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Review

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A Systematic Review with Meta-analysis of Biomarkers for detection of Pulmonary Arterial Hypertension

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Take home message

Meta-analysis of 26 biomarkers yielded 17 differentially expressed biomarkers in PAH. NT-proBNP had the highest diagnostic accuracy, but had a low specificity for PAH. Other markers, including IL-6, RDW, LDL-c, d-dimer and UA lacked clinical validation.

ABSTRACT

Rationale The blood is a rich source of potential biomarkers for the diagnosis of idiopathic and hereditary pulmonary arterial hypertension (iPAH and hPAH, referred to as "PAH"). While a lot of biomarkers have been identified for PAH, the clinical utility of these biomarkers often remains unclear. Here, we used unbiased meta-analysis of published biomarkers to identify biomarkers with the highest performance in the detection of PAH.

Methods A literature search (in PubMed, Embase.com, Clarivate Analytics/Web of Science Core Collection and Wiley/Cochrane Library) was performed up to January 28, 2021. Primary end points were blood biomarker levels in PAH versus asymptomatic controls or patients suspected of pulmonary hypertension (PH) with proven normal haemodynamic profiles.

Results 149 articles were identified by the literature search. Meta-analysis of 26 biomarkers yielded 17 biomarkers that were differentially expressed in PAH and non-PH control subjects. Red cell distribution width, LDL-c, d-dimer, NT-proBNP, IL-6 and uric acid were biomarkers with the largest observed differences, largest sample sizes and a low risk of publication bias. Receiver operating characteristic curves and sensitivity/specificity analyses demonstrated that NT-proBNP had a high sensitivity, but low specificity for PAH. For the other biomarkers, insufficient data on diagnostic accuracy with receiver operating characteristic curves were available for meta-analysis.

Conclusion This meta-analysis validates NT-proBNP as a biomarker with high sensitivity for PAH, albeit with low specificity. The majority of biomarkers evaluated in this meta-analysis lacked either external validation or data on diagnostic accuracy. Further validation studies are required, and studies that test combinations of biomarkers to improve specificity.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a cardiovascular condition in which progressive occlusive remodelling leads to increased pulmonary vascular resistance and ultimately right ventricular failure. PAH can be hereditary (hPAH) or idiopathic (iPAH) after exclusion of significant co-morbidity[1], referred to as "PAH" throughout this study. The diagnosis of PAH is a complex, specialist process, attributing to a mean time to diagnosis of 17-24 months[2]. Availability of non-invasive biomarkers for faster diagnosis and initiation of treatment prior to the development of right heart failure may improve survival and quality of life[3].

Until now, NT-proBNP remains the most useful clinical marker of myocardial strain and is employed for risk stratification of patients in guidelines and clinical practice[1]. However, improved understanding of the pathways leading to PAH, which include endothelial dysfunction, immunity and altered cellular metabolism, may result in the emergence of novel biomarkers that can detect proliferation and occlusive remodelling of the vascular wall with higher specificity. With the ongoing interest to develop biomarkers that help non-invasive diagnosis of PAH, new biomarkers have been proposed. Yet, many of these biomarkers lack external validation, leaving the performance of these biomarkers – in terms of reproducibility and clinical utility – unclear. We used unbiased meta-analysis to identify biomarkers with robust sensitivity and specificity to detect PAH.

We conducted a systematic review and meta-analysis of the literature on published biomarkers of PAH in blood or urine. Here we show: 1) biomarkers differentially expressed in iPAH and hPAH compared to non-pulmonary hypertension (PH) controls; and 2) available evidence supporting the suitability of these biomarkers for clinical implementation, including calculation of diagnostic accuracy employing receiver operating curve analyses.

MATERIALS AND METHODS

Search strategy

The conduct and reporting of this review adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-statement (www.prismastatement.org)[4] and is registered in PROSPERO(CRD42020215820).

Four bibliographic databases (PubMed, Embase.com, Clarivate Analytics/Web of Science Core Collection, Wiley/Cochrane Library) were searched for relevant literature from inception to January 28, 2021. Searches were constructed in collaboration with a medical information specialist (KAZ). Search terms including synonyms, closely related words and keywords were used as index terms or free-text words. The searches contained no methodological search filter, date or language restrictions that would limit results to specific study designs, date or language (detailed search; supplementary table 1). Duplicate articles were excluded using Endnote (X9.3.3), Amsterdam Efficient Deduplication-method and Bramer-method[5]).

Two reviewers (JS and LB) independently screened all potentially relevant titles and abstracts for eligibility using Rayyan. If necessary, the full text article was checked for the eligibility criteria. Differences in judgement were resolved through; 1) discussion among reviewers (JS and LB), 2) arbitration of a third reviewer (JA), or 3) contacting the author. Studies were included if they met the following criteria: 1) analysis of potential blood and urine biomarkers in any form, including growth factors, inflammatory mediators, circulating cells, protein, (micro)RNA, or microvesicles; and 2) involved group 1 PAH, provided that iPAH or hPAH patients were included. The following studies were excluded: 1) animal studies; 2) studies involving subjects < 18 years of age; 3) studies that did not report biomarker levels for group 1 PAH, or lacked inclusion of iPAH or hPAH patients; 3) studies that lacked a control group, or included a control group suspected of PH without measurement of hemodynamics; 4) certain publication types: editorials, letters, legal cases, interviews etc. The full text of the selected articles was obtained for further review and data extraction. In a minority of articles data were estimated from figures. Biomarker levels were conversed to a uniform unit of measurement. Two reviewers (JS and LB) independently evaluated the methodological quality of the full text papers using QUADAS-2[6]. Articles were scored as low, unclear or high on domains ‘patients inclusion

(P)', 'index test (I)', 'reference test (R)' and 'flow and timing (T)'[6]. The risk of bias assessment tool was optimized by JS and LB from a pilot of 10 studies and are presented in **table S2.**

A similar search strategy was adopted in identical databases to identify 'omics' studies performed in patients with iPAH and hPAH, compared to non-PH control subjects. Studies were included if they met the following criteria; 1) adopted an 'omics' technology, including transcriptomics, proteomics, metabolomics, glycomics or lipidomics in blood or urine; and 2) involved patients with group 1 PAH, including iPAH or hPAH. Equal exclusion criteria applied as described above.

Data extraction

The following data were extracted from each publication: mean with standard deviation (SD) and the number of patients for each group (PAH versus non-PAH controls), area under the receiving-operating-curve (AUC/ROC), cut-off values, as well as sensitivity and specificity of a given biomarker for the diagnosis of PAH.

Statistics

Primary outcomes were biomarker concentrations in PAH and asymptomatic controls. Meta-analyses were performed when original data (expressed in mean with SD) were available from a minimum of three publications using Review Manager 5.3.5 software, The Nordic Cochrane Center, Copenhagen, Denmark. A randomized model for continuous data was adopted, due to possible risk of bias. Based on population size, mean and SD, the standardized mean difference, mean difference and odds ratio (OR) of biomarker levels in patients with PAH and non-PH controls were calculated. Mean and standardized mean differences are represented as mean with 95% confidence intervals (95% CI), or OR with 95% CI. Biomarkers were ranked according to effect size and statistical significance. I^2 and Tau^2 statistics were performed to assess heterogeneity among studies, and explainable heterogeneity was solved by exclusion of the aberrant publication.

Publication bias was assessed in Comprehensive Meta-Analysis software V3, Biostat, Englewood, NJ) using funnel plots, Egger's regression test ($p < 0.10$), Duval and Tweedie's trim and

fill and Orwin's Fail safe N-test. The failsafe number estimates the number of unpublished studies required to turn the meta-analysis result in a clinically insignificant value. The clinically irrelevant value was arbitrarily set at a standardized mean difference of less than -0.25 or 0.25.

Selection of biomarkers for clinical implementation

We made a selection of differentially expressed biomarkers based on statistical significance ($p < 0.05$) of the observed difference, sample size, and quality of validation outside the discovery cohort by means of calculation of sensitivity and specificity values using ROC analyses in an independent validation cohort. Additionally, we selected for a negligible risk for publication bias, defined by Egger's regression $p > 0.10$, Duval & Tweedie's trim and fill ($p < 0.05$), and a minimum of five publications predicted to bring the result to a clinically insignificant value (standardized mean difference – 0.25, 0.25).

All biomarkers were grouped in six pathobiological domains: haematological, metabolic, coagulation, inflammatory, cardiac and renal. In each domain, we selected one preferred biomarker on the basis of observed difference, sample size, quality of external validation, and risk of publication bias, see table S1 .

RESULTS

Inclusion and selection of publications

The literature search yielded a total of 3456 references: 887 in PubMed, 1506 in Embase.com, 976 in Clarivate Analytics/Web of Science Core Collection and 87 in Wiley/Cochrane Library. After removal of duplicates 1356 remained. 1207 full-text articles were excluded based on inclusion and exclusion criteria (**fig. 1a**)**.** 149 publications remained eligible for data extraction. 45 publications were identified that describe biomarkers meeting criteria for meta-analysis and risk of publication bias assessment. A detailed overview of biomarker origin (whole blood, plasma or serum), location of blood draw (peripheral or central (RHC) blood draw), demographic criteria, treatment and concerns regarding inclusion procedure of these publications is provided in **table S3.** Risk of bias, attributable to the procedure of patient selection, index and reference test, as well as timing of the biomarker blood draw, see **table S2** was systematically assessed using QUADAS-2[6] and is reported in **fig. S1.**

Exclusion of urine and non-protein blood biomarkers

In several publications, biomarker expression was studied on circulating platelets [7, 8], immune cells [9-12] and progenitor cells [13-16]. Heterogeneity in measurement methods, characterization and FACS gating precluded meta-analysis of these publications.

Three publications reported on different types of extracellular vesicles as biomarker [17, 18] and three to different types of miRNA as biomarker [19-22]. A single publication reported on a urine biomarker [23]. These publications did not meet the criteria for meta-analysis.

Selection of eligible biomarkers

26 biomarkers were eligible for meta-analysis (**table 1**). A significant difference in expression was detected for 17 biomarkers in six pathobiological domains. In the haematological domain, these were red blood cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV) and thrombocytes. In the metabolic domain, total cholesterol, low density lipid-cholesterol (LDL-c), triglycerides and fasting glucose. In the coagulation domain, d-dimer was differentially expressed. In the inflammatory domain, interleukin-6 (IL-6), c-reactive protein (CRP), soluble

vascular adhesion molecule-1 (sVCAM-1), C-X-C motif chemokine ligand-10 (CXCL-10) and tissue inhibitor metalloproteinase-1 (TIMP1) were differentially expressed. In the cardiac domain, N-terminal prohormone of brain natriuretic protein (NT-proBNP), and in the renal domain, uric acid (UA) and blood urea nitrogen (BUN) were differentially expressed. Biomarkers described in fewer than three publications or as median with IQR are summarized in **table S4 and S5**. Selected biomarkers are shown in **fig. 2 (see Materials and Methods).** These include RDW, LDL-c, d-dimer, IL-6, NT-proBNP and UA. Forest plots for PDW, MPV, thrombocytes, total cholesterol, triglycerides, fasting glucose, CRP, sVCAM-1, CXCL-10, TIMP1, BUN are provided in the supplement (**fig. S2-7, table S6**).

Evaluation of publication bias

Egger's regression analysis revealed a significant association ($p < 0.10$) between effect size and standard error for MPV and thrombocytes. After correction for possible publication bias by Duval & Tweedie's trim and fill, the mean difference between PAH and control groups remained significant. The failsafe test indicated that a minimum of five publications were required to bring the differences to a clinically trivial value, defined as a standardized mean difference of less than -0.25 or 0.25. This suggests that the chance that the observed difference relies on publication bias is small (**table S7)**. Funnel plots of all meta-analyses are given in **fig. S8a-z**.

Haematological markers: RDW

All five publications on RDW were eligible for meta-analysis. RDW was determined in treatment naive iPAH[24] and PAH[25] patients, and in PAH patients receiving vasodilatory treatment[11, 26]. As a reference, asymptomatic controls[11, 24-26] and patients suspected of PH[26] or common disease controls[24] were included (**fig. 2a**). Meta-analysis confirmed a positive mean difference of 1.67% [1.45, 1.89], $p<0.00001$ between PAH and non-PH control (**table 1**). For RDW no sensitivity, specificity or diagnostic accuracy could be extracted from the original data.

A rise in RDW is predictive for the presence of PH in patients with acute pulmonary embolism [27] or systemic sclerosis[26, 28]. RDW was positively associated with pulmonary artery pressure[11,

24], right atrial pressure[24], pulmonary vascular resistance[24], BNP[26] and NT-proBNP[29], and inversely with six minute walking distance[24, 26, 29]. Remarkably, in one study RDW performed better than NT-proBNP and IL-6 as prognostic markers in PAH patients[27].

Other markers in the haematological domain are summarized in **table 1**. PDW was increased with a mean difference of 1.42% [0.16, 2.67], p<0.00001, **fig. S2a**), as well as MPV (0.95 fL [0.76, 1.13], p < 0.00001, **fig. S2b**), while thrombocyte count was decreased by a mean of -23.9 x 10^9 cells/L [-38.6, -9.2], p 0.001, **fig. S2c**. Eligible for meta-analysis but without significant differences were haemoglobin, haematocrit and leukocytes (**fig. S2d-f**).

Metabolic markers: LDL-c

LDL-c was reported in six publications eligible for meta-analysis and determined in patients with PAH receiving vasodilatory treatment. Asymptomatic controls[11, 30-32] or patients with cardiovascular disease or patients suspected of PH[8] were included as reference (**fig. 2b**). All measurements were performed in blood obtained after >8 hours of fasting. LDL-c was lower in patients with PAH, with a mean difference of -15.82 mg/dL [-26.18, -5.46], p < 0.00001 (**table 1**). For LDL-c no sensitivity, specificity or diagnostic accuracy could be extracted from the original data. Decreased insulin sensitivity and altered lipid metabolism in iPAH are a possible consequence of chronic inflammation, malnourishment and alterations in liver function[33, 34]. LDL-c was not related to haemodynamic parameters, NT-proBNP, six minute walking distance or BMI. LDL-c was negatively associated with 3-year survival in PAH (hazard-ratio 0.18/mmol/L (0.07-0.47), p<0.01, corrected for statin use)[30]. A similar relationship has been described in chronic heart failure[35, 36].

A lower LDL-c in patients with PAH was accompanied by a lower mean total cholesterol of -17.70 mg/dL [-24.15, -11.26], p < 0.00001 (**fig. S3a**) and lower mean triglycerides of -32.56 mg /dL [-54.17, -10.94], p 0.004, **fig. S3b**). Despite the availability of six publications, no significant difference was found in meta-analyses for HDL-c (mean difference -6.15 mg/dL [-2.11, 14.40], p 0.13, **fig. S3d**) or fasting glucose (**fig. S3c**).

Coagulation markers: D-dimer

From the available markers representing coagulation pathways, meta-analyses could be performed for fibrinogen and D-dimer levels. D-dimer was studied in treatment-naive iPAH patients [37] and in PAH patients receiving vasodilatory treatment[8, 38] and results were compared to asymptomatic controls (**fig. 2c**). Meta-analysis revealed a significantly higher D-dimer level in patients with PAH compared to asymptomatic controls, with a mean difference of 245.99 ng/mL [148.55, 343.43], p 0.001**, table 1**, in contrast to fibrinogen (73.75 [-2.58, 150.08], p 0.09, **fig. S4**); all consistent with the hypothesis that hypercoagulability and in situ thrombosis may contribute to disease pathobiology in PAH[39].

Inflammatory markers: IL-6

From ten publications reporting on IL-6, five were eligible for meta-analysis. All studies detected elevated levels of circulating IL-6 in treatment-naïve iPAH[40], or iPAH receiving vasodilatory treatment[27, 41-45] and naïve PAH[46, 47] or PAH patients receiving treatment[48]. Findings were compared to asymptomatic controls (**fig. 2d**). A significant rise in IL-6 levels was observed in PAH compared to non-PH controls (mean difference (5.01 [2.06, 7.96] pg/mL, p 0.0005 (**table 1**).

Il-6 levels were negatively associated with the number of circulating endothelial progenitor cells[41], and were elevated in parallel to several interleukins[44], as well as CXCL-10[42], MCP-1[47, 48], TNF-a[40, 46-48], PlGF[40], sVEGFR-1[40], VEGF-A[40], VEGF-D[40] and markers related to thrombogenesis[45]. IL-6 was negatively associated with RV function[47], 6MWD[27, 40], while positively to WHO-functional class[27], NT-proBNP[27, 40] and mean right atrial pressure[40]. IL-6 levels were predictive for all-cause mortality[27, 44] in PAH. No data on diagnostic accuracy, including ROC and AUC were available for meta-analysis.

Eight publications detected a subtle elevation in CRP levels in PAH[11, 41, 49-57] (**fig. S5a**), (mean difference 0.74 mg/L [0.13, 1,6], p 0.02 (**table 1**). However, since only one study was predicted to bring the difference to an clinically insignificant value, the risk of bias is significant. The study of Wang et al. [50] yielded an area-under-the-curve (AUC) of 0.51 (p 0.899) with a 85% specificity but low (39%) sensitivity[50], when using a diagnostic cut-off of 2.7 mg/L CRP, indicating diagnostic accuracy is low in an external validation cohort consisting of iPAH and asymptomatic controls. CRP

is commonly attributed to other cardiovascular or inflammatory disease[58], and these data indicate that an elevated CRP lacks the specificity required for detection of PAH among non-PH controls.

Other inflammatory markers that were eligible for meta-analysis and significantly increased in patients with iPAH compared to non-PH controls included: sVCAM-1 (mean difference of 626.72 ng/mL [29.38, 1224.07], p 0.003, **fig. S5b**), CXCL-10 (mean difference 99.77 pg/mL [54.53, 145.01], p<0.00001, **fig. S5c**) and TIMP-1 (mean difference of 15.58 ng/mL [-2.56, 33.72], p 0.003 ,**fig. S5d**). No significant difference was observed for sP-selectin (**fig. S5e**). From these markers no sensitivity, specificity or diagnostic accuracy could be extracted from the original data.

Cardiac markers: NT-proBNP

11 publications reporting on NT-proBNP met the inclusion criteria, ten of which were eligible for meta-analysis. NT-proBNP was measured in treatment naïve iPAH patients [32, 59-63], as well as in iPAH[50-52, 62-64] and PAH patients receiving vasodilatory treatment[55, 56, 65, 66]. Data were compared to asymptomatic controls[32, 57, 59-63, 66] or subjects suspected of PH[55, 56, 65] (**fig. 2e**). The overall mean difference was 1684 pg/mL [1035, 2330], p <0.00001 (**table 1**).

Wang et al.[50] determined the diagnostic accuracy of NT-proBNP in patients with iPAH among asymptomatic controls employing a cut-off >89.25 pg/mL (AUC 0.87, p<0.0001) with a sensitivity of 89%, and 78% specificity. Similarly, Malhotra et al.[52] detected PAH patients receiving vasodilatory treatment among asymptomatic controls with an AUC of 0.714. However, with a specificity of 78%[50], NT-proBNP is not suitable for identifying PAH amongst patients with left heart disease.

NT-proBNP was positively associated with markers of disease severity, including right ventricular function, including pulmonary vascular resistance[60, 65], right atrial pressure[60], right ventricular dimensions[59, 61, 66], and exercise tolerance (WHO functional class[51, 60, 65]. NT-proBNP was inversely related to six minute walking distance [51, 65]), cardiac index [60, 65] and mixed venous oxygen concentration [60, 65]. In addition, NT-proBNP decreased significantly after initiation of treatment, in line with decreased pulmonary vascular resistance and is predictive of

survival l[59, 60, 65]. NT-proBNP was not dependent on the location of blood draw or pulmonary capillary wedge procedure[55].

Renal markers: Uric acid

Six publications reporting on uric acid (UA) levels were included in this review, five of which were eligible for meta-analysis. UA levels were measured in treatment naive iPAH patients[32, 62, 67], iPAH patients receiving treatment[8, 68] and PAH patients on treatment [54, 69], and compared to asymptomatic controls [8, 32, 54, 62, 67-69] (**fig. 2f**). Meta-analyses detected a significantly higher UA level in PAH compared to control with a mean difference of 1.77 mg/dL [1.06, 2.48], p<0.00001 (**table 1**).

UA levels in PAH patients were positively associated with right ventricular volume[68], pulmonary vascular resistance[67, 68] and WHO functional class[67, 68], and negatively correlated with cardiac output[67, 68] and mixed venous saturation[68]. UA decreased significantly after initiation of vasodilatory treatment, proportional to the decrease in pulmonary vascular resistance[67, 68]. UA is an independent predictor of 3-year mortality in iPAH[67] and heart failure[70].

BUN was the second renal marker that was analysed. We observed a significant increase of 1.76 mg/dL [0.51, 3.01], p < 0.0001, (**fig. S6a**). Creatinine and eGFR were eligible but not significantly altered (**fig. S6b-c**).

Hepatic markers

In three individual studies reporting on alanine aminotransferase (ALT) in treatment naive iPAH patients[62], iPAH patients receiving vasodilatory treatment[49] and treatment naive PAH patients[37], no significant difference was observed in our meta-analysis (**fig. S7**). No other hepatic marker was eligible for meta-analysis.

Omics studies

The omics search strategy generated at total of 643 articles: 148 in PubMed, 309 in Embase.com, 183 in Clarivate Analytics/Web of Science Core Collection, and 3 in Wiley/Cochrane Library. After

removal of duplicates, 247 remained (represented in **figure 1b**). We identified 15 publications that analysed metabolomic[71-80] and proteomic profiles [81-85] in iPAH and PAH patients in plasma[71-76, 78, 79, 81, 83, 85, 86] and serum [77, 80, 84, 85, 87]. 14 studies compared signatures to asymptomatic controls, while two studies used common disease controls[72, 74]. Liquid and gas chromatography coupled with mass spectrometry (LC-MS) or multiplex assays were the most frequently used methods to detect altered metabolites, proteins or antigens. Targeting component analysis was performed employing a variety of statistical tests (**table S1**). Metabolomic studies mainly described glycolytic shift and increased fatty-acid metabolism in patients with PAH, implicating an enhanced glycolytic catabolic state [72-74, 76-79, 88], which Rhodes et al.[72], and He et al.[75] validated in independent cohorts. Proteomic studies describe induced growth factors [82], including erythropoietin[85], hepatic growth factor[82], and inflammatory or immune-response pathways, including complement C4a[81] and several interleukins[85]. Outcomes are summarized in **table S8.**

DISCUSSION

Biomarkers may contribute to early non-invasive detection and monitoring of disease. To our knowledge, this is the first systematic review with meta-analyses to evaluate the performance of diagnostic blood markers in patients with group 1 PAH. In this meta-analysis, we identified RDW, LDL-c, d-dimer, NT-proBNP, IL-6 and UA as biomarkers with the largest observed difference and sample size. Plasma NT-proBNP levels showed the largest difference between PAH and non-PH controls. Although it has a high sensitivity for PAH, NT-proBNP lacks specificity to distinguish PAH from other heart diseases. For other biomarkers, including IL-6, RDW, LDL-c, d-dimer and UA insufficient data were available for meta-analysis of diagnostic accuracy. Due to the lack of clinical validation, none of the newly proposed biomarkers could equal the sensitivity and specificity of NT-proBNP for detection of PAH.

Performance of current biomarkers in PAH diagnosis

Clinical adoption and implementation of new biomarkers is subject to strict performance metrics, and involves: 1) an evidence-based relation between a biomarker and disease, 2) statistical quantification of the predictive strength of biomarker level for the presence of disease, by using calculation of clinical sensitivity and specificity or evaluating ROC curves in diagnostic studies, 3) availability of multiple independent data sources with sufficient sample sizes and power [98]. When considering the first criterion, the current meta-analysis demonstrates that for various biomarkers a consistent and reproducible relation between PAH and biomarker levels can be found. By using a predefined search and selection strategy 26 biomarkers showed differential expression between the PAH and control population, reflecting the various pathophysiological processes (domains) that contribute to PAH. The number of biomarkers identified in this review is limited by the requirement of a minimum of three publications reporting on a given biomarker to perform a meta-analysis. This approach visualizes biomarkers that have consistently shown to relate PAH (i.e. in at least three studies), but may ignore promising biomarkers that have not been reproduced in other studies. Markers included in lesser than three studies or expressed as medians were rendered unsuitable for meta-analysis and are depicted in table S4 and S5. These markers include 5-Ht, ADMA, Ang-1, BNP, endostatin, ET-1, Gal-3, HGF,

HMGB1, IL-8, MCP-1, MMP, Na, PlGF, SCF, sF-selectin, SOD, sVCAM, TGF, Tie-2, TIMP-4, VEGF and TNF-a (**table S4**), and CAV-1, HbA1c, IL-12, K, MCV, NO, OPN, Pim-1, Se-p, FGF-2, Eng, KYN, MCP-1, NO, OPG, PIIINO, sFLT, TFPI, thrombomodulin, TRP, VEGFR1 (**table S5)**. More studies focussing on these markers would clarify the relation between these markers and PAH.

With regard to the second criterion, while out of 26 meta-analyses, 17 biomarkers were consistently related to the presence of disease, data on ROC curves and calculation of clinical sensitivity and specificity for diagnosis of PAH were only available for NT-proBNP and CRP[50]. Independent validation, preferably in studies including a heterogeneous group of patients and including patients suspected or at risk of developing PAH are needed to clarify diagnostic accuracy, with a focus on providing sensitivity and specificity of a biomarker for disease at relevant and reproducible cut-off values. The latter is an essential step in the identification of biomarkers that may replace invasive diagnostics.

With regard to the third criterion, the drawback of most studies included in this review is a low sample size. The combined sample sizes were largest for NT-proBNP and LDL-c (resp. 1152 and 3035), most other analyses are based on a combined sample size below 450 subjects. Including low sample sizes carries the risk of bias, and skewing of data to a selected patient population. This is a general limitation that may be addressed by biobanking, or concurrent analysis of biomarkers in clinical trials. A more systematic approach to biomarker studies may aid authors to increase the amount of subjects in biomarker studies

Altogether, our systemic review and meta-analysis reveals a considerable number of biomarkers that were consistently found to be altered in PAH. However, these biomarkers lack the scientific underpinning to replace invasive diagnostics in PAH, either because data on are lacking or because a lack of specificity.

Future directions for biomarker development in PAH

Considering the fact that research on single biomarkers has failed to identify a single biomarker with sufficient sensitivity and specificity to foster non-invasive PAH diagnosis, various approaches may be considered to improve non-invasive diagnostics in the future. The first involves combining biomarkers

with a strong relation to PAH pathophysiology, which have insufficient diagnostic accuracy on an individual basis. For example, implementing a panel of circulating biomarkers from several domains, weighed by importance to improve biomarker specificity. Based on our meta-analyses, a set of readily available biomarkers may be proposed: a panel including NT-proBNP, IL-6, RDW, UA and LDL-c could potentially be used to score the risk of PAH among clinically similar diseases. A second approach involves combining biomarkers with the strength of non-invasive radiological or hemodynamic measurements. This approach has proven successful in the OPTICS study[89] or DETECT study[90] to exclude iPAH, and in the ERS/ERJ risk criteria and the REVEAL risk stratification[91] to predict outcome in PAH. A third approach may involve unbiased collection of large data sets, including proteomics, transcriptomics and metabolomics, which measure multiple diagnostic biomarkers representative for multiple disease domains in PAH[92]. A PAH-like signature can be used to distinguish iPAH from other diseases. An example is provided by Rhodes et al. [93], employing a selection of nine proteins derived from plasma proteomics, which accurately predict disease outcome in iPAH patients. We believe collaborative biobanks and concomitant analysis of biomarkers in clinical trials and registries are an efficient step forward to improve translation to a clinical setting. External validation cohorts should include patients suspected of PH, and a thoroughly characterized control cohort that contains clinically similar and common diseases.

Strengths & Limitations

This review has certain strengths. First, the search strategy of the current study was designed to cover all diagnostic biomarkers research in PAH thus far, resulting in a database on PAH biomarkers of unanticipated size. Second, the meta-analysis was designed to identify biomarkers with consistent performance over several studies. Although this approach may neglect novel, promising biomarker to a certain extent, the design guarantees identification of biomarkers that were identified in at least three studies, thereby providing surrogate external validation of the biomarker. Third, we focussed on easily accessible blood biomarkers thereby potentially bridging the technical gap towards implementation diagnostic biomarkers in clinical care. In addition, this meta-analysis has a number of limitations. The major limitation is the lack of validation and calculation of diagnostic accuracy of biomarkers outside

their discovery cohort. This renders the reviewing process of sensitivity and specificity for detection of PAH impossible.

Second, the meta-analyses were hampered by the limited number of publications addressing iPAH uniquely. Handling iPAH and hPAH patients together as one group, and extracting data of group 1 PAH as second best, meant inclusion of patients with PAH associated with connective tissue disease, congenital heart disease and drug or toxin use, which may have introduced bias. Next, due to the limited amount of studies, we chose not to exclude publications based on QUADAS-2 risk of bias scores, which may have led to inclusion of unreliable data and may have attributed to heterogeneity. However, correction of the most evident sources of bias (treatment status, diagnosis) indicated that bias was negligible.

Conclusion

This study summarizes a large number of biomarker studies performed in PAH during the last three decades. Most of the described studies investigated the performance of one single blood biomarker. We conclude that none of these biomarkers have sufficient diagnostic accuracy to replace invasive diagnostics, as all single biomarkers lacked specificity. Using a combination of multiple biomarkers may improve specificity, and this can be achieved by either combining a number of routinely available blood tests as well as via an unbiased omics approach.

Conflicts of interest

MW reports personal (speaker) fee's from Actelion, Morphogen-IX, Novartis. HJB reports (speaker) fee from Janssen and MSD, and received grants from Janssen, MSD and Ferrer. AVN, KZ, JA, JS, LB, report no conflict of interest.

TABLES

Marker	Studies (n)	Participants (n)	Mean difference	St. mean difference	Overall effect (p)	Tau^2	I^2 (%)	Heterogeneity (p)	Forest plot
Haematological markers									
RDW, %	4	427	1.83 [1.39, 2.26]	0.98 [0.61, 2.17]	<0.00001	0.07	51	0.11	Fig. 2a
PDW, %	3	245	1.42 [0.16, 2.67]	0.81 [0.50, 1.12]	<0.00001	0.02	19	0.29	Fig. S2a
MPV, fL	5	361	0.95 [0.76, 1.13]	1.0 [0.81, 1.25]	<0.00001	0.00	0	0.68	Fig. S2b
	6*	395	0.66 [0.24, 1.09]	0.72 [0.24, 1.19]	0.003	0.27	78	0.0003	
Thrombocytes, 10^9/L	7	334	-23.9 [-38.6, -9.2]	-0.38 [-0.62, -0.15]	0.001	0.01	5	0.39	Fig. S2c
Hb, g/dL	9	400	-0.59 [-1.23, 0.06]	-0.18 [-0.43, 0.07]	0.15	0.04	29	0.19	Fig. S2d
Hct, %	5	229	-1.07 [-3.91, 1.76]	-0.21 [-0.76, 0.34]	0.46	0.29	74	0.004	Fig. S2e
Leukocytes, 10^9/L	7	294	-0.23 [-0.70,0.24]	-0.10 [-0.41, 0.21]	0.52	0.07	39	0.13	Fig. S2f
Metabolic markers									
LDL-c, mg/dL	6	3035	-15.82 [-26.18, -5.46]	-0.44 [-0.65, -0.22]	<0.00001	0.03	46	0.10	Fig. 2b
Total cholesterol, mg/dL	4	408	-17.70 [-24.15, -11.26]	-0.52 [-0.73, -0.32]	<0.00001	0.00	67	0.67	Fig. S3a
TG, mg/dL	4	198	-32.56 [-54.17, -10.94]	-0.52 [-0.87, -0.17]	0.004	0.04	34	0.21	Fig. S3b
Glucose (fasted), mg/dL	3	103	24.06 [0.54, 7.58]	0.48 [0.08, 0.87]	0.02	0.00	0	0.85	Fig. S3c
HDL-c, mg/dL	6	577	-6.15 [-2.11, 14.40]	-0.53 [-1.20, 0.15]	0.13	0.63	91	<0.00001	Fig. S3d
Coagulation markers									
D-dimer, ng/mL	3	142	245.99 [148.55, 343.43]	0.69 [0.27, 1.11]	0.001	0.04	27	0.26	Fig. 2c
Fibrinogen, mg/dL	4	227	73.75 [-2.58, 150.08]	0.84 [-0.14, 1.81]	0.09	0.88	90	<0.00001	Fig. S4
Inflammatory markers									
IL-6, pg/mL	5	389	5.01 [2.06, 7.96]	0.64 [0.28, 0.99]	0.0005	0.08	47	0.11	Fig. 2d
CRP, mg/L	8	387	0.74 [0.13, 1,6]	0.25 [0.04, 0.47]	0.02	0.02	0	0.98	Fig. S5a
	9*	493	0.13 [0.10, 0.17]	0.77 [-0.08, 1.61]	0.08	1.57	94	<0.00001	
sVCAM-1, ng/mL	3	150	626.72 [29.38, 1224.07]	1.03 [0.53, 1.52]	<0.00001	0.08	40	0.19	Fig. S5b
CXCL-10, pg/mL	3	171	99.77 [54.53, 145.01]	0.82 [0.49, 1.16]	<0.00001	0.00	0	0.46	Fig. S5c
TIMP-1, ng/mL	3	224	15.58 [-2.56, 33.72]	0.40 [0.13, 0.67]	0.003	0.00	0	0.54	Fig. S5d
	4*	329	40.15 [1.02, 79.29]	0.67 [0.14, 1.21]	0.01	0.24	82	0.0009	
sP-selectin, ng/mL	4	180	0.52 [-11.10, 12.14]	-0.04 [0.35, 0.28]	0.82	0.00	0	0.72	Fig. S5e
Cardiac markers									
NT-proBNP, pg/mL	10	1152	1684 [1035, 2330]	1.13 [0.93, 1.33]	<0.00001	0.03	30	0.17	Fig. 2e
	11*	1258	1004 [787, 1221]	1.37 [0.96, 1.79]	<0.00001	0.39	85	<0.00001	
Renal markers									
UA, mg/dL	5	441	1.77 [1.06, 2.48]	0.89 [0.58, 1.12]	<0.00001	0.06	51	0.09	Fig. 2f
	6*	531	1.52 [0.77, 2.27]	0.81 [0.53, 1.09]	<0.00001	0.09	59	0.03	
BUN, mg/dL	5	891	1.76 [0.51, 3.01]	0.43 [0.29, 0.56]	<0.00001	0.00	0	0.48	Fig. S6a
Creatinine, mg/dL	10	475	0.03 [-0.04, 0.10]	0.13 [-0.08, 0.34]	0.23	0.02	20	0.26	Fig. S6b
eGFR, mL/min/1.73 m^2	4	180	1.70 [5.98, 9.37]	0.09 [-0.32, 0.49]	0.67	0.08	47	0.13	Fig. S6c
Hepatic markers									
ALT, U/L	3	115	3.57 [-4.18, 11.31]	0.18 [-0.56, 0.92]	0.37	0.30	71	0.03	Fig. S7

Table 1 Summary of 26 meta-analyses.

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Figure 1

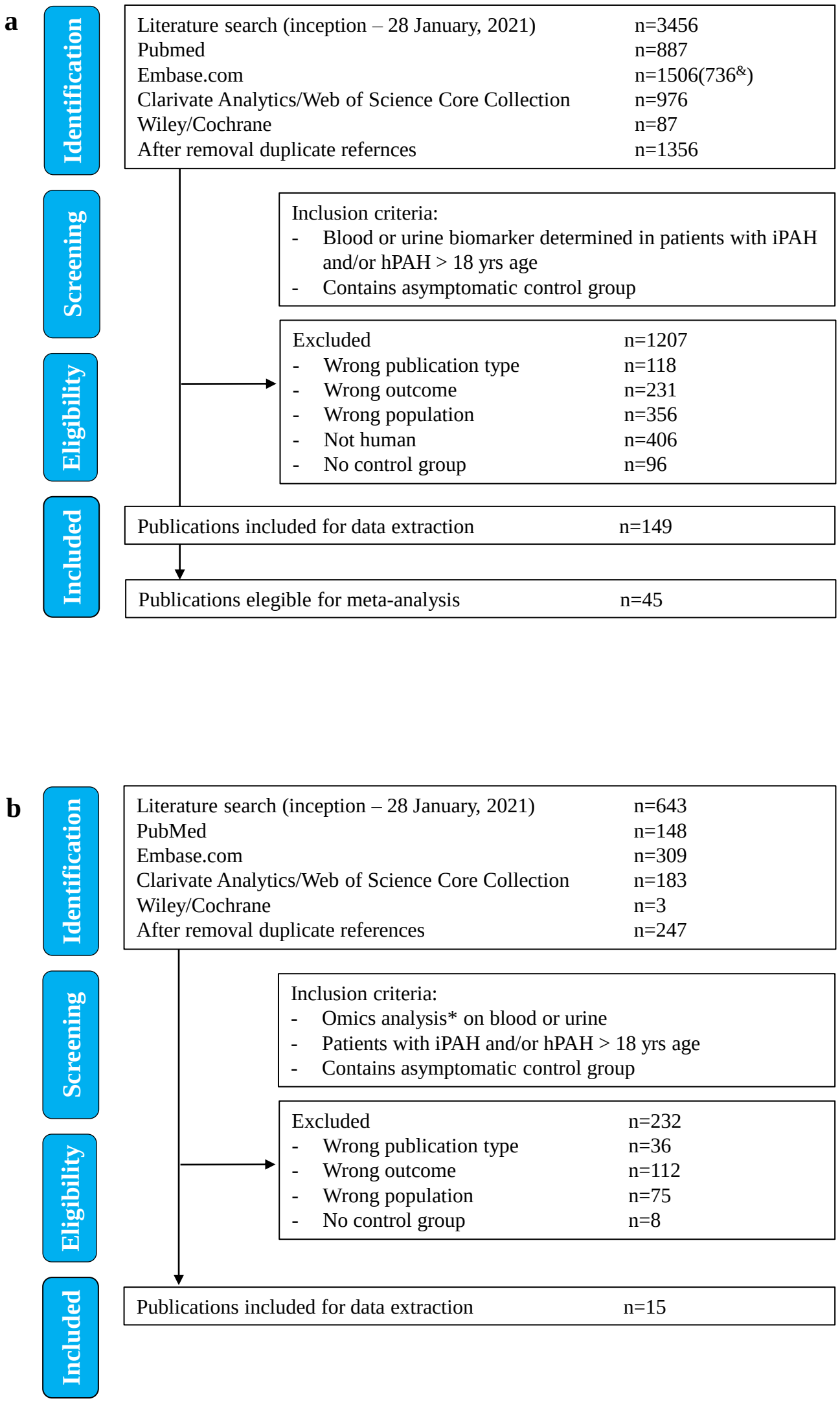
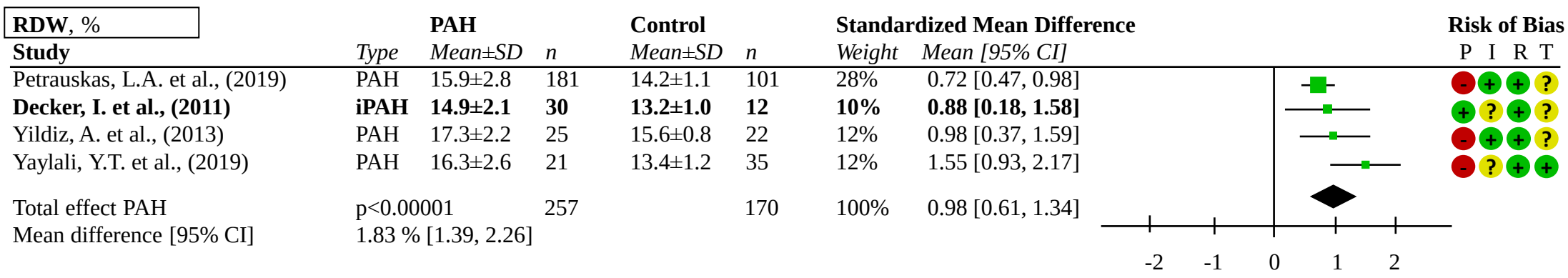


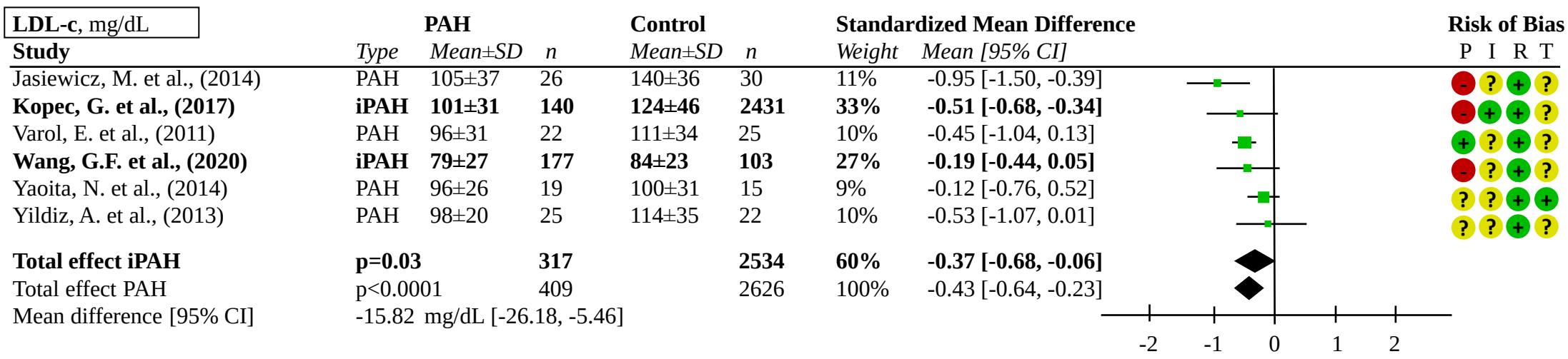
Fig. 1 Flow chart visualizing identification of publications, in- and exclusion criteria, and selection of publications eligible for meta-analysis & excluding conference abstracts. **a** biomarker search, **b** omics search. * transcriptomics, proteomics, metabolomics, glycomics and lipidomics

Figure 2

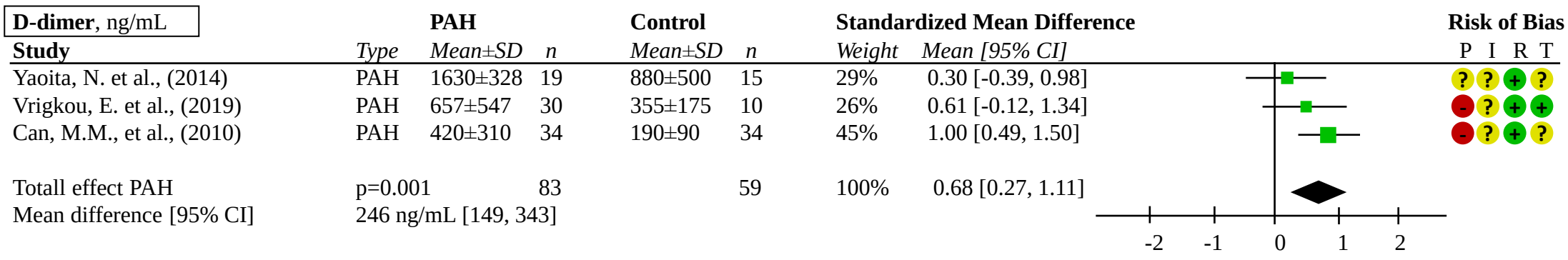
a Haematological



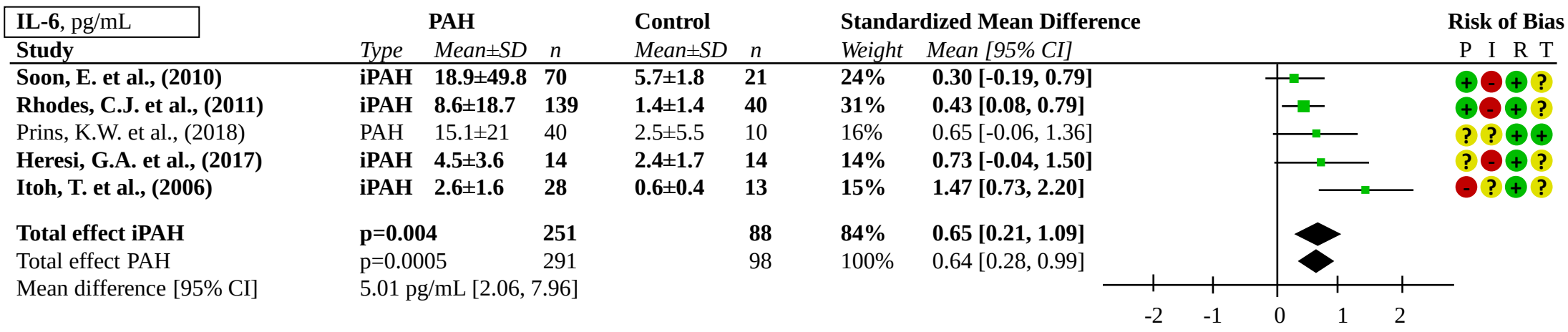
b Metabolic



c Coagulation

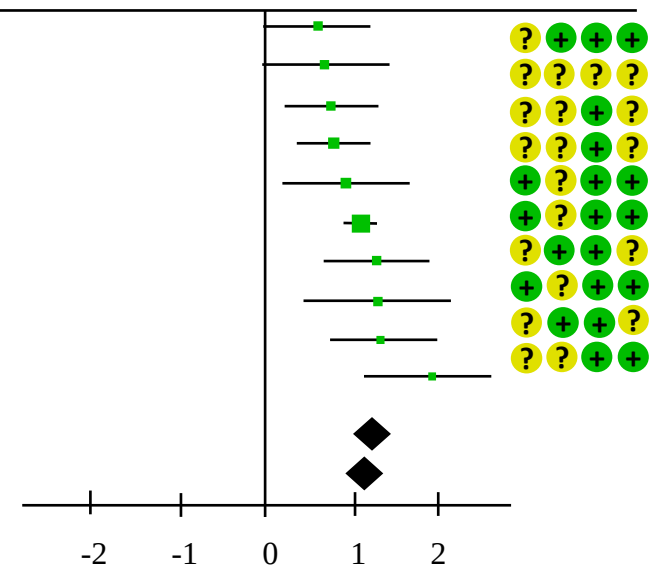


d Inflammatory



e Cardiac

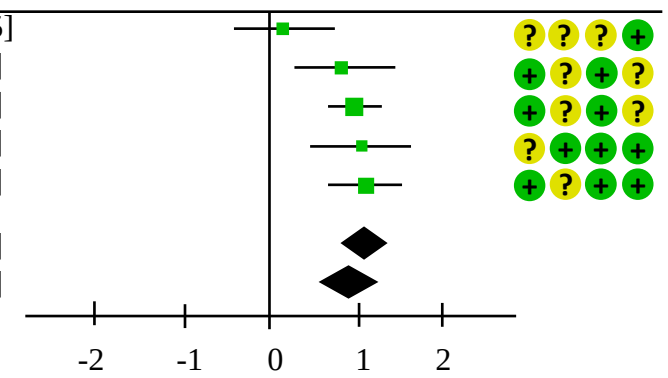
NT-proBNP, pg/mL		**PAH**		**Control**		**Standardized Mean Difference**		**Risk of Bias**
Study	*Type*	*Mean±SD*	*n*	*Mean±SD*	*n*	*Weight*	*Mean, 95% CI*	P I R T
Hennigs, J.K. et al., (2014)	PAH	3106±4661	52	240±173	11	8%	0.66 [0.00, 1.33]	? + + +
Calvier, L. et al., (2016)	**iPAH**	**1575±1863**	**41**	**250±141**	**8**	**5%**	**0.76 [-0.02, 1.53]**	? ? ? ?
Fares, W.H. et al., (2012)	PAH	7420±6682	25	3601±1230	33	10%	0.84 [0.30, 1.39]	? ? + ?
Renard, S. et al., (2013)	**iPAH**	**1917±2497**	**49**	**335±331**	**50**	**15%**	**0.87 [0.46, 1.29]**	? ? + ?
Fijalkowska, A. et al., (2006)	**iPAH**	**2562±2713**	**36**	**46±24**	**9**	**5%**	**1.01 [0.25, 1.77]**	+ ? + +
Lu, G.H. et al., (2020)	**iPAH**	409±126	338	285±74	338	30%	1.20 [1.04, 1.37]	+ ? + +
Zhu, T. et al., (2019)	**iPAH**	**2142±1920**	**27**	**87±63**	**20**	**8%**	**1.38 [0.74, 2.03]**	? + + ?
Andreassen, A.K. et al., (2006)	**iPAH**	**2875±2402**	**17**	**59±50**	**10**	**5%**	**1.42 [0.54, 2.30]**	+ ? + +
Wang, K.Y. et al., (2015)	**iPAH**	**934±891**	**21**	**60±65**	**27**	**8%**	**1.46 [0.81, 2.10]**	? + + ?
Yang, D. et al., (2013)	**iPAH**	**1579±778**	**20**	**465±11**	**20**	**6%**	**1.99 [1.22, 2.76]**	? ? + +
Total effect iPAH	**p<0.00001**		**549**		**482**	**52%**	**1.20 [1.00, 1.41]**	
Total effect PAH	p<0.00001		626		526	100%	1.13 [0.93, 1.33]	
Mean difference [95% CI]	1684 pg/mL [1035, 2330]							



* Malhotra, R. et al.(2013), excluded (method)

f Renal

Uric Acid, mg/dL		**PAH**		**Control**		**Standardized Mean Difference**		**Risk of Bias**
Study	*Type*	*Mean±SD*	*n*	*Mean±SD*	*n*	*Weight*	*Mean, 95% CI*	P I R T
Suzuki, S. et al., (2016)	PAH	6.3±1.7	18	6.0±1.8	30	17%	0.17 [-0.42, 0.75]	? ? ? +
Jasiewicz, M. et al., (2014)	PAH	6.3±2.4	26	4.5±1.5	24	17%	0.85 [0.27, 1.43]	+ ? + ?
Jiang, X. et al., (2008)	**iPAH**	**6.3±2.0**	**78**	**4.5±1.4**	**98**	**28%**	**1.03 [0.71, 1.34]**	+ ? + ?
Zhu, T. et al., (2019)	**iPAH**	**7.6±2.4**	**27**	**5.3±1.4**	**20**	**15%**	**1.10 [0.48, 1.73]**	? + + +
Nagaya, N. et al., (1999)	**iPAH**	**7.5±2.5**	**90**	**4.9±1.2**	**30**	**23%**	**1.15 [0.71, 1.59]**	+ ? + +
Total effect iPAH	**p<0.00001**		**195**		**148**	**66%**	**1.07 [0.84, 1.31]**	
Total effect PAH	p<0.00001		239		202	100%	0.89 [0.58, 1.21]	
Mean difference [95% CI]	1.77 mg/dL [1.06, 2.48]							



*Yaoita, N. et al., (2014) excluded (control group severe CVD)

Fig. 2 Forest plots of selected biomarkers, including; RDW; red cell distribution width, LDL-c; low density lipid-cholesterol; IL-6; interleukin-6, NT-proBNP; N-terminal prohormone of brain natriuretic peptide, UA; uric acid. Risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; refence standard (diagnosis), T; flow and timing. Publications pressed in bold represent biomarker levels of iPAH and/or hPAH uniquely.

Supplementary Appendix
Manuscript Title

A Systematic Review with Meta-analysis of Biomarkers for detection of Pulmonary Arterial Hypertension

Table of Contents

Fig. S1

Fig. S1 Summarized risk of bias table, P; patients, I; index (biomarker) test, R; reference test (diagnosis), T; flow and timing. QUADAS-2.

Fig. S2 Haematologic markers

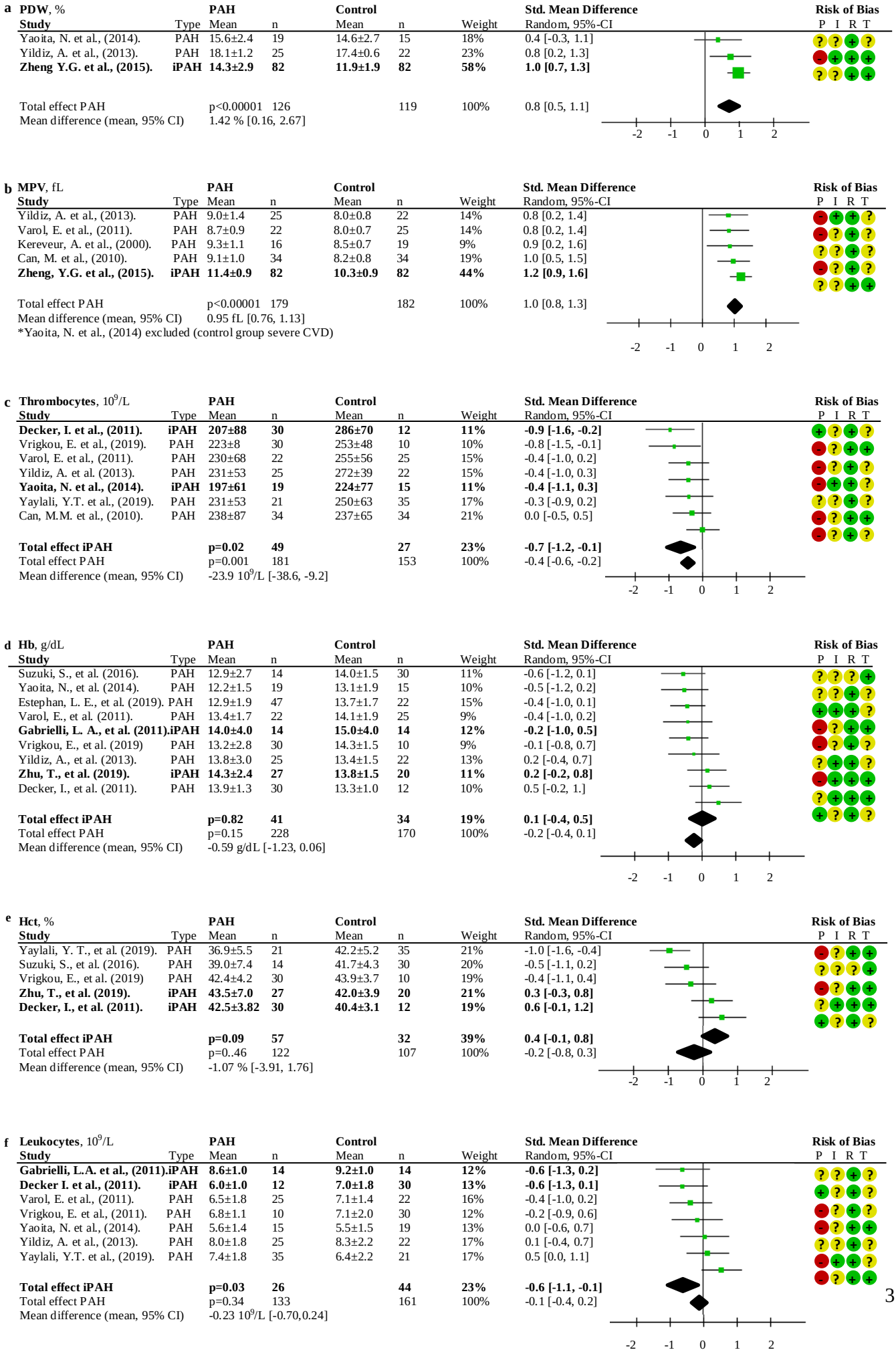


Fig. S2 Forest plots of non-selected haematologic biomarkers, including; PDW; platelet distribution width, MPV; mean platelet volume, thrombocytes, Hb; hemoglobin, Hct; hematocrit, leukocytes. Risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; reference standard (diagnosis), T; flow and timing. Publications pressed in bold measured biomarker levels in iPAH and/or hPAH uniquely.

Fig. S3

Metabolic markers

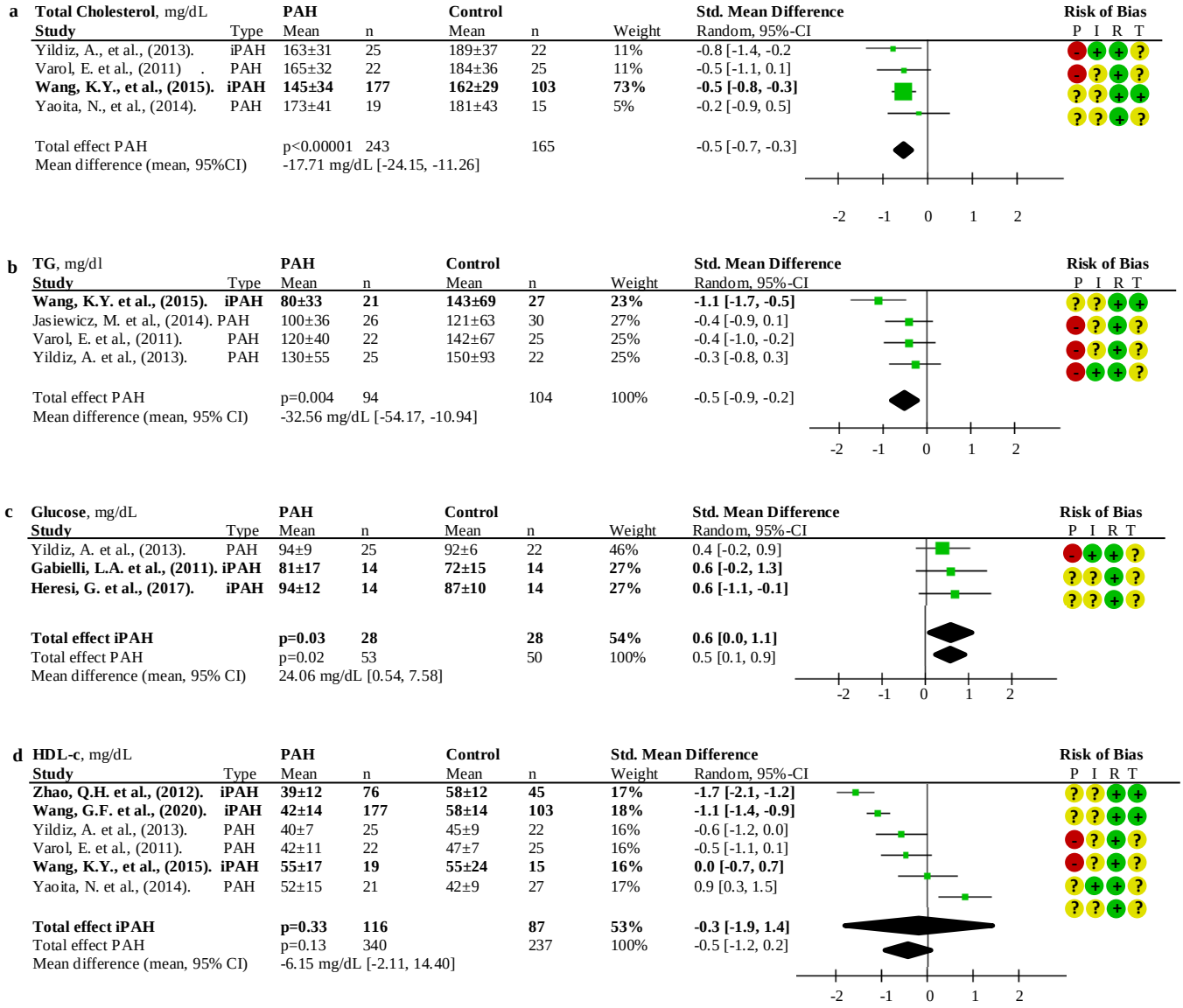


Fig. S3 Forest plots of non-selected metabolic biomarkers, including total cholesterol, TG; triglycerides, glucose, HDL-c; high density lipid-cholesterol. risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; refence standard (diagnosis), T; flow and timing. Publications pressed in bold measured biomarker levels in iPAH and/or hPAH uniquely.

Fig. S4

Coagulation markers

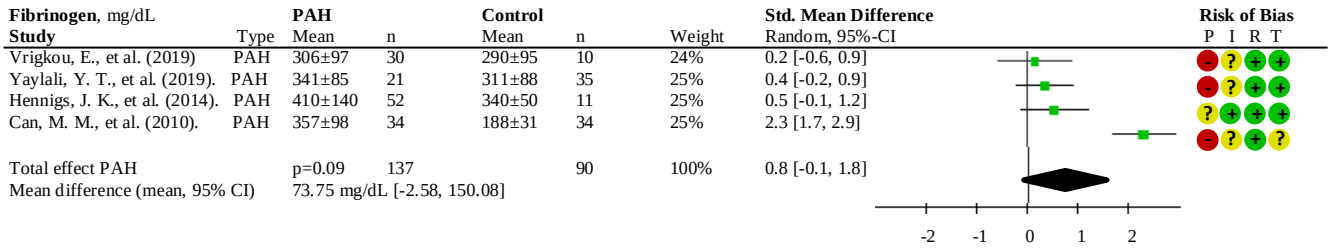


Fig. S4 Forest plots of non-selected coagulation biomarkers, including fibrinogen. Risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; reference standard (diagnosis), T; flow and timing. Publications pressed in bold measured biomarker levels in iPAH and/or hPAH uniquely.

Fig. S5

Inflammation

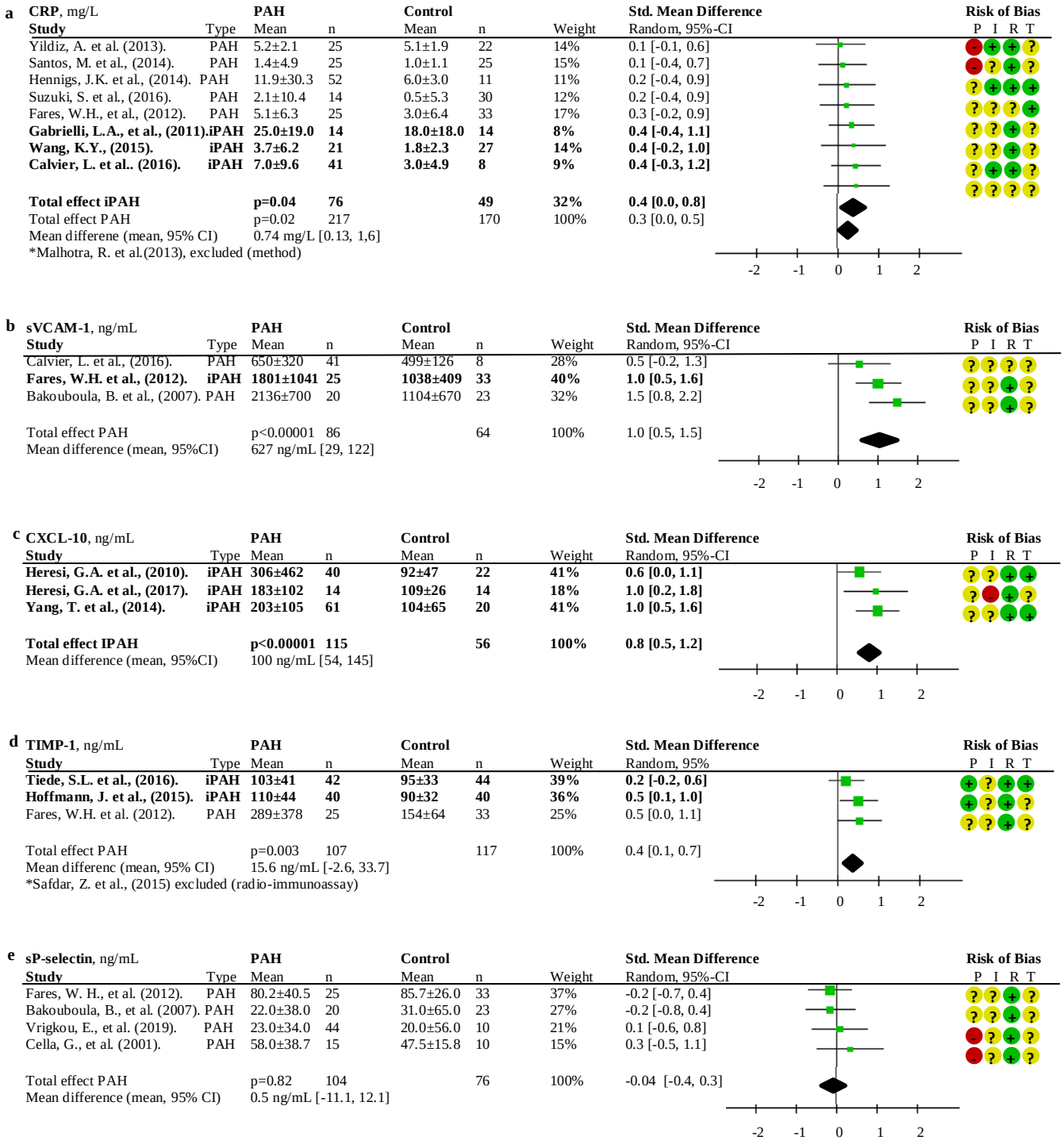


Fig. S5 Forest plots of non-selected inflammatory biomarkers, including; sVCAM-1; circulating vascular cell adhesion molecule-1, CXCL-10; C-X-C motif chemokine ligand-10, CRP; C-reactive protein, TIMP-1; tissue inhibitors of metalloproteinases-1, sP-selectin; soluble P-selectin. Risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; reference standard (diagnosis), T; flow and timing. Publications pressed in bold measured biomarker levels in iPAH and/or hPAH uniquely.

Fig. S6

Renal

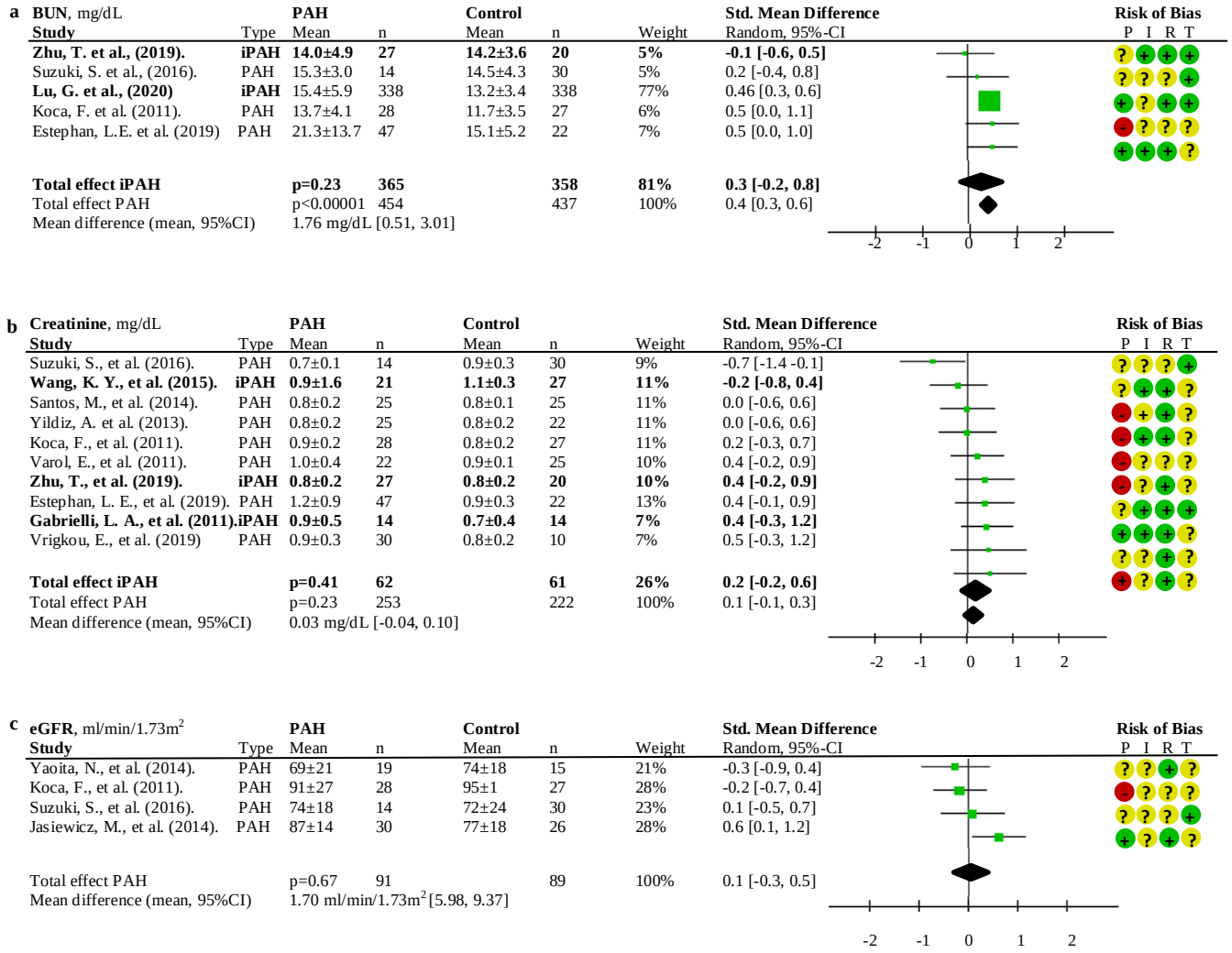


Fig. S6 Forest plots of non-selected renal biomarkers, including; BUN; brain urea nitrogen, creatinine, eGFR; estimated glomerular filtration rate. Risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; reference standard (diagnosis), T; flow and timing. Publications pressed in bold measured biomarker levels in iPAH and/or hPAH uniquely.

Fig. S7

Hepatic

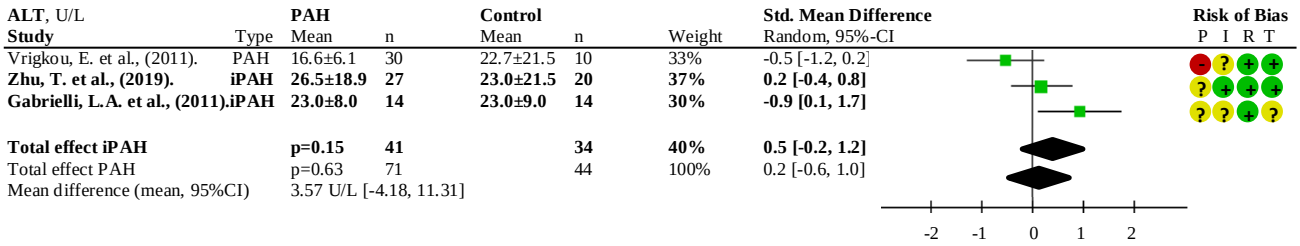
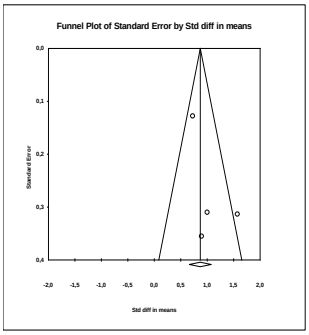


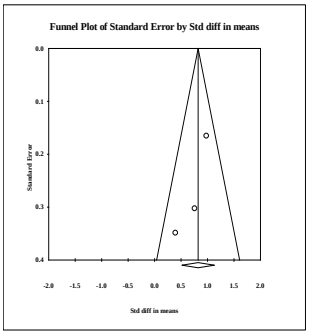
Fig. S7 Forest plots of non-selected hepatic biomarkers, including; ALT; alanine transaminase. Risk of bias (QUADAS-2), P: patient inclusion, I; index-test (biomarker), R; reference standard (diagnosis), T; flow and timing. Publications pressed in bold measured biomarker levels in iPAH and/or hPAH uniquely.

Figure S8

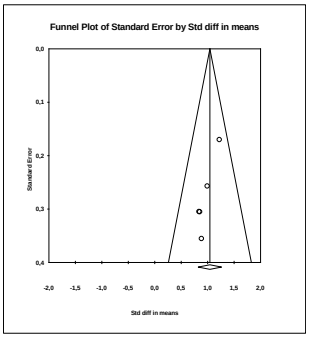
a. RDW



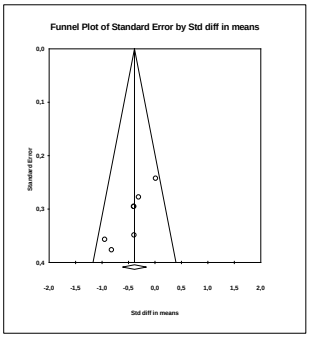
b. PDW



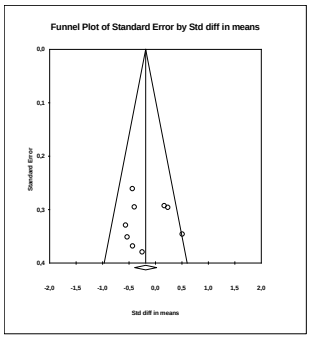
c. MPV



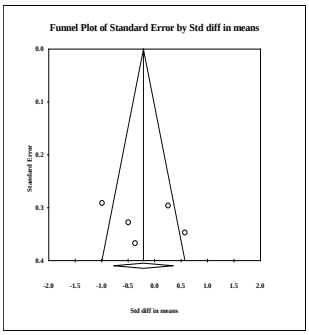
d. Thrombocytes



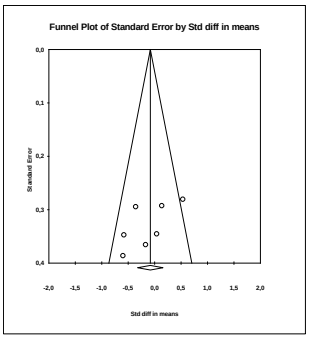
e. Hb



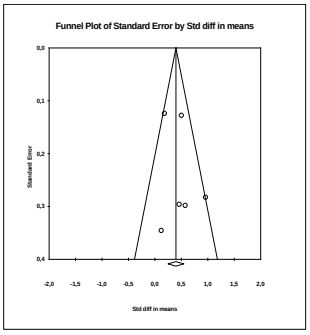
f. Hct



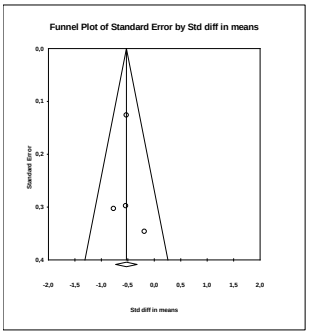
g. Leukocytes



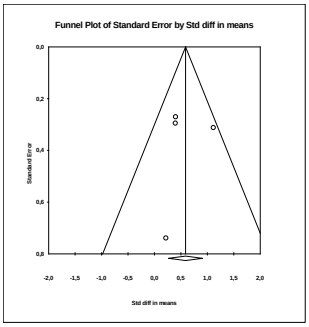
h. LDL-c



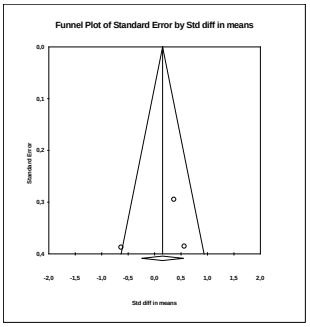
i. Total cholesterol



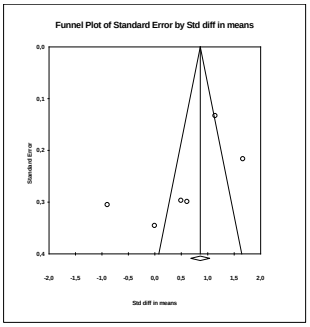
j. TG



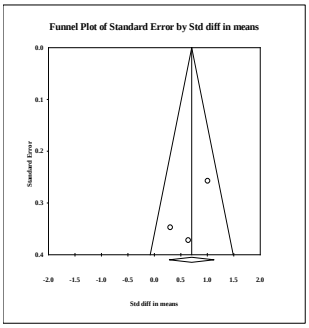
k. Glucose (fasted)



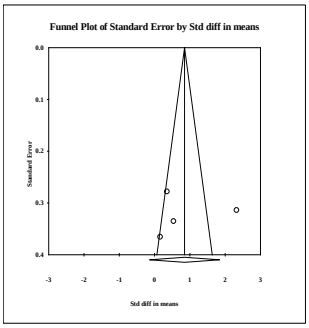
l. HDL-c



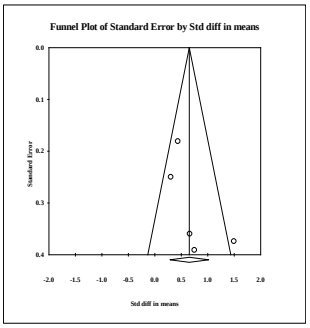
m. D-dimer



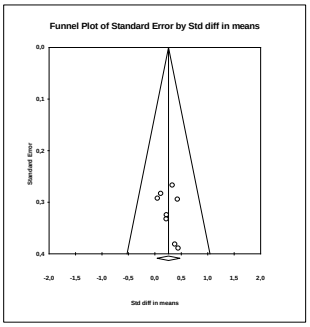
n. Fibrinogen



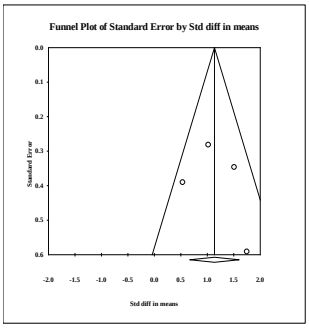
o. IL-6



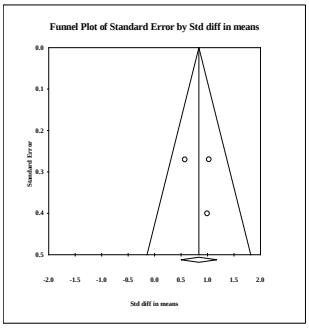
p. CRP



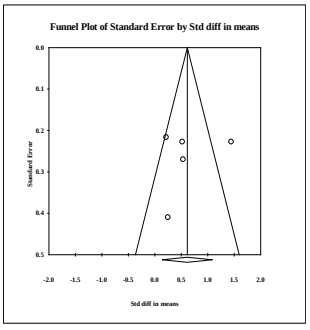
q. sVCAM



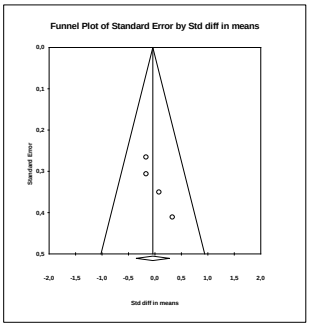
r. CXCL-10



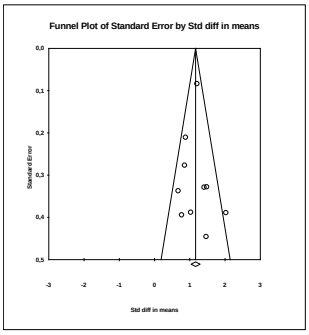
s. TIMP-1



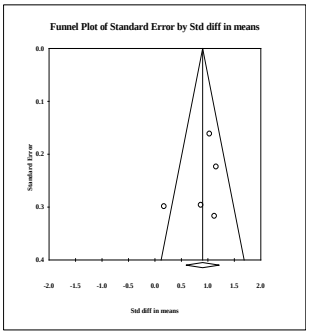
t. sP-selectin



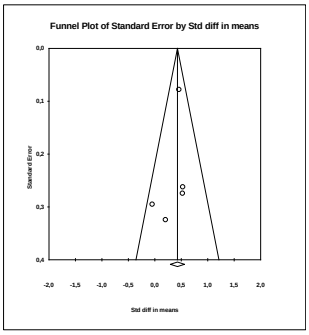
u. NT-proBNP



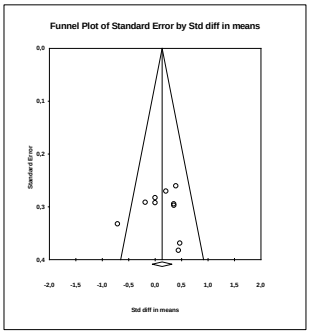
v. UA



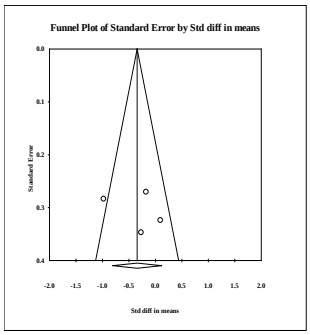
w. BUN



x. Creatinine



y. eGFR



z. ALT

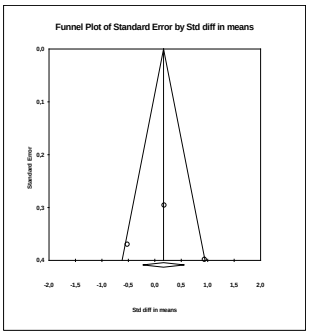


Fig. S8 Funel plots of all meta-analysis indicating publication bias. X-axis; standardized difference in means, y-axis; standard error. Each dot represents one publication.

Table S1

Search strategy Biomarkers

PubMed 887 results (28 January, 2021)

Search	Query	Results
#8	(#1 AND #2 AND (#3 OR #4 OR #5 OR #6 OR #7))	887
#7	"Blood"[Mesh] OR "blood*"[tiab] OR "Plasma"[Mesh] OR "plasma*"[tiab] OR "Serum"[Mesh] OR "serum*"[tiab] OR "sera*"[tiab] OR "Urine"[Mesh] OR "urin*"[tiab]	4519455
#6	"adipogenesis inhibitory factor"[tiab] OR "amcf i"[tiab] OR "antiheparin factor"[tiab] OR "autocrine motility factor"[tiab] OR "b cell differentiation factor"[tiab] OR "b cell growth factor"[tiab] OR "b cell proliferating factor"[tiab] OR "b cell stimulatory factor"[tiab] OR "beta 2 thromboglobulin"[tiab] OR "beta thromboglobulin"[tiab] OR "bsf 1"[tiab] OR "bsf 2"[tiab] OR "Chemokines, CC"[Mesh] OR "chemotactic factor"[tiab] OR "chemotactic peptide"[tiab] OR "colony stimulating factor"[tiab] OR "colony stimulating factors"[tiab] OR "csif 10"[tiab] OR "ctla 8"[tiab] OR "Cytokines"[mesh] OR "cytotoxic t lymphocyte associated antigen"[tiab] OR "eosinophil differentiation factor"[tiab] OR "epidermal cell derived thymocyte activating factor"[tiab] OR "erythrocyte burst promoting factor"[tiab] OR "gamma thromboglobulin"[tiab] OR "gdf 15"[tiab] OR "growth and development factor"[tiab] OR "growth differentiation factor 15"[tiab] OR "heparin neutralizing protein"[tiab] OR "heparin neutralizing proteins"[tiab] OR "hepatocyte growth factor"[tiab] OR "hepatocyte stimulating factor"[tiab] OR "hybridoma growth factor"[tiab] OR "ifn beta 2"[tiab] OR "ifn gamma inducing factor"[tiab] OR "il 1"[tiab] OR "il 10"[tiab] OR "il 11"[tiab] OR "il 12"[tiab] OR "il 12p35"[tiab] OR "il 12p40"[tiab] OR "il 13"[tiab] OR "il 15"[tiab] OR "il 16"[tiab] OR "il 17"[tiab] OR "il 17a"[tiab] OR "il 17b"[tiab] OR "il 17c"[tiab] OR "il 17d"[tiab] OR "il 17e"[tiab] OR "il 17f"[tiab] OR "il 18"[tiab] OR "il 1ra"[tiab] OR "il 23 p19"[tiab] OR "il 23"[tiab] OR "il 23p19"[tiab] OR "il 3"[tiab] OR "il 4"[tiab] OR "il 5"[tiab] OR "il 6"[tiab] OR "il 7"[tiab] OR "il 8"[tiab] OR "il 9"[tiab] OR "kit ligand"[tiab] OR "lcf factor"[tiab] OR "lymphocyte activating factor"[tiab] OR "lymphocyte chemoattractant factor"[tiab] OR "lymphocyte mitogenic factor"[tiab] OR "lymphopoietin 1"[tiab] OR "macrophage cell factor"[tiab] OR "macrophage granulocyte inducer"[tiab] OR "macrophage inflammatory protein"[tiab] OR "macrophage inflammatory proteins"[tiab] OR "mast cell growth factor"[tiab] OR "mcgf 2"[tiab] OR "mgdf factor"[tiab] OR "mgi 1"[tiab] OR "mgi 2"[tiab] OR "monocyte chemotactic proteins"[tiab] OR "mpl ligand"[tiab] OR "myeloid cell growth inducer"[tiab] OR "myeloid differentiation inducing protein"[tiab] OR "myeloproliferative leukemia virus oncogene ligand"[tiab] OR "natural killer cell stimulatory factor"[tiab] OR "neutrophil activating peptide"[tiab] OR "neutrophil activation factor"[tiab] OR "Orphan Nuclear Receptors"[Mesh] OR "p cell stimulating factor"[tiab] OR "plasmacytoma growth factor"[tiab] OR "prostate differentiation factor"[tiab] OR "protein inducer mgi"[tiab] OR "Receptors, Chemokine"[Mesh] OR "Receptors, Cytokine"[Mesh] OR "Receptors, Interleukin-7"[Mesh] OR "recombinant g csf"[tiab] OR "recombinant gm csf"[tiab] OR "ro 23 6019"[tiab] OR "ro 236019"[tiab] OR "ru 49637"[tiab] OR "scatter factor"[tiab] OR "steel factor"[tiab] OR "stem cell factor"[tiab] OR "t cell growth factor"[tiab] OR "t cell replacing factor"[tiab] OR "t cell stimulating factor"[tiab] OR "t helper factor"[tiab] OR "thrombocytopoiesis stimulating factor"[tiab] OR "thymocyte stimulating factor"[tiab] OR "b cell activating factor"[tiab] OR "b cell maturation protein a"[tiab] OR "b lymphocyte activating factor"[tiab] OR "b lymphocyte stimulator"[tiab] OR "betac interleukin receptor subunit"[tiab] OR "br3 b cell activation factor receptor"[tiab] OR "cd 127"[tiab] OR "cd134l protein"[tiab] OR "cd27l protein"[tiab] OR "cd95l"[tiab] OR "csf2rb receptor"[tiab] OR "cytokine receptor gp130"[tiab] OR "enbrel"[tiab] OR "erelzi"[tiab] OR "gp130 signal transducer"[tiab] OR "il6st gp130"[tiab] OR "leukemia inhibitory factor oncostatin m shared receptor"[tiab] OR "leukemia inhibitory factor receptor"[tiab] OR "lin"[tiab] OR "lin+"[tiab] OR "nf kappa b receptor activator"[tiab] OR "nf kappab receptor activator"[tiab] OR "oncostatin m leukemia inhibitory factor shared receptor"[tiab] OR "oncostatin m receptor beta"[tiab] OR "oncostatin m type i receptor"[tiab] OR "oncostatin m type ii receptor"[tiab] OR "osteoclast differentiation factor"[tiab] OR "p145 c kit"[tiab] OR "p145c kit"[tiab] OR "proto oncogene protein c kit"[tiab] OR "proto oncogene protein fms"[tiab] OR "proto oncogene protein kit"[tiab] OR "proto oncogene proteins c kit"[tiab] OR "rankl"[tiab] OR "receptor activator of nf kappa b"[tiab] OR "receptor activator of nf kappab"[tiab] OR "receptor activator of nuclear factor kappa b"[tiab] OR "sgp130"[tiab] OR "signal transducer gp130"[tiab] OR "signal transducing receptor gp130"[tiab] OR "soluble glycoprotein 130"[tiab] OR "soluble gp130"[tiab] OR "t b cell activating molecule"[tiab] OR "t cell gp39 antigen"[tiab] OR "tall 1 protein"[tiab] OR "tnfr fc fusion protein"[tiab] OR "tnfrsf11a protein"[tiab] OR "tnfrsf5 receptor"[tiab] OR "tnfrsf8 receptor"[tiab] OR "tnfsf13b"[tiab] OR "tnr 001"[tiab] OR "tnr001"[tiab] OR "tntr fc"[tiab] OR "trance protein"[tiab] OR "trance r"[tiab] OR "transmembrane activator and caml interactor protein"[tiab] OR "tweakr"[tiab] OR "4 1bb ligand*"[tiab] OR "4 1bbl protein*"[tiab] OR "apo 1 antigen*"[tiab] OR "b cell maturation antigen*"[tiab] OR "baff ligand*"[tiab] OR "baff receptor*"[tiab] OR "bcgf"[tiab] OR "bcma protein*"[tiab] OR "ber h2 antigen*"[tiab] OR "blys protein*"[tiab] OR "c fms protein*"[tiab] OR "c kit protein*"[tiab] OR "c kit receptor*"[tiab] OR "catabolin*"[tiab] OR "ccl1"[tiab] OR "ccl11"[tiab] OR "ccl17"[tiab] OR "ccl18"[tiab] OR "ccl19"[tiab] OR "ccl2"[tiab] OR "ccl20"[tiab] OR "ccl21"[tiab] OR "ccl22"[tiab] OR "ccl24"[tiab] OR "ccl26"[tiab] OR "ccl27"[tiab] OR "ccl3"[tiab] OR "ccl4"[tiab] OR "ccl5"[tiab] OR "ccl7"[tiab] OR "ccl8"[tiab] OR "ccr"[tiab] OR "ccr1"[tiab] OR "ccr10"[tiab] OR "ccr2"[tiab] OR "ccr3"[tiab] OR "ccr4"[tiab] OR "ccr5"[tiab] OR "ccr6"[tiab] OR "ccr7"[tiab] OR "ccr8"[tiab] OR "cd115 antigen*"[tiab] OR "cd116 antigen*"[tiab] OR "cd117 antigen*"[tiab] OR "cd118 antigen*"[tiab] OR "cd127"[tiab] OR "cd130 antigen*"[tiab] OR "cd131 antigen*"[tiab] OR "cd134 antigen*"[tiab] OR "cd134 ligand*"[tiab] OR "cd137 ligand*"[tiab] OR "cd153 antigen*"[tiab] OR "cd154 antigen*"[tiab] OR "cd178 antigen*"[tiab] OR "cd254 antigen*"[tiab] OR "cd257 antigen*"[tiab] OR "cd265 antigen*"[tiab] OR "cd266 antigen*"[tiab] OR "cd267 antigen*"[tiab] OR "cd268 antigen*"[tiab] OR "cd27 ligand*"[tiab] OR "cd30 antigen*"[tiab] OR "cd30 ligand*"[tiab] OR "cd357 antigen*"[tiab] OR "cd40 antigen*"[tiab] OR "cd40 ligand*"[tiab] OR "cd40l"[tiab] OR "cd70 antigen*"[tiab] OR "cd95 antigen*"[tiab] OR "cd95 ligand*"[tiab] OR "cdw40 antigen*"[tiab] OR "chemokin*"[tiab] OR "chemokine*"[tiab] OR "colony stimulating factor receptor*"[tiab] OR "csf 1 receptor*"[tiab] OR "csf receptor*"[tiab] OR "ctla8"[tiab] OR "cx3c"[tiab] OR "cxcl8"[tiab] OR "cxcr"[tiab] OR "cxcr3"[tiab] OR "cxcr4"[tiab] OR "cxcr5"[tiab] OR "cxcr6"[tiab] OR "cytokin*"[tiab] OR "ectodysplasin*"[tiab] OR "erythropoietin receptor*"[tiab] OR "erythropoietin*"[tiab] OR "etanercept"[tiab] OR "fas antigen*"[tiab] OR "fas cell surface death receptor*"[tiab] OR "fas ligand*"[tiab] OR "fas receptor*"[tiab] OR "fasl protein*"[tiab] OR "fms proto oncogene protein*"[tiab] OR "fn14 receptor*"[tiab] OR "g csf receptor*"[tiab] OR "glucocorticoid induced tnfr related protein*"[tiab] OR "gm csf receptor*"[tiab] OR "gp130 transducing protein*"[tiab] OR "granulocyte colony stimulating factor receptor*"[tiab] OR "hematopoieti*"[tiab] OR "hepatopoietin*"[tiab] OR "il1"[tiab] OR "il10"[tiab] OR "il11"[tiab] OR "il12"[tiab] OR "il13"[tiab] OR "il15"[tiab] OR "il16"[tiab] OR "il17"[tiab] OR "il17a"[tiab] OR "il17b"[tiab] OR "il17c"[tiab] OR "il17d"[tiab] OR "il17e"[tiab] OR "il17f"[tiab] OR "il18"[tiab] OR "il23"[tiab] OR "il3"[tiab] OR "il4"[tiab] OR "il5"[tiab] OR "il6"[tiab] OR "il7"[tiab] OR "il8"[tiab] OR "il9"[tiab] OR "interferon*"[tiab] OR "interleukin*"[tiab] OR "ki 1 antigen*"[tiab] OR "kit proto oncogene protein*"[tiab] OR "lif receptor*"[tiab] OR "lineage negative"[tiab] OR "lymphokine*"[tiab] OR "lymphotoxin*"[tiab] OR "m csf receptor*"[tiab] OR "macrophage colony stimulating factor receptor*"[tiab] OR "monocyte chemoattractant protein*"[tiab] OR "monocyte chemotactic protein*"[tiab] OR "opgl protein*"[tiab] OR "osm lif receptor*"[tiab] OR "osteoprotegerin ligand*"[tiab] OR "ox40 ligand*"[tiab] OR "ox40 receptor*"[tiab] OR "ox40l	1211502

	protein*"[tiab] OR "rank ligand*"[tiab] OR "recombinant human dimeric tnf receptor type ii igg fusion protein*"[tiab] OR "ro236019"[tiab] OR "ru49637"[tiab] OR "scf receptor*"[tiab] OR "stem cell factor receptor*"[tiab] OR "taci receptor*"[tiab] OR "tcgf"[tiab] OR "thank protein*"[tiab] OR "thrombocytopoietin*"[tiab] OR "thrombopoietin*"[tiab] OR "tnfrsf6 receptor*"[tiab] OR "tnt receptor fusion protein*"[tiab] OR "trance receptor*"[tiab] OR "tweak receptor*"[tiab] OR "transforming growth factor*"[tiab] OR "tumor necrosis factor*"[tiab]	
#5	"Blood Cells"[Mesh] OR "blood cell*"[tiab] OR "thrombocyt*"[tiab] OR "platelet*"[tiab] OR "erythrocyt*"[tiab] OR "hemocyt*"[tiab] OR "leukocyt*"[tiab] OR "reticulocyt*"[tiab] OR "granulocyt*"[tiab] OR "mononuclear cell*"[tiab] OR "stem cell*"[tiab] OR "progenitor cell*"[tiab] OR "mother cell*"[tiab] OR "colony forming"[tiab] OR "basophil*"[tiab] OR "eosinophil*"[tiab] OR "neutrophil*"[tiab] OR "lymphocyt*"[tiab] OR "monocyt*"[tiab] OR "killer cell*"[tiab] OR "nk cell*"[tiab] OR "precursor cell*"[tiab] OR "suppressor cell*"[tiab] OR "myelocyt*"[tiab] OR "myeloblast*"[tiab] OR "B-cell*"[tiab] OR "T-cell*"[tiab] OR "T helper cel*"[tiab] OR "Treg*"[tiab] OR "macrophage*"[tiab] OR "myeloid cell*"[tiab] OR "dendritic cell*"[tiab] OR "antigen-presenting cell*"[tiab] OR "immune cell*"[tiab] OR "inflammatory cell*"[tiab] OR "CD4"[tiab] OR "CD8"[tiab]	2350640
#4	"Extracellular Vesicles"[Mesh] OR "microparticle*"[tiab] OR "microvesicle*"[tiab] OR "exosom*"[tiab] OR "ectosom*"[tiab] OR "extracellular vesicle*"[tiab] OR "exovesicle*"[tiab] OR "apoptotic bod*"[tiab]	46380
#3	"MicroRNAs"[Mesh] OR "MicroRNA*"[tiab] OR "Micro RNA*"[tiab] OR "miRNA*"[tiab] OR "pri-miRNA*"[tiab] OR "stRNA*"[tiab] OR "Small Temporal RNA*"[tiab] OR "pre-miRNA*"[tiab] OR "lncRNA* "[tiab] OR "non-coding RNA*"[tiab] OR "noncoding RNA*"[tiab] OR "ncRNA*"[tiab]	150417
#2	("Biomarkers"[Mesh] OR "biomarker*"[tiab] OR "marker*"[tiab] OR "indicator*"[tiab])	1729998
#1	("Familial Primary Pulmonary Hypertension"[Mesh] OR "pulmonary arterial hypertensi*"[tiab] OR "pulmonary artery hypertensi*"[tiab] OR "idiopathic pulmonary hypertens*"[tiab] OR "hereditary pulmonary hypertens*"[tiab] OR "heritable pulmonary hypertens*"[tiab] OR "primary pulmonary hypertensi*"[tiab] OR "primary pulmonary hypertens*"[tiab])	16546

Embase.com 1506 results, 736 excluding conference abstracts (28 January, 2021)

No.	Query	Results
#10	#9 NOT 'conference abstract'/it	736
#9	#8 NOT ([animals]/lim NOT [humans]/lim)	1506
#8	#1 AND #2 AND (#3 OR #4 OR #5 OR #6 OR #7)	1740
#7	'urine'/exp OR 'blood'/exp OR 'blood*':ti,ab,kw OR 'plasma*':ti,ab,kw OR 'serum*':ti,ab,kw OR 'sera*':ti,ab,kw OR 'urin*':ti,ab,kw	6345741
#6	'cytokine'/exp OR 'orphan nuclear receptor'/exp OR 'cytokine receptor'/exp OR 'adipogenesis inhibitory factor*':ti,ab,kw OR 'amcf i':ti,ab,kw OR 'antiheparin factor*':ti,ab,kw OR 'autocrine motility factor*':ti,ab,kw OR 'apo 1 antigen*':ti,ab,kw OR 'b cell differentiation factor*':ti,ab,kw OR 'b cell growth factor*':ti,ab,kw OR 'b cell proliferating factor*':ti,ab,kw OR 'b cell stimulatory factor*':ti,ab,kw OR 'beta 2 thromboglobulin':ti,ab,kw OR 'beta thromboglobulin':ti,ab,kw OR 'bsf 1':ti,ab,kw OR 'bsf 2':ti,ab,kw OR 'b cell activating factor*':ti,ab,kw OR 'b cell maturation protein a':ti,ab,kw OR 'b lymphocyte activating factor*':ti,ab,kw OR 'b lymphocyte stimulator':ti,ab,kw OR 'betac interleukin receptor subunit':ti,ab,kw OR 'br3 b cell activation factor receptor':ti,ab,kw OR 'b cell maturation antigen*':ti,ab,kw OR 'baff ligand*':ti,ab,kw OR 'baff receptor*':ti,ab,kw OR 'bcgf':ti,ab,kw OR 'bcma protein*':ti,ab,kw OR 'ber h2 antigen*':ti,ab,kw OR 'blys protein*':ti,ab,kw OR 'chemotactic factor*':ti,ab,kw OR 'chemotactic peptid*':ti,ab,kw OR 'colony stimulating factor*':ti,ab,kw OR 'csif 10':ti,ab,kw OR 'ctla 8':ti,ab,kw OR 'cytotoxic t lymphocyte associated antigen':ti,ab,kw OR 'cd 127':ti,ab,kw OR 'cd134l protein':ti,ab,kw OR 'cd27l protein':ti,ab,kw OR 'cd95l':ti,ab,kw OR 'csf2rb receptor':ti,ab,kw OR 'cytokine receptor gp130':ti,ab,kw OR 'c fms protein*':ti,ab,kw OR 'c kit protein*':ti,ab,kw OR 'c kit receptor*':ti,ab,kw OR 'catabolin*':ti,ab,kw OR 'ccl1*':ti,ab,kw OR 'ccl2*':ti,ab,kw OR 'ccl3*':ti,ab,kw OR 'ccl4':ti,ab,kw OR 'ccl5':ti,ab,kw OR 'ccl7':ti,ab,kw OR 'ccl8':ti,ab,kw OR 'ccr':ti,ab,kw OR 'ccr1*':ti,ab,kw OR 'ccr2':ti,ab,kw OR 'ccr3':ti,ab,kw OR 'ccr4':ti,ab,kw OR 'ccr5':ti,ab,kw OR 'ccr6':ti,ab,kw OR 'ccr7':ti,ab,kw OR 'ccr8':ti,ab,kw OR 'cd115 antigen*':ti,ab,kw OR 'cd116 antigen*':ti,ab,kw OR 'cd117 antigen*':ti,ab,kw OR 'cd118 antigen*':ti,ab,kw OR 'cd127':ti,ab,kw OR 'cd130 antigen*':ti,ab,kw OR 'cd131 antigen*':ti,ab,kw OR 'cd134 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'hybridoma growth factor':ti,ab,kw OR 'hematopoieti*':ti,ab,kw OR 'hepatopoietin*':ti,ab,kw OR 'ifn beta 2':ti,ab,kw OR 'ifn gamma inducing factor':ti,ab,kw OR 'il 1':ti,ab,kw OR 'il 10':ti,ab,kw OR 'il 11':ti,ab,kw OR 'il 12':ti,ab,kw OR 'il 12p35':ti,ab,kw OR 'il 12p40':ti,ab,kw OR 'il 13':ti,ab,kw OR 'il 15':ti,ab,kw OR 'il 16':ti,ab,kw OR 'il 17':ti,ab,kw OR 'il 17a':ti,ab,kw OR 'il 17b':ti,ab,kw OR 'il 17c':ti,ab,kw OR 'il 17d':ti,ab,kw OR 'il 17e':ti,ab,kw OR 'il 17f':ti,ab,kw OR 'il 18':ti,ab,kw OR 'il 1ra':ti,ab,kw OR 'il 23 p19':ti,ab,kw OR 'il 23':ti,ab,kw OR 'il 23p19':ti,ab,kw OR 'il 3':ti,ab,kw OR 'il 4':ti,ab,kw OR 'il 5':ti,ab,kw OR 'il 6':ti,ab,kw OR 'il 7':ti,ab,kw OR 'il 8':ti,ab,kw OR 'il 9':ti,ab,kw OR 'il6st gp130':ti,ab,kw OR 'il1':ti,ab,kw OR 'il10':ti,ab,kw OR 'il11':ti,ab,kw OR 'il12':ti,ab,kw OR 'il13':ti,ab,kw OR 'il15':ti,ab,kw OR 'il16':ti,ab,kw OR 'il17':ti,ab,kw OR 'il17a':ti,ab,kw OR 'il17b':ti,ab,kw OR 'il17c':ti,ab,kw OR 'il17d':ti,ab,kw OR 'il17e':ti,ab,kw OR 'il17f':ti,ab,kw OR 'il18':ti,ab,kw OR 'il23':ti,ab,kw OR 'il3':ti,ab,kw OR 'il4':ti,ab,kw OR 'il5':ti,ab,kw OR 'il6':ti,ab,kw OR 'il7':ti,ab,kw OR 'il8':ti,ab,kw OR 'il9':ti,ab,kw OR 'interferon*':ti,ab,kw OR 'interleukin*':ti,ab,kw OR 'kit ligand':ti,ab,kw OR 'lcf factor':ti,ab,kw OR 'ki 1 antigen*':ti,ab,kw OR 'kit proto oncogene protein*':ti,ab,kw OR 'lymphocyte activating factor':ti,ab,kw OR 'lymphocyte chemoattractant factor':ti,ab,kw OR 'lymphocyte mitogenic factor':ti,ab,kw OR 'lymphopoietin 1':ti,ab,kw OR 'leukemia inhibitory factor oncostatin m shared receptor':ti,ab,kw OR 'leukemia inhibitory factor receptor':ti,ab,kw OR 'lin':ti,ab,kw OR 'lin+':ti,ab,kw OR 'lif receptor*':ti,ab,kw OR 'lineage negative':ti,ab,kw OR 'lymphokine*':ti,ab,kw OR 'lymphotoxin*':ti,ab,kw OR 'macrophage cell factor':ti,ab,kw OR 'macrophage granulocyte inducer':ti,ab,kw OR 'macrophage inflammatory	2048571

	protein':ti,ab,kw OR 'macrophage inflammatory proteins':ti,ab,kw OR 'mast cell growth factor':ti,ab,kw OR 'mcgf 2':ti,ab,kw OR 'mgdf factor':ti,ab,kw OR 'mgi 1':ti,ab,kw OR 'mgi 2':ti,ab,kw OR 'monocyte chemotactic proteins':ti,ab,kw OR 'mpl ligand':ti,ab,kw OR 'myeloid cell growth inducer':ti,ab,kw OR 'myeloid differentiation inducing protein':ti,ab,kw OR 'myeloproliferative leukemia virus oncogene ligand':ti,ab,kw OR 'm csf receptor*':ti,ab,kw OR 'monocyte chemoattractant protein*':ti,ab,kw OR 'monocyte chemotactic protein*':ti,ab,kw OR 'natural killer cell stimulatory factor*':ti,ab,kw OR 'neutrophil activating peptide':ti,ab,kw OR 'neutrophil activation factor':ti,ab,kw OR 'nf kappa b receptor activator':ti,ab,kw OR 'nf kappab receptor activator':ti,ab,kw OR 'p cell stimulating factor':ti,ab,kw OR 'oncostatin m leukemia inhibitory factor shared receptor':ti,ab,kw OR 'oncostatin m receptor beta':ti,ab,kw OR 'oncostatin m type i receptor':ti,ab,kw OR 'oncostatin m type ii receptor':ti,ab,kw OR 'osteoclast differentiation factor':ti,ab,kw OR 'opgl protein*':ti,ab,kw OR 'osm lif receptor*':ti,ab,kw OR 'osteoprotegerin ligand*':ti,ab,kw OR 'ox40 ligand*':ti,ab,kw OR 'ox40 receptor*':ti,ab,kw OR 'ox40l protein*':ti,ab,kw OR 'plasmacytoma growth factor':ti,ab,kw OR 'prostate differentiation factor':ti,ab,kw OR 'protein inducer mgi':ti,ab,kw OR 'p145 c kit':ti,ab,kw OR 'p145c kit':ti,ab,kw OR 'proto oncogene protein c kit':ti,ab,kw OR 'proto oncogene protein fms':ti,ab,kw OR 'proto oncogene protein kit':ti,ab,kw OR 'proto oncogene proteins c kit':ti,ab,kw OR 'recombinant g csf':ti,ab,kw OR 'recombinant gm csf':ti,ab,kw OR 'ro 23 6019':ti,ab,kw OR 'ro 236019':ti,ab,kw OR 'ru 49637':ti,ab,kw OR 'rankl':ti,ab,kw OR 'receptor activator of nf kappa b':ti,ab,kw OR 'receptor activator of nf kappab':ti,ab,kw OR 'receptor activator of nuclear factor kappa b':ti,ab,kw OR 'rank ligand*':ti,ab,kw OR 'recombinant human dimeric tnf receptor type ii igg fusion protein*':ti,ab,kw OR 'ro236019':ti,ab,kw OR 'ru49637':ti,ab,kw OR 'scatter factor':ti,ab,kw OR 'steel factor':ti,ab,kw OR 'stem cell factor':ti,ab,kw OR 'sgp130':ti,ab,kw OR 'signal transducer gp130':ti,ab,kw OR 'signal transducing receptor gp130':ti,ab,kw OR 'soluble glycoprotein 130':ti,ab,kw OR 'soluble gp130':ti,ab,kw OR 'scf receptor*':ti,ab,kw OR 'stem cell factor receptor*':ti,ab,kw OR 't cell growth factor':ti,ab,kw OR 't cell replacing factor':ti,ab,kw OR 't cell stimulating factor':ti,ab,kw OR 't helper factor':ti,ab,kw OR 'thrombocytopoiesis stimulating factor':ti,ab,kw OR 'thymocyte stimulating factor':ti,ab,kw OR 't b cell activating molecule':ti,ab,kw OR 't cell gp39 antigen':ti,ab,kw OR 'tall 1 protein':ti,ab,kw OR 'tnfr fc fusion protein':ti,ab,kw OR 'tnfrsf11a protein':ti,ab,kw OR 'tnfrsf5 receptor':ti,ab,kw OR 'tnfrsf8 receptor':ti,ab,kw OR 'tnfsf13b':ti,ab,kw OR 'tnr 001':ti,ab,kw OR 'tnr001':ti,ab,kw OR 'tntr fc':ti,ab,kw OR 'trance protein':ti,ab,kw OR 'trance r':ti,ab,kw OR 'transmembrane activator and caml interactor protein':ti,ab,kw OR 'tweakr':ti,ab,kw OR 'taci receptor*':ti,ab,kw OR 'tcgf':ti,ab,kw OR 'thank protein*':ti,ab,kw OR 'thrombocytopoietin*':ti,ab,kw OR 'thrombopoietin*':ti,ab,kw OR 'tnfrsf6 receptor*':ti,ab,kw OR 'tnt receptor fusion protein*':ti,ab,kw OR 'trance receptor*':ti,ab,kw OR 'tweak receptor*':ti,ab,kw OR 'transforming growth factor*':ti,ab,kw OR 'tumor necrosis factor*':ti,ab,kw OR '4 1bb ligand*':ti,ab,kw OR '4 1bbl protein*':ti,ab,kw	
#5	'blood cell'/exp OR 'blood cell*':ti,ab,kw OR 'thrombocyt*':ti,ab,kw OR 'platelet*':ti,ab,kw OR 'erythrocyt*':ti,ab,kw OR 'hemocyt*':ti,ab,kw OR 'leukocyt*':ti,ab,kw OR 'reticulocyt*':ti,ab,kw OR 'granulocyt*':ti,ab,kw OR 'mononuclear cell*':ti,ab,kw OR 'stem cell*':ti,ab,kw OR 'progenitor cell*':ti,ab,kw OR 'mother cell*':ti,ab,kw OR 'colony forming':ti,ab,kw OR 'basophil*':ti,ab,kw OR 'eosinophil*':ti,ab,kw OR 'neutrophil*':ti,ab,kw OR 'lymphocyt*':ti,ab,kw OR 'monocyt*':ti,ab,kw OR 'killer cell*':ti,ab,kw OR 'nk cell*':ti,ab,kw OR 'precursor cell*':ti,ab,kw OR 'suppressor cell*':ti,ab,kw OR 'myelocyt*':ti,ab,kw OR 'myeloblast*':ti,ab,kw OR 'b-cell*':ti,ab,kw OR 't-cell*':ti,ab,kw OR 't helper cel*':ti,ab,kw OR 'treg*':ti,ab,kw OR 'macrophage*':ti,ab,kw OR 'myeloid cell*':ti,ab,kw OR 'dendritic cell*':ti,ab,kw OR 'antigen-presenting cell*':ti,ab,kw OR 'immune cell*':ti,ab,kw OR 'inflammatory cell*':ti,ab,kw OR 'cd4':ti,ab,kw OR 'cd8':ti,ab,kw	3208435
#4	'microparticle*':ti,ab,kw OR 'microvesicle*':ti,ab,kw OR 'exosom*':ti,ab,kw OR 'ectosom*':ti,ab,kw OR 'extracellular vesicle*':ti,ab,kw OR 'exovesicle*':ti,ab,kw OR 'apoptotic bod*':ti,ab,kw	64493
#3	'microrna'/exp OR 'microrna*':ti,ab,kw OR 'micro rna*':ti,ab,kw OR 'mirna*':ti,ab,kw OR 'pri-mirna*':ti,ab,kw OR 'strna*':ti,ab,kw OR 'small temporal rna*':ti,ab,kw OR 'pre-mirna*':ti,ab,kw OR 'lncrna*':ti,ab,kw OR 'non-coding rna*':ti,ab,kw OR 'noncoding rna*':ti,ab,kw OR 'ncrna*':ti,ab,kw	209930
#2	'biological marker'/exp OR 'biomarker*':ti,ab,kw OR 'marker*':ti,ab,kw OR 'indicator*':ti,ab,kw	1876051
#1	'pulmonary arterial hypertens*':ti,ab,kw OR 'pulmonary artery hypertens*':ti,ab,kw OR 'idiopathic pulmonary hypertensi*':ti,ab,kw OR 'primary pulmonary hypertens*':ti,ab,kw OR 'heritable pulmonary hypertensin':ti,ab,kw OR 'hereditary pulmonary hypertens*':ti,ab,kw	28468

Clarivate Analytics/ Web of Science Core Collection 976 results (28 January, 2021)

Set	Result	
#8	#1 AND #2 AND (#3 OR #4 OR #5 OR #6 OR #7) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	976
#7	TS=("blood*" OR "plasma*" OR "serum*" OR "sera*" OR "urin*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	4312314

#6	TS=("adipogenesis inhibitory factor*" OR "amcf i" OR "antiheparin factor*" OR "autocrine motility factor*" OR "apo 1 antigen*" OR "b cell differentiation factor*" OR "b cell growth factor*" OR "b cell proliferating factor*" OR "b cell stimulatory factor*" OR "beta 2 thromboglobulin" OR "beta thromboglobulin" OR "bsf 1" OR "bsf 2" OR "b cell activating factor*" OR "b cell maturation protein a" OR "b lymphocyte activating factor*" OR "b lymphocyte stimulator" OR "betac interleukin receptor subunit" OR "br3 b cell activation factor receptor" OR "b cell maturation antigen*" OR "baff ligand*" OR "baff receptor*" OR "bcgf" OR "bcma protein*" OR "ber h2 antigen*" OR "blys protein*" OR "chemotactic factor*" OR "chemotactic peptid*" OR "colony stimulating factor*" OR "csif 10" OR "ctla 8" OR "cytotoxic t lymphocyte associated antigen" OR "cd 127" OR "cd 134l protein" OR "cd27l protein" OR "cd95l" OR "csf2rb receptor" OR "cytokine receptor gp130" OR "c fms protein*" OR "c kit protein*" OR "c kit receptor*" OR "catabolin*" OR "ccl1*" OR "ccl2*" OR "ccl3*" OR "ccl4" OR "ccl5" OR "ccl7" OR "ccl8" OR "ccr" OR "ccr1*" OR "ccr2" OR "ccr3" OR "ccr4" OR "ccr5" OR "ccr6" OR "ccr7" OR "ccr8" OR "cd115 antigen*" OR "cd116 antigen*" OR "cd117 antigen*" OR "cd118 antigen*" OR "cd127" OR "cd130 antigen*" OR "cd131 antigen*" OR "cd134 antigen*" OR "cd134 ligand*" OR "cd137 ligand*" OR "cd153 antigen*" OR "cd154 antigen*" OR "cd178 antigen*" OR "cd254 antigen*" OR "cd257 antigen*" OR "cd265 antigen*" OR "cd266 antigen*" OR "cd267 antigen*" OR "cd268 antigen*" OR "cd27 ligand*" OR "cd30 antigen*" OR "cd30 ligand*" OR "cd357 antigen*" OR "cd40 antigen*" OR "cd40 ligand*" OR "cd40l" OR "cd70 antigen*" OR "cd95 antigen*" OR "cd95 ligand*" OR "cdw40 antigen*" OR "chemokin*" OR "chemokine*" OR "csf 1 receptor*" OR "csf receptor*" OR "ctla8" OR "cx3c" OR "cxcl8" OR "cxcr" OR "cxcr3" OR "cxcr4" OR "cxcr5" OR "cxcr6" OR "cytokin*" OR "eosinophil differentiation factor" OR "epidermal cell derived thymocyte activating factor" OR "erythrocyte burst promoting factor" OR "enbrel" OR "erelzi" OR "ectodysplasin*" OR "erythropoietin receptor*" OR "erythropoietin*" OR "etanercept" OR "fas antigen*" OR "fas cell surface death receptor*" OR "fas ligand*" OR "fas receptor*" OR "fasl protein*" OR "fms proto oncogene protein*" OR "fn14 receptor*" OR "gamma thromboglobulin" OR "gdf 15" OR "growth and development factor" OR "growth differentiation factor 15" OR "gp130 signal transducer" OR "g csf receptor*" OR "glucocorticoid induced tnfr related protein*" OR "gm csf receptor*" OR "gp130 transducing protein*" OR "heparin neutralizing protein" OR "heparin neutralizing proteins" OR "hepatocyte growth factor" OR "hepatocyte stimulating factor" OR "hybridoma growth factor" OR "hematopoieti*" OR "hepatopoietin*" OR "ifn beta 2" OR "ifn gamma inducing factor" OR "il 1" OR "il 10" OR "il 11" OR "il 12" OR "il 12p35" OR "il 12p40" OR "il 13" OR "il 15" OR "il 16" OR "il 17" OR "il 17a" OR "il 17b" OR "il 17c" OR "il 17d" OR "il 17e" OR "il 17f" OR "il 18" OR "il 1ra" OR "il 23 p19" OR "il 23" OR "il 23p19" OR "il 3" OR "il 4" OR "il 5" OR "il 6" OR "il 7" OR "il 8" OR "il 9" OR "il6st gp130" OR "il1" OR "il10" OR "il11" OR "il12" OR "il13" OR "il15" OR "il16" OR "il17" OR "il17a" OR "il17b" OR "il17c" OR "il17d" OR "il17e" OR "il17f" OR "il18" OR "il23" OR "il3" OR "il4" OR "il5" OR "il6" OR "il7" OR "il8" OR "il9" OR "interferon*" OR "interleukin*" OR "kit ligand" OR "lcf factor" OR "ki 1 antigen*" OR "kit proto oncogene protein*" OR "lymphocyte activating factor" OR "lymphocyte chemoattractant factor" OR "lymphocyte mitogenic factor" OR "lymphopoietin 1" OR "leukemia inhibitory factor oncostatin m shared receptor" OR "leukemia inhibitory factor receptor" OR "lin" OR "lin+" OR "lif receptor*" OR "lineage negative" OR "lymphokine*" OR "lymphotoxin*" OR "macrophage cell factor" OR "macrophage granulocyte inducer" OR "macrophage inflammatory protein" OR "macrophage inflammatory proteins" OR "mast cell growth factor" OR "mcgf 2" OR "mgdf factor" OR "mgi 1" OR "mgi 2" OR "monocyte chemotactic proteins" OR "mpl ligand" OR "myeloid cell growth inducer" OR "myeloid differentiation inducing protein" OR "myeloproliferative leukemia virus oncogene ligand" OR "m csf receptor*" OR "monocyte chemoattractant protein*" OR "monocyte chemotactic protein*" OR "natural killer cell stimulatory factor*" OR "neutrophil activating peptide" OR "neutrophil activation factor" OR "nf kappa b receptor activator" OR "nf kappab receptor activator" OR "p cell stimulating factor" OR "oncostatin m leukemia inhibitory factor shared receptor" OR "oncostatin m receptor beta" OR "oncostatin m type i receptor" OR "oncostatin m type ii receptor" OR "osteoclast differentiation factor" OR "opgl protein*" OR "osm lif receptor*" OR "osteoprotegerin ligand*" OR "ox40 ligand*" OR "ox40 receptor*" OR "ox40l protein*" OR "plasmacytoma growth factor" OR "prostate differentiation factor" OR "protein inducer mgi" OR "p145 c kit" OR "p145c kit" OR "proto oncogene protein c kit" OR "proto oncogene protein fms" OR "proto oncogene protein kit" OR "proto oncogene proteins c kit" OR "recombinant g csf" OR "recombinant gm csf" OR "ro 23 6019" OR "ro 236019" OR "ru 49637" OR "rankl" OR "receptor activator of nf kappa b" OR "receptor activator of nf kappab" OR "receptor activator of nuclear factor kappa b" OR "rank ligand*" OR "recombinant human dimeric tnf receptor type ii igg fusion protein*" OR "ro236019" OR "ru49637" OR "scatter factor" OR "steel factor" OR "stem cell factor" OR "sgp130" OR "signal transducer gp130" OR "signal transducing receptor gp130" OR "soluble glycoprotein 130" OR "soluble gp130" OR "scf receptor*" OR "stem cell factor receptor*" OR "t cell growth factor" OR "t cell replacing factor" OR "t cell stimulating factor" OR "t helper factor" OR "thrombocytopoiesis stimulating factor" OR "thymocyte stimulating factor" OR "t b cell activating molecule" OR "t cell gp39 antigen" OR "tall 1 protein" OR "tnfr fc fusion protein" OR "tnfrsf11a protein" OR "tnfrsf5 receptor" OR "tnfrsf8 receptor" OR "tnfsf13b" OR "tnr 001" OR "tnr001" OR "tntr fc" OR "trance protein" OR "trance r" OR "transmembrane activator and caml interactor protein" OR "tweakr" OR "taci receptor*" OR "tcgf" OR "thank protein*" OR "thrombocytopoietin*" OR "thrombopoietin*" OR "tnfrsf6 receptor*" OR "tnt receptor fusion protein*" OR "trance receptor*" OR "tweak receptor*" OR "transforming growth factor*" OR "tumor necrosis factor*" OR "4 1bb ligand*" OR "4 1bbl protein*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	1316499
# 5	TS=("blood cell*" OR "thrombocyt*" OR "platelet*" OR "erythrocyt*" OR "hemocyt*" OR "leukocyt*" OR "reticulocyt*" OR "granulocyt*" OR "mononuclear cell*" OR "stem cell*" OR "progenitor cell*" OR "mother cell*" OR "colony forming" OR "basophil*" OR "eosinophil*" OR "neutrophil*" OR "lymphocyt*" OR "monocyt*" OR "killer cell*" OR "nk cell*" OR "precursor cell*" OR "suppressor cell*" OR "myelocyt*" OR "myeloblast*" OR "B-cell*" OR "T-cell*" OR "T helper cel*" OR "Treg*" OR "macrophage*" OR "myeloid cell*" OR "dendritic cell*" OR "antigen-presenting cell*" OR "immune cell*" OR "inflammatory cell*" OR "CD4" OR "CD8") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	2677862
#4	TS=("microparticle*" OR "microvesicle*" OR "exosom*" OR "ectosom*" OR "extracellular vesicle*" OR "exovesicle*" OR "apoptotic bod*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	73190
#3	TS=("MicroRNA*" OR "Micro RNA*" OR "miRNA*" OR "pri-miRNA*" OR "stRNA*" OR "Small Temporal RNA*" OR "pre-miRNA*" OR "lncRNA*" OR "non-coding RNA*" OR "noncoding RNA*" OR "ncRNA*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	170639
#2	TS=("biomarker*" OR "marker*" OR "indicator*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	1719569
# 1	TS=("pulmonary arterial hypertens*" OR "pulmonary artery hypertens*" OR "idiopathic pulmonary hypertensi*" OR "primary pulmonary hypertens*" OR "heritable pulmonary hypertensin" OR "hereditary pulmonary hypertens*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*	21537

Wiley/Cochrane Library 87 results (28 January, 2021)

ID	Search	Hits
#8	#1 AND #2 AND (#3 OR #4 OR #5 OR #6 OR #7)	83
#7	(blood* OR plasma* OR serum* OR sera* OR urin*):ti,ab,kw	461866
#6	((“pulmonary arterial” NEXT hypertens*) OR (“pulmonary artery” NEXT hypertens*) OR (“idiopathic pulmonary” NEXT hypertensi*) OR (“primary pulmonary” NEXT hypertens*) OR (“heritable pulmonary” NEXT hypertens*) OR (“hereditary pulmonary” NEXT hypertens*)):ti,ab,kw	1606
#5	(biomarker* OR marker* OR indicator*):ti,ab,kw	92775
#4	(MicroRNA* OR (Micro NEXT RNA*) OR miRNA* OR pri-miRNA* OR stRNA* OR (“Small Temporal” NEXT RNA*) OR pre-miRNA* OR lncRNA* OR (non-coding NEXT RNA*) OR (noncoding NEXT RNA*) OR ncRNA*):ti,ab,kw	1127
#3	(microparticle* OR microvesicle* OR exosom* OR ectosom* OR (extracellular NEXT vesicle*) OR exovesicle* OR (apoptotic NEXT bod*)):ti,ab,kw	769
#2	((blood NEXT cell*) OR thrombocyt* OR platelet* OR erythrocyt* OR hemocyt* OR leukocyt* OR reticulocyt* OR granulocyt* OR (mononuclear NEXT cell*) OR (stem NEXT cell*) OR (progenitor NEXT cell*) OR (mother NEXT cell*) OR “colony forming” OR basophil* OR eosinophil* OR neutrophil* OR lymphocyt* OR monocyt* OR (killer NEXT cell*) OR (nk NEXT cell*) OR (precursor NEXT cell*) OR (suppressor NEXT cell*) OR myelocyt* OR myeloblast* OR B-cell* OR T-cell* OR (“T helper” NEXT cell*) OR Treg* OR macrophage* OR myeloid cell* OR (dendritic NEXT cell*) OR (“antigen-presenting” NEXT cell*) OR (immune NEXT cell*) OR (inflamm* NEXT cell*) OR CD4 OR CD8 OR “stem cell factor receptor”):ti,ab,kw	118610
#1	(("adipogenesis inhibitory" NEXT factor*) OR ("amcf i") OR (antiheparin NEXT factor*) OR ("autocrine motility" NEXT factor*) OR ("apo 1" NEXT antigen*) OR ("b-cell differentiation" NEXT factor*) OR ("b-cell growth" NEXT factor*) OR ("b cell proliferating" NEXT factor*) OR ("b cell stimulatory" NEXT factor*) OR ("beta 2 thromboglobulin") OR ("beta thromboglobulin") OR (bsf 1) OR (bsf 2) OR ("b cell activating" NEXT factor*) OR ("b cell maturation protein a") OR ("b lymphocyte activating" NEXT factor*) OR ("b lymphocyte stimulator") OR ("betac interleukin receptor subunit") OR ("br3 b cell activation factor receptor") OR ("b cell maturation" NEXT antigen*) OR (baff NEXT ligand*) OR (baff NEXT receptor*) OR (bcgf) OR ("bcma protein") OR ("ber h2" NEXT antigen*) OR ("blys protein") OR (chemotactic NEXT factor*) OR ("chemotactic peptid") OR ("colony stimulating" NEXT factor*) OR ("csif 10") OR ("ctla 8") OR ("cytotoxic t lymphocyte associated" NEXT antigen*) OR ("cd 127") OR ("cd134l protein") OR ("cd27l protein") OR ("cd95l") OR ("csf2rb receptor") OR ("cytokine receptor gp130") OR ("c fms protein") OR ("c kit protein") OR ("c kit receptor") OR (catabolin*) OR (ccl1*) OR (ccl2*) OR (ccl3*) OR ("ccl4") OR ("ccl5") OR ("ccl7") OR ("ccl8") OR ("ccr") OR (ccr1*) OR ("ccr2") OR ("ccr3") OR ("ccr4") OR ("ccr5") OR ("ccr6") OR ("ccr7") OR ("ccr8") OR (cd115 NEXT antigen*) OR (cd116 NEXT antigen*) OR (cd117 NEXT antigen*) OR (cd118 NEXT antigen*) OR ("cd127") OR (cd130 NEXT antigen*) OR (cd131 NEXT antigen*) OR (cd134 NEXT antigen*) OR (cd134 NEXT ligand*) OR (cd137 NEXT ligand*OR cd153 NEXT antigen*) OR (cd154 NEXT antigen*) OR (cd178 NEXT antigen*) OR (cd254 NEXT antigen*) OR (cd257 NEXT antigen*) OR (cd265 NEXT antigen*) OR (cd266 NEXT antigen*) OR (cd267 NEXT antigen*) OR (cd268 NEXT antigen*) OR (cd27 NEXT ligand*) OR (cd30 NEXT antigen*) OR (cd30 NEXT ligand*) OR (cd357 NEXT antigen*) OR (cd40 NEXT antigen*) OR (cd40 NEXT ligand*) OR ("cd40l") OR (cd70 NEXT antigen*) OR (cd95 NEXT antigen*) OR (cd95 NEXT ligand*) OR (cdw40 NEXT antigen*) OR (chemokin*) OR ("csf 1 receptor") OR ("csf receptor") OR ("ctla8") OR ("cx3c") OR ("cxcl8") OR ("cxcr") OR ("cxcr3") OR ("cxcr4") OR ("cxcr5") OR ("cxcr6") OR (cytokin*) OR ("eosinophil differentiation factor") OR ("epidermal cell derived thymocyte activating factor") OR ("erythrocyte burst promoting factor") OR ("enbrel") OR ("erelzi") OR (ectodysplasin*) OR ("erythropoietin") OR ("etanercept") OR (fas NEXT antigen*) OR ("fas cell surface death receptor") OR (fas NEXT ligand*) OR ("fas receptor") OR ("fasl protein") OR ("fms proto oncogene protein") OR ("fn14 receptor") OR ("gamma thromboglobulin") OR ("gdf 15") OR ("growth and development factor") OR ("growth differentiation factor 15") OR ("gp130 signal transducer") OR ("g csf receptor") OR ("glucocorticoid induced tnfr related protein") OR ("gm csf receptor") OR ("gp130 transducing protein") OR ("heparin neutralizing protein") OR ("heparin neutralizing proteins") OR ("hepatocyte growth factor") OR ("hepatocyte stimulating factor") OR ("hybridoma growth factor") OR (hematopoieti*) OR (hepatopoietin*) OR ("ifn beta 2") OR ("ifn gamma inducing factor") OR ("il 1") OR ("il 10") OR ("il 11") OR ("il 12") OR ("il 12p35") OR ("il 12p40") OR ("il 13") OR ("il 15") OR ("il 16") OR ("il 17") OR ("il 17a") OR ("il 17b") OR ("il 17c") OR ("il 17d") OR ("il 17e") OR ("il 17f") OR ("il 18") OR ("il 1ra") OR ("il 23 p19") OR ("il 23") OR ("il 23p19") OR ("il 3") OR ("il 4") OR ("il 5") OR ("il 6") OR ("il 7") OR ("il 8") OR ("il 9") OR ("il6st gp130") OR ("il1") OR ("il10") OR ("il11") OR ("il12") OR ("il13") OR ("il15") OR ("il16") OR ("il17") OR ("il17a") OR ("il17b") OR ("il17c") OR ("il17d") OR ("il17e") OR ("il17f") OR ("il18") OR ("il23") OR ("il3") OR ("il4") OR ("il5") OR ("il6") OR ("il7") OR ("il8") OR ("il9") OR (interferon*) OR (interleukin*) OR (kit NEXT ligand*) OR ("lcf factor") OR ("ki 1" NEXT antigen*) OR ("kit proto oncogene protein") OR ("lymphocyte activating" NEXT factor*) OR ("lymphocyte chemoattractant" NEXT factor*) OR ("lymphocyte mitogenic" NEXT factor*) OR ("lymphopoietin 1") OR ("leukemia inhibitory oncostatin m shared receptor") OR ("leukemia inhibitory factor receptor") OR ("lin") OR ("lif receptor") OR ("lineage negative") OR (lymphokine*) OR (lymphotoxin*) OR ("macrophage cell" NEXT factor*) OR ("macrophage granulocyte inducer") OR ("macrophage inflammatory protein") OR ("macrophage inflammatory proteins") OR ("mast cell growth" NEXT factor*) OR ("mcgf 2") OR (mgdf NEXT factor*) OR ("mgi 1") OR ("mgi 2") OR ("monocyte chemotactic proteins") OR ("mpl ligand") OR ("myeloid cell growth inducer") OR ("myeloid differentiation inducing protein") OR ("myeloproliferative leukemia virus oncogene ligand") OR ("m csf receptor") OR ("monocyte chemoattractant protein") OR ("monocyte chemotactic protein") OR ("natural killer cell stimulatory" NEXT factor*) OR ("neutrophil activating peptide") OR ("neutrophil activation" NEXT factor*) OR ("nf kappa b receptor activator") OR ("nf kappab receptor activator") OR ("p cell stimulating" NEXT factor*) OR ("oncostatin m leukemia inhibitory factor shared receptor") OR ("oncostatin m receptor beta") OR ("oncostatin m type i receptor") OR ("oncostatin m type ii receptor") OR ("osteoclast differentiation factor") OR ("opgl protein") OR ("osm lif receptor") OR (osteoprotegerin NEXT ligand*) OR (ox40 NEXT ligand*) OR ("ox40 receptor") OR ("ox40l protein") OR ("plasmacytoma growth factor") OR ("prostate differentiation" NEXT factor*) OR ("protein inducer mgi") OR ("p145 c kit") OR ("p145c kit") OR ("proto oncogene protein c kit") OR ("proto oncogene protein fms") OR ("proto oncogene protein kit") OR ("proto oncogene proteins c kit") OR ("recombinant g csf") OR ("recombinant gm csf") OR ("ro 23 6019") OR ("ro 236019") OR ("ru 49637") OR ("rankl") OR ("receptor activator of nf kappa b") OR ("receptor activator of nf kappab") OR ("receptor activator of nuclear factor kappa b") OR (rank NEXT ligand*) OR ("recombinant human dimeric tnf receptor type ii igg fusion protein") OR ("ro236019") OR ("ru49637") OR (scatter NEXT factor) OR ("steel factor") OR ("stem cell factor") OR ("sgp130") OR ("signal transducer gp130") OR ("signal transducing receptor gp130") OR ("soluble glycoprotein 130") OR ("soluble gp130") OR ("scf receptor") OR ("stem cell factor receptor") OR ("t cell growth" NEXT factor*) OR ("t cell replacing" NEXT factor*) OR ("t cell stimulating" NEXT factor*) OR ("t helper" NEXT factor*) OR ("thrombocytopoiesis stimulating" NEXT factor*) OR ("thymocyte stimulating" NEXT factor*) OR ("t b cell activating molecule") OR ("t cell gp39 antigen") OR ("tall 1 protein") OR ("tnfr fc fusion protein") OR ("tnfrsf11a protein") OR ("tnfrsf5 receptor") OR ("tnfrsf8 receptor") OR ("tnfsf13b") OR ("tnr 001") OR ("tnr001") OR ("tntr fc") OR ("trance protein") OR ("trance r") OR	74840

	("transmembrane activator and caml interactor protein") OR ("tweakr") OR ("taci receptor") OR ("tcgf") OR ("thank protein") OR (thrombocytopoietin*) OR (thrombopoietin*) OR ("tnfrsf6 receptor") OR ("tnt receptor fusion protein") OR ("trance receptor") OR ("tweak receptor") OR ("transforming growth" NEXT factor*) OR ("tumor necrosis" NEXT factor*) OR ("4 1bb" NEXT ligand*) OR ("4 1bbl protein")):ti,ab,kw	

Search Omics (28th of January 2021)

Search		Query #1 and #2	Items found
PubMed	#1	"Familial Primary Pulmonary Hypertension"[Mesh] OR "pulmonary arterial hypertensi*"[tiab] OR "pulmonary artery hypertensi*"[tiab] OR "idiopathic pulmonary hypertens*"[tiab] OR "hereditary pulmonary hypertens*"[tiab] OR "heritable pulmonary hypertens*"[tiab] OR "primary pulmonary hypertensi*"[tiab] OR "primary pulmonary hypertens*"[tiab]	148
	#2	"Glycomics"[Mesh] OR "Proteomics"[Mesh] OR "Metabolomics"[Mesh] OR "glycom*"[tiab] OR "proteom*"[tiab] OR "metabolom*"[tiab] OR "lipidom*"[tiab] OR "transcriptom*"[tiab]	
Embase	#1	('pulmonary arterial hypertens*' OR 'pulmonary artery hypertens*' OR 'idiopathic pulmonary hypertensi*' OR 'primary pulmonary hypertens*' OR 'heritable pulmonary hypertensin' OR 'hereditary pulmonary hypertens*'):ti,ab,kw	309
	#2	'glycomics'/exp OR 'proteomics'/exp OR 'metabolomics'/exp OR 'lipidomics'/exp OR 'transcriptomics'/exp OR ('glycom*' OR 'proteom*' OR 'metabolom*' OR 'lipidom*' OR 'transcriptom*'):ti,ab,kw	
Web of Science	#1	TS=("pulmonary arterial hypertens*" OR "pulmonary artery hypertens*" OR "idiopathic pulmonary hypertensi*" OR "primary pulmonary hypertens*" OR "heritable pulmonary hypertensin" OR "hereditary pulmonary hypertens*")	183
	#2	TS=("glycom*" OR "proteom*" OR "metabolom*" OR "lipidom*" OR "transcriptom*")	
Cochrane	#1	(("pulmonary arterial" NEXT hypertens*) OR ("pulmonary artery" NEXT hypertens*) OR ("idiopathic pulmonary" NEXT hypertensi*) OR ("primary pulmonary" NEXT hypertens*) OR ("heritable pulmonary" NEXT hypertens*) OR ("hereditary pulmonary" NEXT hypertens*)):ti,ab,kw	3
	#2	(glycom* OR proteom* OR metabolom* OR lipidom* OR transcriptom*):ti,ab,kw	

Table S2

	Question 1	**Question 2**	**Question 3**	**Question 4**
Patient inclusion (P) **Risk of bias:** 0 or 1 = low risk 2 = unclear risk 3 or 4 = high risk	Was a consecutive or random sample of patients enrolled? Random = +1 point	Was a case-control design avoided? Case-control = +1	Did the study avoid inappropriate exclusions? No = +1 point	Did the study report data for iPAH uniquely? No = +1 point
Index test (I) **Risk of bias:** 0 = low risk 1 = unclear risk 2 = high risk	Were the index test results interpreted without knowledge of the reference standard? No= +1 point	If a threshold was used, was it predifined or based on an ROC? No ROC = +1	-	-
Reference test (R) **Risk of bias:** 0 = low risk 1 = high risk	Is a diagnosis made by RHC? Echocardiography = + 1	Was the reference standard interpreted without knowledge of the of the index test? No = +1	-	-
Flow and timing (T) **Risk of bias:** 0 = low risk 1 = unclear risk 2 = high risk	Was the index test before the reference standard and initiation of treatment? No = +1	Did all patients receive the same reference standard? No = +1	Were all patients inlcuded in the analysis? No = +1	-

Table S2 Adjusted risk of bias assessment tool according to the QUADAS-2.

Table S3 **Author (year)**	**Markers**	**Material**	**Location**	**Con (n)**	**iPAH (n)**	**Exclusively iPAH**	**Treatment**	**Comments inclusion**
Andreassen, A. K., et al. (2006).	NT-proBNP	plasma	RHC (PA)	10	17	yes	incident	-
Calvier, L., et al. (2016).	sVCAM-1	plasma	peripheral vein (non fasting)	8	41	yes	under treatment	included during conference, unclear reference test
Can, M. M., et al. (2010).	Thrombocytes, d-dimer, fibrinogen, MPV	plasma and whole blood	peripheral vein	34	34	no	under treatment	exclusion comorbidity
Cella, G., et al. (2001).	sP-selectin	plasma	peripheral vein	10	15	no	under treatment	-
Decker, I., et al. (2011).	RBC, MCV, thrombocytes, leukocytes, Hb, Hct, RDW	plasma and whole blood	peripheral vein	12	30	yes	under treatment	-
Estephan, L. E., et al. (2019).	BUN, creatinine, Hb	plasma	RHC (specified)	22	47	no	under treatment	Controls RHC
Fares, W. H., et al. (2012).	CRP, NT-proBNP, TIMP-1	serum	RHC (PA)	33	25	no	under treatment	-
Fijalkowska, A., et al. (2006).	NT-proBNP	serum	peripheral vein	9	36	yes	incident	-
Gabrielli, L. A., et al. (2011).	ALT, leukocytes, CRP, glucose (fasted), Hb	plasma and whole blood	peripheral vein	14	14	yes	under treatment	exclusion comorbidity, anti-inflammatory treatment
Hennigs, J. K., et al. (2014).	CRP, fibrinogen, NT-proBNP	plasma	peripheral vein	11	52	no	incident	exclusion comorbidity, controls RHC
Heresi, G. A., et al. (2010).	CXCL-10	serum	peripheral vein	11	10	yes	under treatment	exclusion comorbidity
Heresi, G. A., et al. (2010).	HDL-C, TG	plasma and whole blood	RHC (PA) and peripheral vein	229	69	no	incident	-
Heresi, G. A., et al. (2017).	CXCL-10, glucose (fasted), IL-6	plasma	peripheral vein	14	14	yes	under treatment	exclusion comorbidity
Hoffmann, J., et al. (2015).	TIMP-1	serum	unclear	40	40	yes	under treatment	-
Itoh, T., et al. (2006).	IL-6	serum	peripheral vein	13	28	yes	under treatment	-
Jasiewicz, M., et al. (2014).	Thrombocytes, leukocytes, creatinine, UA	serum and whole blood	peripheral vein (fasted)	24	26	no	under treatment	-
Jiang, X., et al. (2008).	UA	serum	RHC (VCI)	98	78	yes	under treatment	-
Kereveur, A., et al. (2000).	MPV	plasma and whole blood	peripheral vein	19	16	no	under treatment	only patients PGI2
Koca, F., et al. (2011).	BUN, creatinine	serum	peripheral vein	27	28	no	under treatment,	exclusion comorbidity, unclear reference test
Kopeć, G., et al. (2017).	LDL-c	plasma	peripheral vein (fasted)	2431	63	no	under treatment	-
Lu, G.H. et al. (2020).	Creatinine, NT-proBNP	plasma	peripheral vein	338	338	no	under treatment	-
Malhotra, R., et al. (2013).	CRP, NT-proBNP	serum	peripheral vein	56	50	yes	under treatment	-
Nagaya, N., et al. (1999).	UA	serum	peripheral vein (fasted)	30	90	yes	incident	exclusion renal failure
Petrauskas, L. A., et al. (2019).	RDW	unclear	peripheral vein	101	181	no	under treatment	exclusion comorbidity
Prins, K. W., et al. (2018).	IL-6	serum	peripheral vein	10	40	no	incident	-
Renard, S., et al. (2013).	NT-proBNP	plasma	RHC (VCI)	50	49	yes	under treatment	exclusion comorbity
Rhodes, C. J., et al. (2011).	IL-6	plasma	unclear	40	139	yes	under treatment	-
Safdar, Z., et al. (2015).	TIMP-1	serum	peripheral vein	37	68	yes	under treatment	-
Santos, M., et al. (2014).	BNP, creatinine, CRP, glucose (fasted), Hb, HDL-c, TG	serum	peripheral vein	25	25	no	under treatment	exclusion comorbidity, anti-inflammatory treatment
Soon, E., et al. (2010).	IL-6	serum	peripheral vein	21	70	yes	under treatment	-
Suzuki, S., et al. (2016).	BUN, creatinine, CRP, eGFR,	unclear	unclear	30	16	no	incident	-

	Hb, Hct							
Tiede, S. L., et al. (2016).	TIMP-1	plasma	RHC (unclear)	44	42	yes	incident	-
Varol, E., et al. (2011).	platelets, leukocytes, creatinine, Hb, HDL-c, LDL-c, MPV, TG, total cholesterol	plasma and whole blood	peripheral vein	25	22	no	under treatment	exclusion comorbidity, anti-coagulant treatment
Vrigkou, E. et al (2019)	d-dimer, fibrinogen, Hb, Hct, creatinine, leukocytes, thrombocytes,, ALT	plasma	RHC (PA) or peripheral vein	10	30	no	incident	exclusion comorbidity, anti-coagulant treatment
Wang, G. F., et al. (2020).	TG, total cholesterol, glucose (fasted), bilirubin, creatinine,UA, NT-proBNP, LDL-c, HDL-c	serum	peripheral vein	103	177	no	incident	Only Han chineese
Wang, K. Y., et al. (2015).	creatinine, CRP, HDL-c, NT-proBNP, TG	serum	unclear	27	21	yes	under treatment	exclusion comorbidity
Yang, D., et al. (2013).	NT-proBNP	plasma	peripheral vein (fasted)	20	20	yes	incident	exclusion comorbidity
Yang, T., et al. (2014).	CXCL-10	plasma	peripheral vein	20	61	yes	incident	exclusion comorbidity
Yaoita, N., et al. (2014).	thrombocytes, leukocytes, d-dimer, eGFR, Hb, HDL-c, LDL-c, MPV, PDW, total cholesterol, UA	unclear	peripheral vein	15	19	no	under treatment	controls were hypertension, hyperlipidemia, hypertrophic cardiomyopathies and paroxysmal atrial fibrillation
Yaylali, Y. T., et al. (2019).	RBC, MCV, thrombocytes, leukocytes, fibrinogen, Hb, Hct, RDW	plasma and whole blood	peripheral vein	35	21	no	incident	exclusion treatment
Yildiz, A., et al. (2013).	leukocytes, platelets, creatinine, CRP, glucose (fasted), Hb, HDL-c, LDL-c, MPV, PDW, RDW, TG, total cholesterol	plasma and whole blood	peripheral vein (fasted)	22	25	no	under treatment	exclusion comorbidity, anti-coagulation treatment
Zhao, Q. H., et al. (2012).	HDL-c	serum	peripheral vein (fasted)	45	76	yes	incident	exclusion CVD risk factors
Zheng, Y. G., et al. (2015).	MPV, PDW	plasma and whole blood	peripheral vein (fasted)	82	82	yes	incident	exclusion comorbidity, anti-coagulant treatment
Zhu, T., et al. (2019).	ALT, BUN, creatinine, Hb, Hct, NT-proBNP	plasma	peripheral vein, (12 hr fast)	20	27	yes	incident	age > 14 yrs, exclusion comorbidity

Table S3 A detailed overview of 45 included publications, describing markers extracted from the publication, location /type of blood draw, number of control and PAH subjects included, the treatment status of included patients, and concerns regarding inclusion methodology.

Table S4

Marker	Studies (n)	Data distribution	Control (n)	Weighted average	PAH (n)	Weighted average
5-HT, ng/mL	2	mean/SD[#]	28	4.0 ± 1.1	25	7.5 ± 3.7
ADMA, µmol/mL	1	mean/SD	22	0.36 ± 0.05	57	0.53 ± 0.15
	2	median (IQR)	75	0.51 (0.47 – 0.57)	77	0.83 (0.68 – 1.04)
Ang-1, ng/mL	2	median (IQR)	18	4.2 (3.2 – 5.4)	90	13.7 (10.9 – 16.5)
BNP, pg/mL	1	mean/SD	20	34 ± 32	26	141 ± 1233
	8	median (IQR)	203	20 (10 – 37)	266	129 (34 – 457)
Endostatin, ng/mL	2	mean/SD	73	52.9 ± 34.4	65	55.4 ± 48.7
	1	median[#]	39	28.1	37	62.9
ET-1, ng/mL	2	mean/SD	34	0.8 ± 0.4	34	2.0 ± 1.4
	1	median/IQR	9	1.8 ± 1.1	33	2.6 ± 2.2
Gal-3, ng/mL	2	mean/SD	22	7.7 ± 2.0	67	13.2 ± 3.8
	1	median/IQR	10	10.1 (9.0 – 12.7)	15	17.3 (13.2 – 21.1)
HGF, ng/mL	1	median/IQR	62	1.1 (1.0 – 1.3)	52	1.8 (1.3 – 2.6)
HMGB1, ng/mL	2	mean/SD	53	8.6 ± 4.7	50	12.1 ± 7.2
IL-8, pg/mL	1	mean/SD	21	14.3 ± 4.9	70	52.8 ± 148.1
	2	median (IQR)	13	4.5 (4.2 – 5.78)	31	5.5 (3.9 – 8.7)
MCP-1, pg/mL	2	Mean/SD	36	166 ± 152	48	331 ± 180
	1	Median (IQR)	20	79 (49 -93)	29	109 (65 – 142)
MMP-2, ng/mL	2	mean/SD	77	304.7 ± 122.2	67	305.3 ± 101.2
MMP-9, ng/mL	2	mean/SD	77	106 ± 119	67	62.0 ± 75
	1	median (IQR)	37	237 (171 – 370)	68	434 (292 – 663)
Na, mmol/L	2	mean/SD	52	140 ± 2	61	138 ± 4
	1	median/IQR	39	142 (139 – 144)	107	139 (137 – 142)
PlGF, pg/mL	1	mean/SD	40	21.8 ± 1.5	62	45.6 ± 3.5
	2	median/IQR	13	29.5 (20.2 – 41.5)	31	82.9 (53.6 – 126.0)
SCF, ng/mL	1	median/IQR	62	0.80 (0.75 – 0.88)	52	1.0 (0.80 – 1.25)
sE-selectin, ng/mL	2	mean/SD	43	56.7 ± 22.1	40	79.6 ± 44.8
	1	median (IQR)	7	45 (32 – 57)	9	29 (19 – 71)
SOD, pg/mL	1	mean/SD	12	142 ± 25	12	70 ± 30
sVCAM-1, ng/mL	2	mean/SD	41	931 ± 374	66	1086 ± 686
	1	Median (IQR)	7	487 (279 – 1084)	9	1167 (455 – 3454)
TGF-b1, ng/mL	2	mean/SD	12	3.6 ± 1.3	16	2.5 ± 2.0
	1	median (IQR)	61	2.6 (1.9 – 4.3)	216	4.8 (3.2 – 7.9)
Tie-2, ng/mL	2	median (IQR)	15	2.13 (1.83 – 2.3)	103	2.12 (1.88 – 2.20)
TIMP-4, ng/mL	2	mean/SD	77	1.9 ± 1.1	67	1.9 ± 1.6
VEGF, pg/mL	2	mean/SD	41	137 ± 101	66	159 ± 195
	4	median (IQR)	126	109 (69 – 227)	197	180 (125 – 411)
VEGF-A, pg/mL	2	median (IQR)	13	41.2 (25.7 – 60.0)	31	35.4 (23.9 – 42.7)
VEGF-D, ng/mL	2	median (IQR)	12	0.99 (0.95 – 1.11)	31	11.32 (0.71 – 1.44)
	1	mean/SD	8	0.88 ± 0.31	41	0.82 ± 0.51
TNF-a, pg/mL	4	median (IQR)	80	1.8 (1.3 – 2.4)	115	3.7 (2.8 – 5.4)
	2	mean/SD	34	5.5 ± 1.4	98	8.3 ± 3.8

Table S4. Overview of pooled biomarkers described in three or more publications, that were not eligible for meta-analyses due to heterogeneity in data distribution (median with IQR, v.s. mean with SD). 5-HT; serotonin, ADMA; asymetric dimethylarginine, Ang-1; angiopoietin-1, BNP; brain natriuretic protein, ET-1; endothelin-1, Gal-3; galectin-3, HGF; hepatocyte growth factor, HMGB1; high mobility group box 1, IL-8; interleukin-8, MMP-2, -8; matrix metalloproteinase-2 and -8, Na; sodium, PlGF; placental growth factor, SCF; stem cell factor, SOD; superoxide dismutase, sVCAM; soluble vascular cell adhesion molecule, TGF-b1; transfor-g growth factor-b1, Tie-2; angiopoietin-1 receptor-2, TIMP-4; tissue inhibitor of metalloproteinase-4, VEGF; vascular endohtelial growth factor, TNF-a; tissue necrosis factor-a. [#] did not report IQR, or SD.

Table S5

Table S5 Marker	Studies (n)	Data distribution	Control (n)	Weighted average	PAH (n)	Weighted average
Cav-1, pg/mL	1	Mean/SD	27	174 ± 135	21	34 ± 36
	1	Median (IQR)	8	100 (35 – 220)	8	200 (100 – 550)
RBC, cells 10^{12}/L	2	Mean/SD	47	4.77 ± 0.46	51	4.74 ± 0.58
HbA1c, %	2	Mean/SD	44	5.57 ± 0.58	37	5.58 ± 0.60
IL-12, pg/mL	2	Mean/SD	29	32.2 ± 23.3	111	102± 102
K, mEq/L	2	Mean/SD	52	4.13 ± 0.38	61	4.0 ± 0.5
MCV, fL	2	Mean/SD	47	87.3 ± 5.0	51	86.0 ± 7.8
MDA, nmol/L	2	Mean/SD	26	3.55 ± 1.91	112	6.39 ± 1.2
NO, µmol/L	2	Mean/SD	30	53.3 ± 22.3	35	60.4 ± 21.7
OPN, ng/mL	2	Mean/SD	44	22.9 ± 2.7	95	40.7 ± 30.9
Pim-1, ng/mL	2	Mean/SD	115	8.21 ± 3.08	46	23.4 ± 9.7
Se-p, mg/L	1	Mean/SD	20	2.43 ± 0.25	65	3.07 ± 0.57
	1	Median (IQR)	20	5.5 (2.8 – 8.0)	26	14.0 (7.0 – 32.0)
sRAGE, ng/mL	2	Mean/SD	53	775 ± 282	37	1216 ± 596
sST2, ng/mL	2	Mean/SD	34	19.0 ± 6.4	65	34.3 ± 16.1
sTWEAK, pg/mL	2	Median (IQR)	49	343 (269 – 431)	180	195 (192 – 296)
Total bilirubin, mg/dL	2	Mean/SD	45	0.83 ± 0.28	36	0.95 ± 0.53
FGF-2, pg/mL	1	Mean/SD	8	14 ± 24	8	41 ± 42
	1	Median (IQR)	8	30 (14 – 41)	9	12 (8-36)
ENG, ng/mL	1	Mean/SD	56	3.66 ± 0.87	50	5.12 ± 1.34
	1	Median (IQR)	49	4.0 (3.4 – 4.9)	43	5.4 (4.2 – 6.4)
KYN, µmol/L	1	Mean/SD	20	2.6 ± 0.1	20	3.6 (0.2)
	1	Median (IQR)	30	1.9 (1.5 – 2.3)	26	2.8 (2.4 – 3.2)
MCP-1, pg/mL	1	Mean/SD	13	91 ± 18	28	253 ± 127
	1	Median (IQR)	20	79 (49 – 93)	29	109 (65 – 142)
NOx, µmol/L	1	Median (95%-CI)	100	29.2 (21.9 – 34.4)	104	9.7 (6.7 – 12.4)
	1	Median (IQR)	50	11 (5 – 19)	58	23 (15 – 34)
OPG, ng/mL	1	Mean/SD	56	2.89 ± 1.17	50	3.21 ± 1.34
	1	Median (IQR)	35	1.35 (0.82 – 2.02)	28	4.81 (3.52 – 5.87)
PIIINP, ng/mL	1	Mean/SD	37	3.08 ± 0.93	68	5.30 ± 1.87
	1	Median (IQR)	10	4.1 (3.8 – 6.0)	15	4.5 (3.9 – 7.0)
sFLT-1, ng/mL	1	Mean/SD	40	3.09 ± 0.25	62	5.05 ± 0.46
	1	Median (IQR)	5	0.08 (0.06 – 0.08)	22	0.12 (0.09 – 0.14)
TFPI, ng/mL	1	Mean/SD	10	77.68 ± 10.37	15	82.73 ± 34.90
	1	Median (IQR)	29	10.5 (4.0 – 16.0)	16	14.3 (4.0 – 27.6)
Thrombomodulin, ng/mL	1	Mean/SD	10	13.00 ± 7.91	15	8.00 ± 11.62
	1	Median (range)	29	40.6 (14.0 – 117.0)	16	28.4 (6.5 – 54.0)
TRP, µmol/L	1	Mean/SD	20	58.4 ± 3.2	20	47.8 ± 2.4
	1	Median (IQR)	30	40.3 (35.2 – 46.3)	2	52.9 (46.3 – 57.5)
VEGFR-1, pg/mL	1	Mean/SD	56	98.7 ± 41.9	50	132.1 ± 44.6
	1	Median (IQR)	8	80 (61 – 85)	9	125 (101 – 150)

Table S5 Pooled biomarker levels described in two publications. Cav-1; caveolin-1, RBC; red blood cells, HbA1c; hemoglobin A1c, IL-12; interleukin, K; potassium, MCV; mean corpuscular volume, MDA; malondialhyde, NO; nitric oxide, OPN; osteopontin, Pim-1; provirus integration site for moloney murine leukaemia virus kinase, Se-P; selenoproteine-P, sRAGE; receptor advanced glycation end products, sST2; soluble suppression of tumorigenicity, sTWEAK; TNF-related weak inducer of apoptosis, FGF-2; fibroblast growth factor-2, ENG; endoglin, KYN; kynurine, MCP-1; monocyte chemoattractant protein-1, Nox; nitrite NO2- and nitrate NO3-, OPG; osteoprotegerin, PIIINP; N-ter-al propeptide of type III procollagen, sFLT-1; soluble fms-like tyrosine kinase 1, TFPI; tissue factor pathway inhibitor, TRP; tryptophan, VEGFR-1; vascular endothelial growth factor-1.

Table S6

Marker	Studies (n)	Participants (n)	Mean difference	St. mean difference	OR	p-value
Haematological markers						
RDW, %	4	427	1.83 [1.39, 2.26]	0.98 [0.61, 2.17]	0.49 [0.31, 0,75]	<0.00001
PDW, %	3	245	1.42 [0.16, 2.67]	0.81 [0.50, 1.12]	0.75 [0.45, 1.13]	<0.00001
MPV, fL	5	361	0.95 [0.76, 1.13]	1.0 [0.81, 1.25]	0.68 [0.25, 1.89]	<0.00001
Thrombocytes, 10^9/L	7	334	-23.9 [-38.6, -9.2]	-0.38 [-0.62, -0.15]	0.82 [0.46, 1.46]	0.001
Hb, g/dL	9	400	-0.59 [-1.23, 0.06]	-0.18 [-0.43, 0.07]	6.06 [3.06. 11.99]	0.15
Hct, %	5	229	-1.07 [-3.91, 1.76]	-0.21 [-0.76, 0.34]	0.49 [0.31, 0,75]	0.46
Leukocytes, 10^9/L	7	294	-0.23 [-0.70,0.24]	-0.10 [-0.41, 0.21]	0.75 [0.45, 1.13]	0.52
Metabolic markers						
LDL-c, mg/dL	6	3035	-15.82 [-26.18, -5.46]	-0.44 [-0.65, -0.22]	0.45 [0.30, 0.68]	<0.00001
Total cholesterol, mg/dL	4	408	-17.70 [-24.15, -11.26]	-0.52 [-0.73, -0.32]	0.39 [0.27, 0.56]	<0.00001
TG, mg/dL	4	198	-32.56 [-54.17, -10.94]	-0.52 [-0.87, -0.17]	0.34 [0.17 0.69]	0.004
Glucose (fasted), mg/dL	3	103	24.06 [0.54, 7.58]	0.48 [0.08, 0.87]	1.25 [0.56, 2.75]	0.02
HDL-c, mg/dL	6	577	-6.15 [-2.11, 14.40]	-0.53 [-1.20, 0.15]	0.38 [0.11, 1.31]	0.13
Coagulation markers						
D-dimer, ng/mL	3	142	245.99 [148.55, 343.43]	0.69 [0.27, 1.11]	3.59 [1.67, 7.73]	0.001
Fibrinogen, mg/dL	4	227	73.75 [-2.58, 150.08]	0.84 [-0.14, 1.81]	4.67 [0.78, 28.1]	0.09
Inflammatory markers						
IL-6, pg/mL	5	389	5.01 [2.06, 7.96]	0.64 [0.28, 0.99]	3.26 [1.67, 6.33]	0.0005
CRP, mg/L	8	387	0.74 [0.13, 1,6]	0.25 [0.04, 0.47]	1.60 [1.08, 2.37]	0.02
sVCAM-1, ng/mL	3	150	626.72 [29.38, 1224.07]	1.03 [0.53, 1.52]	7.83 [3.36, 18.26]	<0.00001
CXCL-10, pg/mL	3	171	99.77 [54.53, 145.01]	0.82 [0.49, 1.16]	4.56 [2.47, 8.42]	<0.00001
TIMP-1, ng/mL	3	224	15.58 [-2.56, 33.72]	0.40 [0.13, 0.67]	3.05 [1.29, 7.21]	0.003
sP-selectin, ng/mL	4	180	0.52 [-11.10, 12.14]	-0.04 [0.35, 0.28]	0.89 [0.47, 1.68]	0.82
Cardiac markers						
NT-proBNP, pg/mL	10	1152	1684 [1035, 2330]	1.13 [0.93, 1.33]	7.99 [5.48, 11.62]	<0.00001
Renal markers						
UA, mg/dL	5	441	1.77 [1.06, 2.48]	0.89 [0.58, 1.12]	5.13 [2.90, 9.06]	<0.00001
BUN, mg/dL	5	891	1.76 [0.51, 3.01]	0.43 [0.29, 0.56]	2.17 [1.7, 2.78]	<0.00001
Creatinine, mg/dL	10	475	0.03 [-0.04, 0.10]	0.13 [-0.08, 0.34]	1.27 [0.86, 1.87]	0.23
eGFR, mL/-/1.73 m^2	4	180	1.70 [5.98, 9.37]	0.09 [-0.32, 0.49]	0.53 [0.23, 1.25]	0.67
Hepatic markers						
ALT, U/L	3	115	3.57 [-4.18, 11.31]	0.18 [-0.56, 0.92]	1.40 [0.36, 5.55]	0.37

Table S6. Mean difference, standardized mean difference and OR of 26 meta-analyses. RDW; red cell distribution width, PDW; platelet distribution width,MPV; mean platelet volume, Hb; hemoglobin, Hct; hematocrit, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein, sVCAM-1; circulating vascular cell adhesion molecule-1, CXCL-10; C-X-C motif chemokine ligand-10, IL-6; interleukin-6, TIMP-1; tissue inhibitors of metalloproteinases-1, soluble p-Selectin, CRP; c-reactive protein, NT-proBNP; N-terminal prohormone of brain natriuretic peptide, UA; uric acid, eGFR; estimated glomerular filtration rate, ALT; alanine transaminase. St. mean difference; standardized mean difference. St. mean difference; OR odds ratio.

Table S7

Table S7 **Publication bias**	**Egger's regression**		**Duval & Tweedie's trim and fill**			**Orwin's fail safe N**	**Funnel plot**
	Intercept	P-value	Original	Studies trimmed	Adjusted	Number of studies*	Figure
Haematological markers							
RDW, %	2.14	0.27	0.98 [0.61, 2.17]	2	0.77 [0.38, 1.14]	10	Fig. S2a
PDW, %	-2.57	0.23	0.81 [0.50, 1.12]	2	0.98 [0.67, 1.30]	8	Fig. S2b
MPV, fL	-2.35	<0.01	1.04 [0.81, 1.25]	3	1.15 [0.96, 1.34]	16	Fig. S2c
Thrombocytes, 10^9/L	-6.02	<0.01	-0.38 [-0.62, -0.15]	3	-0.25 [-0.50, -0.01]	4	Fig. S2d
Hb, g/dL	-0.27	0.94	-0.18 [-0.43, 0.07]	0	-0.18 [-0.43, 0.07]	-	Fig. S2e
Hct, %	6.02	0.62	-0.21 [-0.76, 0.34]	0	-0.21 [-0.76, 0.34]	-	Fig. S2f
Leukocytes, 10^9/L	-6.97	0.11	-0.10 [-0.41, 0.21]	2	-0.04 [-0.35, 0.27]	-	Fig. S2g
Metabolic markers							
LDL-c, mg/dL	-1.07	0.47	-0.44 [-0.65, -0.22]	1	-0.36 [-0.12, -0.61]	4	Fig. S2h
Total cholesterol, mg/dL	0.18	0.89	-0.52 [-0.73, -0.32]	0	-0.52 [-0.73, -0.32]	5	Fig. S2i
TG, mg/dL	0.41	0.88	-0.52 [-0.87, -0.17]	1	-0.61 [-0.94, -0.28]	6	Fig. S2j
Glucose (fasted), mg/dL	-4.51	0.72	0.48 [0.08, 0.87]	0	0.48 [0.08, 0.87]	4	Fig. S2k
HDL-c, mg/dL	5.90	0.15	-0.53 [-1.20, 0.15]	0	-0.53 [-1.20, 0.15]	15	Fig. S2l
Coagulation markers							
D-dimer, ng/mL	-4.84	0.37	0.69 [0.27, 1.11]	2	1.01 [0.54 - 1.48]	6	Fig. S2m
Fibrinogen, mg/dL	-2.38	0.91	0.84 [-0.14, 1.81]	1	1.07 [0.19 - 1.95]	10	Fig. S2n
Inflammatory markers							
IL-6, pg/mL	2.83	0.20	0.64 [0.28, 0.99]	0	0.64 [0.28, 0.99]	7	Fig. S2o
CRP, mg/dL	1.28	0.38	0.25 [0.04, 0.47]	1	0.24 [0.03, 0.45]	1	Fig. S2p
sVCAM-1, ng/mL	1.5	0.67	1.03 [0.53, 1.52]	1	1.04 [0.60, 1.49]	14	Fig. S2q
CXCL-10, pg/mL	1.47	0.78	0.82 [0.49, 1.16]	0	0.82 [0.49, 1.16]	8	Fig. S2r
TIMP-1, ng/mL	-1.98	0.73	0.40 [0.13, 0.67]	1	0.73 [0.29, 1.16]	8	Fig. S2s
sP-selectin, ng/mL	3.34	0.11	-0.04 [0.35, 0.28]	0	-0.07 [-0.42, 0.29]	-	Fig. S2t
Cardiac markers							
NT-proBNP, pg/mL	-0.06	0.94	1.13 [0.93, 1.33]	0	1.13 [0.93, 1.33]	37	Fig. S2u
Renal markers							
UA, mg/dL	-2.11	0.46	0.89 [0.58, 1.12]	1	0.82 [0.53 - 1.12]	14	Fig. S2v
BUN, mg/dL	-0.72	0.40	0.43 [0.29, 0.56]	1	0.43 [0.29, 0.56]	4	Fig. S2w
Creatinine, mg/dL	-0.25	0.94	0.13 [-0.08, 0.34]	1	0.10 [-0.10, 0.31]	-	Fig. S2x
eGFR, mL/-/1.73 m^2	4.87	0.64	0.09 [-0.32, 0.49]	1	-0.07 [-0.09, 0.34]	-	Fig. S2y
Herpetological markers							
ALT, U/L	2.58	0.86	0.18 [-0.56, 0.92]	0	0.18 [-0.56, 0.92]	-	Fig. S2z

Table S7. Estimation of risk of bias by Egger;s regression ($p<0.10$), Duval & Tweedie's trim and fill, and Orwin's fail safe N. PDW; platelet distribution width, RDW; red cell distribution width, MPV; mean platelet volume, Hb; hemoglobin, Hct; hematocrit, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein, sVCAM-1; circulating vascular cell adhesion molecule-1, CXCL-10; C-X-C motif chemokine ligand-10, IL-6; interleukin-6, TIMP-1; tissue inhibitors of metalloproteinases-1, CRP; c-reactive protein, NT-proBNP; N-terminal prohormone of brain natriuretic peptide, UA; uric acid, eGFR; estimated glomerular filtration rate, ALT; alanine transaminase. * publication excluded.

Table S8

Table S8 Publication	Sample size	Sample size	Source	Method	Principle component selection	Validation	Selected principle component
Abdul-Salam, V., et al., 2006.	27 iPAH	26 control	plasma	Proteomics analysis using Mass spec SELDI-TOF MS	ROC curves, AUC	ELISA	C4a des Arg,
Rhodes C.J., et al., 2017.	116 / 174 iPAH	128 control	plasma	Metabolomic profiling using liquid chromatography coupled with mass spectrometry (Metabolon, Durham, NC), logistic regression analysis	Logistic regression analysis	ELISA, validation cohort	Nucleosides (N2,N2-dimethylguanosine, N1-methylinosine), TCA cycle (malate, fumarate), glutamate, fatty acid oxydatin (acylcarnitines), and polyamine metabolites and decreased levels of steroids, sphingomyelins, and phosphatidylcholines
Rafikov, R., et al., 2020.	11 iPAH	23 control	plasma	Metabolomic liquid chromatography coupled with mass spectometry	Supervised clustering analysis	no	TCA cycle, carbohydrates (glycolytic shift). Myo-inositol.
He, Y.Y., 2020.	30 iPAH	30 control	plasma	Metabolomic mass and fragmentation analyses, using liquid chromatography-mass spectrometry	Student t-test ($p < 0.05$),	Validation cohort, rodent, PASMC	Spermine, among 17 other plasma metabolites
Hemnes, A.R., et al., 2019	10 PAH	30 control	plasma	Metabolomics (liquid chromatography-mass spectrometry) and proteomics (SomaLogic aptamer-based assay.)	2-way ANOVA, post hoc tests	Validation cohort, explanted lungs	Long- and medium-chain acylcarnitines (fatty-acid oxidation)
Al-Naamani, N. et al., 2016.	22 PAH	29 control	plasma	Lipidomics using liquid chromatography-mass spectrometry	ROC curves, AUC	Rodent with experimental PAH	Plasma eicosanoids; including 12- and 15-HETE
Amsallem, M., 2021.	121 PAH	76 control	plasma	Proteomics multiplex immunoassay	Regression analysis	Rodent, Cox proportional hazard regression	HGF, Met-c
Bujak, R., 2016.	20 PAH	20 control	plasma	Metabolomic high-performance liquid and gas chromatography (HPLC) coupled with mass spectrometry.	Orthogonal partial least squares discriminant analysis	Glucose tolerance test	Metabolites related to glycolysis, lipid and fatty acid metabolism (acylcarnitines), amino acid metabolism,, TCA and urea cycle
Chen, C. et al., 2020.	40 iPAH	20 control	serum	Metabolomic ultra high-performance liquid and gas chromatography (HPLC) coupled with mass spectrometry.	ROC curves, AUC	Rodent with experimental PAH	LysoPC, PC, decanoylcarnitine (fatty acid oxidation) and l-carnitine
Heresi, G.A., et al., 2020.	31 iPAH	31 control	plasma	Metabolomic high-performance liquid chromatography (HPLC) Online Tandem Mass Spectrometry (LC-MS/MS)	One-way ANOVA, false discovery rate	Random forest analysis	Metabolic profiles
Karamanian, V.A., et al., 2014.	113 PAH	51 control	serum and plasma	Proteomics Multiplex immunoassays	False discovery rate (PaGe)	Random forest analysis, PAEC	EPO, among other growth factors
Mey, J.T., et al., 2020.	21 PAH	31 control	plasma	Metabolomic liquid chromatography coupled with mass spectrometry (Metabolon, Durham, N.C.)	One-way ANOVA	Glucose tolerance test	Acylcarnytines (fatty acid oxidation), fatty acids, ketonic amino-acids
Sanders, J.L., et al., 2019.	26 PAH	26 control	plasma	Metabolomic liquid chromatography coupled with mass spectometry	Two-way ANOVA	Random forest, exercise	higher glycolytic catabolic state (TCA, fatty acid oxydation, glycolysis)
Yu, M., et al., 2007.	20 iPAH	20 control	serum	Metabolomic liquid chromatography coupled with mass spectometry	Statistical test	no	Alpha-1-antitrypsin, vitronectin
Zhang, J. et al., 2009.	10 iPAH	10 control	serum	Proteomics MALDI-TOF-MS, ELISA	Statistical test	no	LRG, among other protein spots