the total of non-PH and PAH patients with available data to enable application of DETECT; 74, 89 and 66 patients were removed due to missing data when applying the 2022 ESC/ERS, 2014 and 6WSPH definitions, respectively. ESC/ERS, European Society of Cardiology/European Respiratory Society; mPAP, mean pulmonary arterial pressure; NPV, negative predictive value; PAH,

pulmonary arterial hypertension; PH, pulmonary hypertension; PPV, positive predictive value; PVR, pulmonary vascular resistance; RHC, right heart catheterization; 6WSPH, 6th PH World Symposium; WU, Wood Units.

FIGURE LEGENDS

Figure 1: Patient classification for the DETECT study population using the 2014 and 2022 ESC/ERS definition. N = 466, all with RHC performed; [a]mPAP <25 mmHg; [b]mPAP ≥25 mmHg, PCWP ≤15 mmHg and (FVC >70% or [FVC 60-70% plus HRCT showing mild-moderate or no parenchymal lung disease]); [c]mPAP ≥25 mmHg, PCWP >15 mmHg; [d]mPAP ≥25 mmHg, PCWP ≤15 mmHg and (FVC <60% or [FVC 60-70% plus HRCT not available or showing moderate-severe parenchymal lung disease]); [e]mPAP ≥25 mmHg, PCWP missing; [f]mPAP ≤20 mmHg; [g]mPAP >20 mmHg, PCWP ≤15 mmHg, PVR >2 WU and (FVC >70% or [FVC 60-70% plus HRCT showing mild-moderate or no parenchymal lung disease]); [h]mPAP >20 mmHg, PCWP >15 mmHg; [i]mPAP >20 mmHg, PCWP ≤15 mmHg, PVR >2 WU and (FVC <60% or [FVC 60-70% plus HRCT not available or showing moderate-severe parenchymal lung disease]); [j]mPAP >20 mmHg and either PCWP missing or PVR ≤2 WU; [k]2 patients had missing PCWP values and 34 patients had PCWP ≤15 mmHg and/or PVR ≤2 WU. ESC/ERS, European Society of Cardiology/European Respiratory Society; FVC, forced vital capacity; HRCT, high resolution computed tomography; LHD, left heart disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WHO, World Health Organization; WU, Wood Units.

Figure 2: Two-step DETECT decision tree for non-PH and PAH patients using the 2014 and 2022 ESC/ERS definition. Data for the 2014 definition have been previously published (7). PAH defined as: mPAP ≥25 mmHg, PCWP ≤15 mmHg (2014 definition); mPAP >20 mmHg, PCWP ≤15 mmHg, PVR >2 WU (2022 ESC/ERS definition); non-PH defined as: mPAP <25 mmHg (2014 definition); mPAP

≤20 mmHg (2022 ESC/ERS definition). ACA, anticentromere antibody; DLCO, pulmonary diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESC/ERS, European Society of Cardiology/European Respiratory Society; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; NTproBNP, N-terminal probrain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TR, tricuspid regurgitant jet; WU, Wood Units.

2014 definition	2022 ESC/ERS definition					
Frequency	**Non-PH[f]**	**WHO Group 1 PH (PAH)[g]**	**WHO Group 2 PH (PH due to LHD)[h]**	**WHO Group 3 PH (PH due to lung disease / hypoxia)[i]**	**Non-classified PH[j]**	**Total**
Non-PH[a]	242	32	5	14	28	**321**
WHO Group 1 PH (PAH)[b]	0	82	0	0	5	**87**
WHO Group 2 PH (PH due to LHD)[c]	0	0	30	0	0	**30**
WHO Group 3 PH (PH due to lung disease / hypoxia)[d]	0	0	0	25	2	**27**
Non-classified PH[e]	0	0	0	0	1	**1**
Total	**242**	**114**	**35**	**39**	**36[k]**	**466**

Figure 1_600dpi.tiff

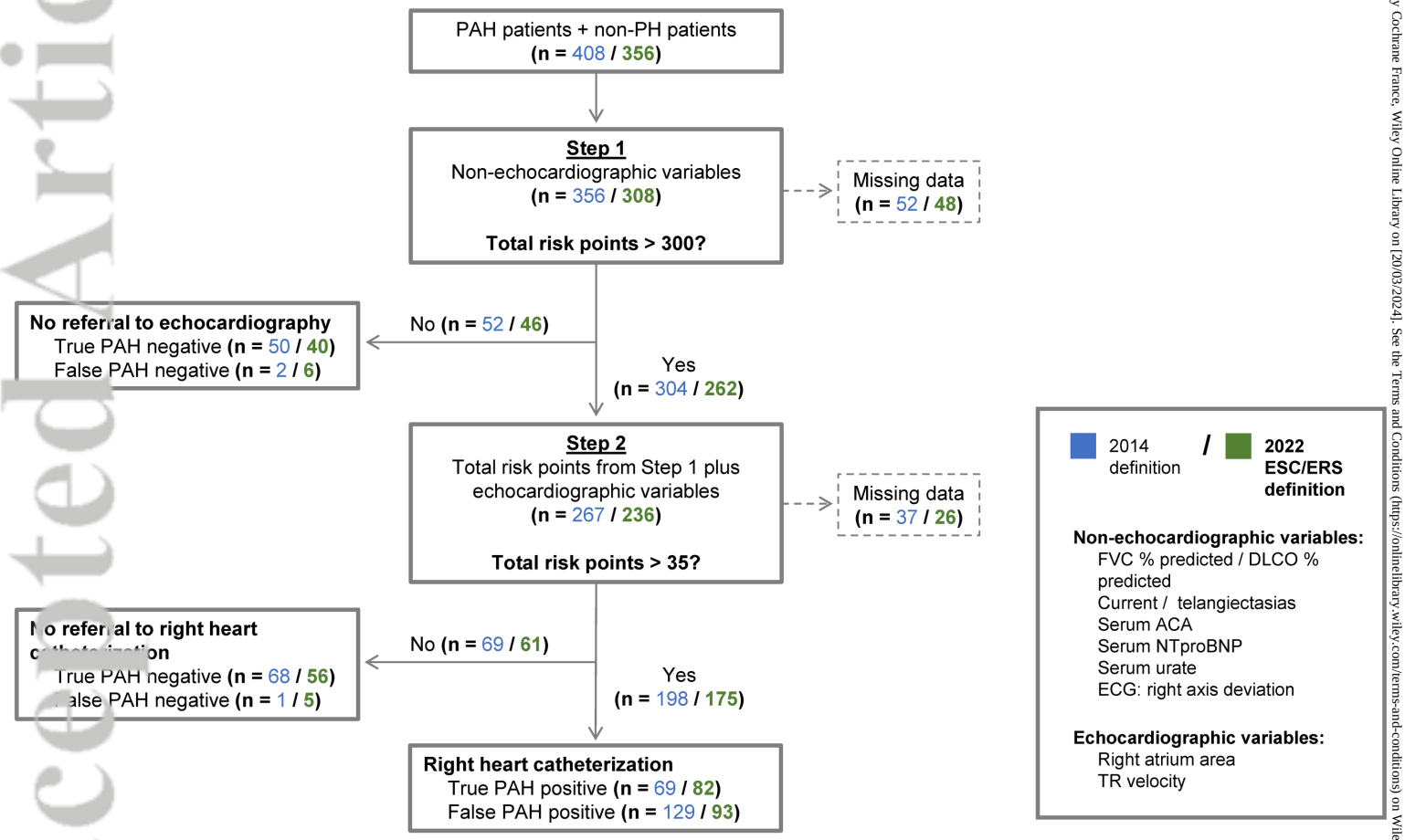

Figure 2_600dpi.tif