Early serum biomarkers to characterise different phenotypes of primary graft dysfunction after lung transplantation: a systematic scoping review

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A knowledge gap exists regarding the early biomarkers of PGD after LUTX. Uniform diagnostic criteria, modern platforms and advanced statistics are needed for future studies aimed at PGD phenotyping https://bit.ly/3TrkuSV

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Abstract

Background Lung transplantation (LUTX) is often complicated by primary graft dysfunction (PGD). Plasma biomarkers hold potential for PGD phenotyping and targeted therapy. This scoping review aims to collect the available literature in search of serum biomarkers for PGD phenotyping.

Methods Following JBI and PRISMA guidelines, we conducted a systematic review searching MEDLINE, Web of Science, EMBASE and The Cochrane Library for papers reporting the association between serum biomarkers measured within 72 h of reperfusion and PGD, following International Society for Heart and Lung Transplantation (ISHLT) guidelines. We extracted study details, patient demographics, PGD definition and timing, biomarker concentration, and their performance in identifying PGD cases.

Results Among the 1050 papers screened, 25 prospective observational studies were included, with only nine conducted in the last decade. These papers included 1793 unique adult patients (1195 double LUTX, median study size 100 (IQR 44–119)). Most (n=21) compared PGD grade 3 to less severe PGD, but only four adhered to 2016 PGD definitions. Enzyme-linked immunosorbent assays and the multiplex bead array technique were utilised in 23 and two papers, respectively. In total, 26 candidate biomarkers were identified, comprising 13 inflammatory, three endothelial activation, three epithelial injury, three cellular damage and two coagulation dysregulation markers. Only five biomarkers (sRAGE, ICAM-1, PAI-1, SP-D, FSTL-1) underwent area under the receiver operating characteristic curve analysis, yielding a median value of 0.58 (0.51–0.78) in 406 patients (276 double LUTX).

Conclusions Several biomarkers exhibit promise for future studies aimed at PGD phenotyping after LUTX. To uncover the significant existing knowledge gaps, further international prospective studies incorporating updated diagnostic criteria, modern platforms and advanced statistical approaches are essential.

Introduction

Lung transplantation (LUTX) is the last therapeutic option for patients with end-stage respiratory failure [1]. Primary graft dysfunction (PGD) is the most common complication and leading cause of early mortality and long-term disability after LUTX [2]. PGD is a form of acute lung injury, graded upon alteration of oxygenation and radiographic criteria [3], occurring within 72 h after graft reperfusion. The PGD definition does not consider the heterogeneity of clinical manifestations or any biomolecular signature after LUTX. The severity of PGD may vary significantly, from mild radiographic infiltration to life-threatening lung injury requiring extracorporeal support [4], and duration may differ. While most patients manifest transient hypoxaemia, only a minority have persistent and unresolving respiratory

failure [5]. Moreover, PGD is frequently associated with haemodynamic failure [6] and renal dysfunction [7], suggesting that rather than an alteration of the sole lung function, it might be considered as a heterogeneous syndrome characterised by multisystemic widespread inflammation and endothelial barrier damage following LUTX. Finally, to date, there is no consensus on the implementation of early biomarkers of PGD after LUTX. In this scenario, implementing biological signatures reflecting epithelial and endothelial injury, dysregulated fibrinolysis/coagulation and inflammatory system activation may improve risk stratification.

Following the paradigm of precision medicine [8, 9], predictive enrichment may allow for understanding the heterogeneity of LUTX recipients, and detecting different, and potentially treatable, subphenotypes (*e.g.*, hypoinflammatory *versus* hyperinflammatory) and applying targeted early treatments to subcohorts. As for other critical illnesses (*i.e.*, acute respiratory distress syndrome (ARDS) [10, 11], sepsis [12]), we envision the possibility of carrying out biological subtyping of LUTX patients to better select the patients with the lowest chance of harm for treatment. In the similar, but not equivalent, context of ARDS, it has been proven that treatments (*e.g.*, higher positive end-expiratory pressure [13], restrictive fluid management [14], simvastatin [15]) that disappointingly failed to benefit the overall patient population could provide significant benefit in specific patient subcohorts.

Thus far, literature regarding possible early serum biomarkers of PGD is scarce [16], and biological sub-phenotyping of LUTX recipients has not been carried out.

Accordingly, with this scoping review, we aim to collate the literature regarding early serum biomarkers of PGD in adult LUTX patients, analyse and identify knowledge gaps, and guide future research aimed at phenotyping LUTX recipients.

Methods

Protocol design

This review was conducted using the updated methodological guidance developed by the Joanna Briggs Institute [17]. The protocol has been prospectively published on the Open Science Framework (https://osf.io/kqv4m/?view_only=b1d40718bee9419ebeb62e3dcfcc15fc), and the review has been reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping review [18].

Eligibility criteria

We aimed to find, assess and synthesise all prospective and retrospective observational studies and randomised controlled trials, including adult LUTX patients (*i.e.*, >18 years old) that measured early (*i.e.*, <72 h from graft reperfusion) serum biomarkers and their association with the primary outcome, defined as the occurrence of PGD defined following 2005 [19] and 2016 [3] International Society for Heart and Lung Transplantation (ISHLT) guidelines (*i.e.*, arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) <300 mmHg and bilateral lung infiltrates). We excluded animal studies, paediatric studies (*i.e.*,<18 years old), studies describing exclusively bronchoalveolar lavage (BAL) biomarkers, and studies describing the association between plasma or serum biomarkers and later outcomes (*e.g.*, CLAD, BOS, survival) exclusively, case reports/series, descriptive cross-sectional studies or studies without a control group (*i.e.*, studies not discriminating PGD *versus* non-PGD cohorts). Pre-prints, non-English investigations, book chapters, conference proceedings and editorials/letters were also excluded.

Search strategy

The following search strategy was built for MEDLINE:

((‘lung transplant’[Title/Abstract]) OR (‘lung transplantation’[Title/Abstract])) AND ((‘IL’ [Title/Abstract] OR ‘interleukin’ [Title/Abstract] OR ‘cytokine’[Title/Abstract] OR ‘biomarker’ [Title/Abstract] OR ‘marker’ [Title/Abstract] OR ‘protein’ [Title/Abstract] OR ‘peptide’ [Title/Abstract] OR ‘chemokine’ [Title/Abstract] OR ‘molecule’ [Title/Abstract] OR ‘factor’ [Title/Abstract] OR ‘agonist’ [Title/Abstract] OR ‘antagonist’ [Title/Abstract])) AND ((‘primary graft dysfunction’ [Title/Abstract] OR ‘PGD’ [Title/Abstract]))

The search was designed using the following tools Polyglot Search Translator [20], SearchRefinery (https://dl.acm.org/doi/abs/10.1145/3269206.3269215/), The Deduplicator and The Systematic Review Accelerator [21]. Searches were done in PubMed, Web of Science, Embase *via* Elsevier, and The Cochrane Library for Cochrane Reviews. Searches were run from inception to 8 May 2023 (see online supplementary Additional Methods for further details).

Finally, the reference lists of the included studies were assessed, and a backward citation analysis was performed.

Study screening and selection

Screening

Four review authors (S.M. Colombo, A. Guzzardella, M. Bosone and G. Turconi) independently screened the titles and abstracts for the inclusion criteria. For records eligible after screening, full texts were retrieved by S.M. Colombo, A. Guzzardella, M. Bosone and G. Turconi, and each record was reviewed by two authors independently. Discrepancies were resolved by referring to V. Scaravilli. The Screenatron/Disputatron tools were utilised to help screen articles. The selection process has been recorded and used to generate a PRISMA flow diagram (see figure 1), and a list of excluded (full-text) studies with reasons for exclusions was produced.

Data extraction

A standardised form was used for data extraction of characteristics of studies and outcomes. S.M. Colombo, A. Guzzardella, M. Bosone, G. Turconi and V. Scaravilli conducted the data extraction. The following data for study characteristics and outcomes were extracted from each included study: first author, country of the study, date of publication, year of data collection, study design, sample size, type of surgical procedure (*i.e.*, single *versus* double lung transplant), PGD definition (*i.e.*, 2005 *versus* 2015), PGD cohorts used for definition (*e.g.*, 3 *versus* <3) and timing of PGD (*i.e.*, <6, 24, or 48 h from graft reperfusion), the incidence of PGD, name of biomarkers analysed, the technique utilised to measure plasma/serum concentration of the biomarker and, when available, performance measured by the study or plasma/serum biomarkers' concentrations in the study cohorts (*i.e.*, sample size, p-value or area under the receiver operating characteristic curve (AUROCC)). Data were obtained directly by article text or extracted in numerical format from images and, when not available, using an online free-to-access extraction tool (https://plotdigitizer.com/app). Candidate biomarkers were defined as molecules for which plasma levels differed with statistical significance among patient cohorts.

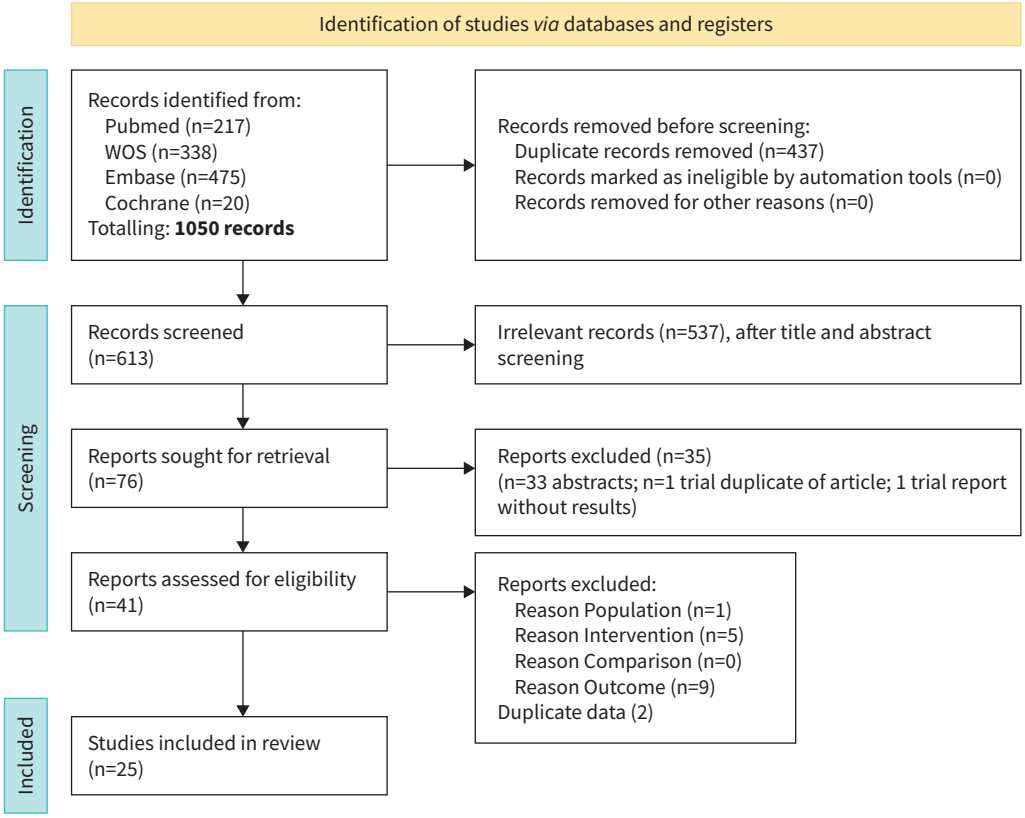


FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. Identification of studies *via* databases and registers. WOS: Web of Science.

Of note, given the study's exploratory nature, which is meant to be a scoping review and not a meta-analysis, we did not formally assess study biases.

Statistics

A meta-analysis was not the primary aim of this study. Variables extracted from the included studies were summarised by comprehensive tables and in visual form utilising a volcano plot. The JMP statistical programme was utilised.

Results

Search, selection and study characteristics

We initially identified a total of 1050 records (see figure 1). After removing 437 duplicates, 613 records underwent screening. Subsequently, 537 irrelevant records were excluded, leaving 76 records for full-text screening. Of these, 35, mainly congress abstracts were removed, and 41 [22–63] were evaluated for eligibility. A further 15 articles [22, 25–34, 36, 53, 55, 57] were excluded, with nine, five and one failing to meet the predefined outcome, intervention and population criteria, respectively (see supplementary table S1, Additional Results for further details).

Furthermore, two articles [22, 45] presented duplicate data of previously included studies [40, 60] and were consequently removed from the analysis. This resulted in a final inclusion of 25 articles in the scoping review.

The included studies, spanning from 2007 to 2023, featured only nine articles from the last decade. All studies were prospective observational studies, with 21 studies (84%) being prospective observational cohort studies. The remaining studies were nested case–control studies comparing selected PGD patient cohorts. Two of these lacked matching between cohorts [39, 54], while the others incorporated some form of matching [38, 62].

The geographical distribution of the studies revealed a predominant focus on the USA (n=17, 68%) and Spain (n=5, 20%). Of note, 12 studies were conducted by the Lung Transplant Outcome Group research team, constituting an ongoing multi-centre, prospective cohort of lung transplant patients in the USA. The remaining three studies originated from Canada, Austria and France.

Characteristics of patient populations

The eligible studies encompassed a cohort of 2527 patients, with 1649 (65%) undergoing double lung transplant. However, five studies [38, 40, 60, 62, 63] reported data for a subset of 734 patients (61% double lung transplant) already included in other studies. Consequently, we considered 1793 unique patients (double lung transplant=1195, 66%). Among these unique LUTX cases, 1180 (65%) and 464 (25%) were conducted in the USA and Spain, with patients from other countries constituting <4% of the overall cases. The study sizes varied from 20 to 317 patients, with a median of 100 (44–119) patients per study and 60 (34–72) double lung transplants per study.

Table 1 presents aggregated characteristics of the patients. Most studies reported all demographic variables relevant to this review. The median age was 51 (49–55) years, and the majority of patients were males affected by restrictive and obstructive end-stage lung diseases, treated with double lung transplant in 67% (53–81%) of cases.

PGD definition

In the majority of studies (n=21, 2328 patients), PGD was defined according to the 2005 ISHLT criteria, comparing the most severe form (PGD grade 3) against less severe cases. After excluding nested case–control studies and considering only unique patients (18 studies, totalling 1624 unique unselected patients), the PGD incidence ranged from 27% (21–29%) for 14 studies comparing PGD grade 3 *versus* PGD grade <3 (1483 patients) to 28% (14–39%) for three studies comparing PGD grade ⩾2 *versus* PGD grade <2 (121 patients) and 55% for a single study comparing PGD grade ⩾1 *versus* PGD grade 0 (20 patients).

In most studies (n=14, 1771 patients), patients were defined as experiencing PGD at any time up to 72 h from the first graft reperfusion. Eight studies used PGD at 72 h from reperfusion as the primary outcome (666 patients), while the remaining three studies employed 6 h, 24 h and 48 h after reperfusion as the primary outcome.

TABLE 1 Patient characteristics of included papers

Variable	Median (IQR) or n (% of the subgroup)	Number of studies
Population size, n	100 (45–120)	25
Population size, double LUTX, n	60 (35–73)	25
Double LUTX %	67 (53–81)	25
Age years	51 (49–55)	24
Sex (male) %	57 (52–62)	25
Indication to LUTX %		
Obstructive	39 (34–45)	22
Restrictive	39 (31–54)	23
Infectious	11 (6–19)	22
Vascular	4 (3–6)	20
Other	1 (0–6)	20
PGD definition		
2005	21 (84)	25
2016	4 (16)	
PGD cohorts		
3 *versus* <3	19 (76)	25
⩾2 *versus* <2	3 (12)	
⩾1 *versus* 0	1 (4)	
3 *versus* 0	1 (4)	
3 *versus* n/a	1 (4)	
PGD timing h		
⩽72 (cumulative incidence)	14 (56)	25
72	8 (32)	
6	1 (4)	
24	1 (4)	
48	1 (4)	

LUTX: lung transplant; PGD: primary graft dysfunction; n/a: not applicable.

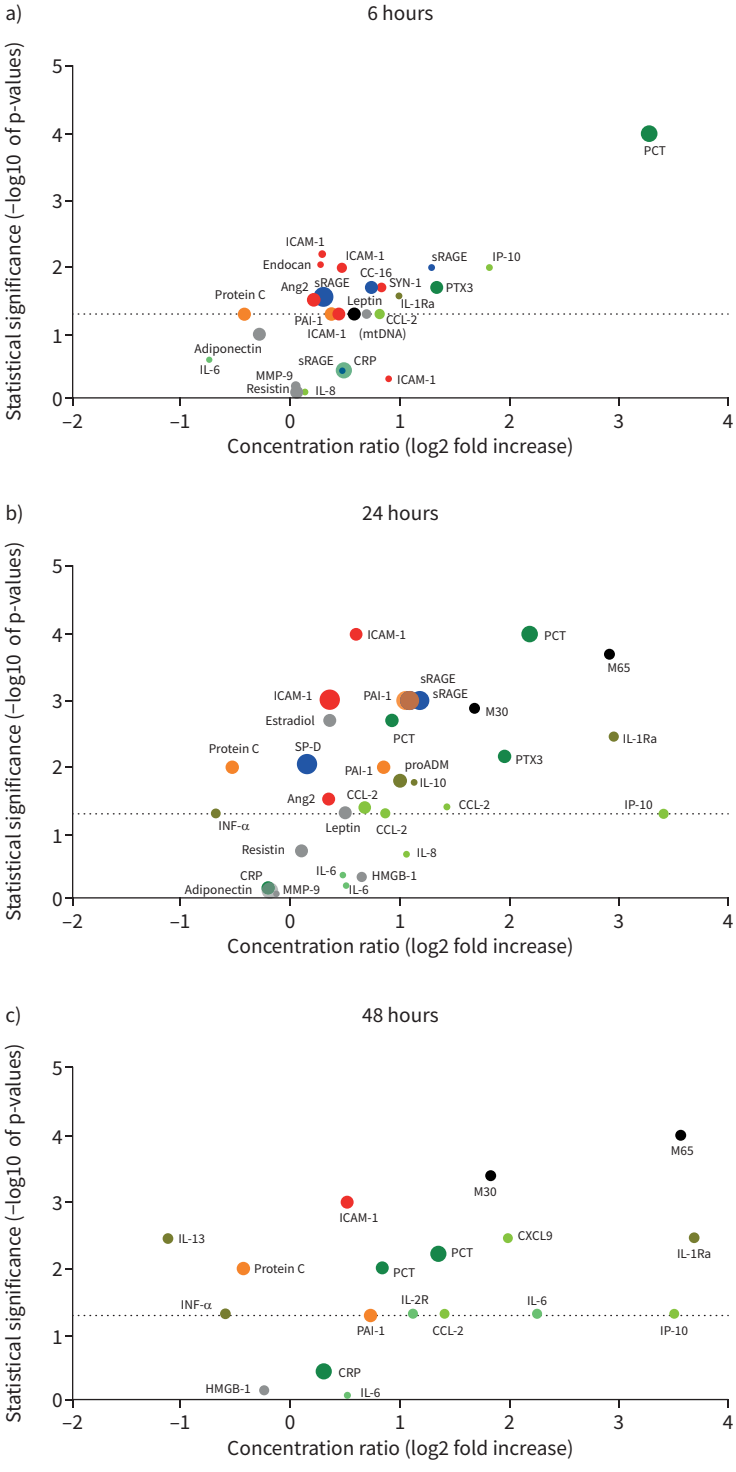
Early biomarkers for PGD

None of the included studies employed proteomics, metabolomics or multi-omics analysis, instead each study conducted assays for specific biomarkers or a predefined panel of selected biomarkers. Among the 25 included studies, two [24, 63] did not document a statistically significant difference in the analysed biomarkers.

The median number of biomarkers assessed per study was 2 (1–4), ranging from 1 to 31 per study. Only two studies [23, 54] analysed >10 biomarkers, utilising the multiplex bead array assay (MBAA) technique, while the remaining studies analysed fewer than 10 biomarkers, primarily employing enzyme-linked immunosorbent assay (ELISA) techniques.

The list of potential biomarkers for PGD phenotyping is detailed in supplementary table S2 (see supplementary material, Additional Results), encompassing a total of 58 studied biomarkers. To visually convey the statistical significance and biological relevance of these potential biomarkers, an enhanced volcano plot was generated (see figure 2). From this pool of potential biomarkers, 26 candidates emerged, defined as molecules demonstrating a statistically significant difference in plasma levels among patient cohorts.

Various inflammatory mediators were explored as potential biomarkers of PGD. These included acute phase reactants like procalcitonin (PCT) and pentraxin-3 (PTX3), cytokines such as interleukin-10 (IL-10), interleukin-1 receptor antagonist (IL-1Ra), interferon-α (INF-α), proAdrenomedullin (proADM), interleukin-13 (IL-13), follistatin-like 1 (FSTL-1) and interleukin-2 receptor (IL-2R). Additionally, chemokines such as chemokine CC motif ligand 2 (CCL-2), interferon-γ-induced protein 10 (IP-10) and chemokine CXC motif ligand 9 (CXCL9) were investigated. Furthermore, mediators associated with the activation of coagulastion were assessed, including protein C and plasminogen activator inhibitor 1 (PAI-1), those linked to endothelial function like intercellular adhesion molecule 1 (ICAM-1), angiopoietin-2 (Ang2) and syndecan 1 (SYN-1), and mediators of epithelial injury such as soluble receptor for advanced glycation end products (sRAGE), surfactant protein D (SP-D) and club cell protein 16 (CC-16). The list of candidate biomarkers also encompassed those tied to cellular damage, specifically serum caspase-cleaved cytokeratin (M30), circulating cytokeratin 18 (M65) and mitochondrial DNA (mtDNA).



Inflammation

Acute phase reactant
- Procalcitonin (PCT)
- C-reactive protein (CRP)
- Pentraxin 3 (PTX3)

Anti-inflammatory cytokines
- Interleukin-10 (IL-10)
- Interleukin-1 receptor antagonist (IL-1Ra)
- Interferon alpha (INF-α)
- proAdrenomedullin (proADM)
- Interleukin-13 (IL-13)

Pro-inflammatory cytokines
- Interleukin-6 (IL-6)
- Interleukin-2 receptor (IL-2R)

Chemokines
- Chemokine CC motif ligand 2 (CCL-2)
- Interferon γ-induced protein 10 (IP-10)
- Interleukin-8 (IL-8)
- Chemokine CXC motif ligand 9 (CXCL9)

Coagulation
- Protein C
- Plasminogen activator inhibitor 1 (PAI-1)

Endothelial activation
- Intercellular adhesion molecule 1 (ICAM-1)
- Angiopoietin-2 (Ang2)
- Syndecan 1 (SYN-1)
- Endocan

Epithelial injury
- Soluble receptor for advanced glycation end products (sRAGE)
- Surfactant protein D (SP-D)
- Club cell protein 16 (CC-16)

Cellular damage
- High mobility group box 1 (HMGB-1)
- Serum caspase-cleaved cytokeratin (M30)
- Circulating cytokeratin 18 (M65)
- Mitochondrial DNA (mtDNA)

Others
- Estradiol
- Leptin
- Adiponectin
- Matrix metallopeptidase 9 (MMP-9)
- Resistin

FIGURE 2 Enhanced volcano plots of the possible early biomarkers for primary graft dysfunction. Timing of biomarker measurement: a) ⩽6 h, b) ⩽24 h and c) ⩽48 h from graft reperfusion. For all panels, the volcano plot shows the −log10 (p-values) *versus* the log2 (fold change) of the possible early biomarkers of primary graft dysfunction. The horizontal line represents the p=0.05 threshold on the p-values. Larger markers represent more populated studies.

As depicted in figure 2, the majority of candidate biomarkers exhibited upregulation in PGD patients. Conversely, a minority of them, including protein C, INF-α and IL-13, displayed decreased levels in PGD patients.

The exploration of potential time points for PGD phenotyping revealed distinctive patterns. Within the initial 6 h post-graft reperfusion, most biomarkers showed a modest upregulation, with a median fold increase (representing the ratio of biomarker concentration in the PGD cohort to the non-PGD cohort) of 1.68 (1.27–2.49). PCT and protein C deviated from the general trend. PCT displayed a robust signal with a fold increase of 9.27, while protein C was the sole biomarker displaying downregulation, with a fold increase of <1 (0.75). Among the other biomarkers, IP-10, FSTL-1 and PTX-3 showed strong signals (fold increase >2). At the 24-h time point, the median fold increase reached 1.82 (1.29–2.49), with the most prominent signal observed in IP-10 (fold increase=10.7). Several other biomarkers were consistently upregulated, with fold increases exceeding 2: M65, M30, PTX-3, PCT, IL-10 and proADM. Conversely, protein C and INF-α exhibited downregulation in PGD patients. By the 48-h time point, the median fold increase increased to 2.18 (1.22–4.21), with M65 and IP-10 showing the strongest signal (fold increase >10). Additionally, there was robust upregulation of IL-6, M30, IL2-R, CCL-2 and PCT. Again, protein C and INF-α were downregulated in PGD patients.

Of the 26 candidate biomarkers identified in this review, only sRAGE, ICAM-1, PA1-1, SP-D and FSTL-1 were evaluated at least once using AUROCC analysis (see table 2), in three different studies [40, 41, 44] including 406 unique patients (276 double LUTX). No single test demonstrated a good diagnostic accuracy (AUROCC >0.75), and the reported AUROCC ranged from 0.58 (0.51–0.65) for ICAM-1, up to 0.73 (0.66–0.79) for PAI-1, with a median value of 0.58 (0.51–0.78).

The remaining candidate biomarkers' discriminative was not documented in the available literature, but the concentration in the different cohorts was numerically or graphically accounted for in 20 studies. The results of those 20 studies are summarised in table 3.

Discussion

PGD stands out as the most prevalent complication and the primary contributor to early mortality and morbidity following LUTX [2]. Identifying biological signatures associated with PGD can enhance early detection and, ultimately, facilitate targeted treatments based on the underlying pathogenesis. To date, no prior scoping review or meta-analysis focused on PGD biomarkers has been conducted. This prompted us to conduct a scoping review to systematically gather existing literature to identify serum biomarkers for PGD phenotyping, predictive enrichment and targeted therapy. The scope of this study did not extend to quantitative analysis, thus precluding an assessment of biases in the included studies or synthesising results to reinterpret previous scientific findings, let alone offering guidance for patient treatment. Instead, we

TABLE 2 Candidate biomarkers evaluated by receiver operating characteristic (ROC) analysis

Author and year Cohort N (n, % double LUTX)	Biomarker	Methods	Performance measured by the study (AUC (95% CI), sensitivity, specificity)	Time point h	PGD incidence, n/N (%)
Shah 2012 [40] **Prospective observational cohort (PGD 3 *versus* PGD <3)** **317 (192, 61%)**	sRAGE	ELISA (R&D Systems, Minneapolis, MN, USA)	0.63 (0.55–0.65) 0.71 (0.64–0.78)	6 24	85/319 (27)
	ICAM-1	ELISA (R&D Systems, Minneapolis, MN, USA)	0.58 (0.51–0.65) 0.63 (0.56–0.70)	6 24	85/319 (27)
	PAI-1	ELISA (American Diagnostica, Greenwich, CT, USA)	0.64 (0.58–0.71) 0.73 (0.66–0.79)	6 24	85/319 (27)
	SP-D	ELISA (Yamasa Corporation, Tokyo, Japan)	0.62 (0.55–0.69) 0.60 (0.53–0.67)	6 24	85/319 (27)
Pottecher 2017 [44] **Prospective observational cohort** **PGD 3 *versus* PGD <3** **47 (42, 89%)**	sRAGE	ELISA (R&D Systems, Minneapolis, MN, USA)	0.66 (0.41–0.91) Cut-off 11 800 pg·mL^{-1}: sensitivity 66.7%, specificity 85.7%	6	10/42 (21)
Veraar 2022 [41] **Prospective observational cohort (PGD 3 *versus* PGD <3)** **42 (42, 100%)**	FSTL-1	ELISA (R&D Systems, Minneapolis, MN, USA)	0.7 (0.5–0.9) Cut-off 10.2 relative increase in FSTL-1: sensitivity 65%, specificity 81%	6	15/42 (35)

LUTX: lung transplant; AUC: area under the curve; PGD: primary graft dysfunction; sRAGE: serum receptor for advanced glycation end products; ELISA: enzyme-linked immunosorbent assay technique; ICAM-1: intracellular adhesion molecule-1; PA1-1: plasminogen activator inhibitor-1; SP-D: surfactant protein D; FSTL-1: Follistatin-like 1.

TABLE 3 Candidate biomarkers evaluated without receiver operating characteristic (ROC) with a statistically significant signal among primary graft dysfunction cohorts

Author and year/cohort N (n, % double LUTX)	Biomarker	Methods	Biomarker concentration in PGD patients	Biomarker concentration in non-PGD patients	p-value	Time point h	PGD incidence, n/N (%)
Allen 2012 [49] Prospective observational cohort PGD ⩾2 *versus* PGD <2 28 (20, 71%)	IL-10	ELISA (R&D Systems, Minneapolis, MN, USA)	339±391 pg·mL^{-1}	154±127 pg·mL^{-1}	0.017	24	8/28 (28)
	CCL-2	ELISA (R&D Systems, Minneapolis, MN, USA)	1019±1294 pg·mL^{-1}	375±287 pg·mL^{-1}	0.04	24	
Bastarache 2012 [50] Prospective observational cohort PGD 3 *versus* PGD <3 111 (73, 66%)	Estradiol	ELISA (BioCheck, Inc., Foster City, CA, USA)	77.4 (62.5–101.1) pg·mL^{-1}	59.6 (45.9–70.6) pg·mL^{-1}	0.002	24	31/111 (27)
Chacon-Alberty 2022 [23] Prospective observational cohort PGD 3 *versus* PGD <3 40 (31, 78%)	IL-1Ra	Multiplex bead array (Bio-Plex, Bio-Rad Laboratories, Hercules, CA, USA)	7523± 1470 pg·mL^{-1}	3773±915 pg·mL^{-1}	0.027	6	12/40 (30)
	IP-10	Multiplex bead array (Bio-Plex, Bio-Rad Laboratories, Hercules, CA, USA)	2620±1330 pg·mL^{-1}	740±150 pg·mL^{-1}	0.01	6	12/40 (30)
Christie 2009 [56] Prospective observational cohort PGD 3 *versus* PGD <3 317 (192, 61%)	sRAGE	ELISA (R&D, Minneapolis, MN, USA)	9.3 (4.7–19.7) ng·mL^{-1} 4.3 (2.6–9.3) ng·mL^{-1}	7.5 (3.8–13.5) ng·mL^{-1} 1.9 (1.0–3.8) ng·mL^{-1}	0.028 0.001	6 24	85/319 (27)
Christie 2007 [48] Prospective observational cohort PGD 3 *versus* PGD <3 128 (68, 53%)	Protein C	Actichrome protein C assay (American Diagnostica, Greenwich, CT, USA)	67.5±38% control 64.0±27% control 73.2±40% control	89.8±42% control 92.0±42% control 97.9±31% control	<0.05 <0.01 <0.01	6 24 48	26/128 (20)
	PAI-1	ELISA (American Diagnostica, Greenwich, CT, USA)	236.7±236 ng·mL^{-1} 213±144 ng·mL^{-1} 129.5±222 ng·mL^{-1}	181.9±173 ng·mL^{-1} 117±89 ng·mL^{-1} 77.1±135 ng·mL^{-1}	<0.05 <0.01 <0.01	6 24 48	26/128 (20)
Coster 2023 [59] Prospective observational cohort PGD 3 *versus* PGD <3 55 (55, 100%)	ICAM-1	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	1711±140 ng	1228±116 ng	<0.01	6	23/55 (42%)
	SYN-1	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	26.6±3.75 ng	14.9±3.11 ng	0.02	6	23/55 (42)
Covarrubias 2007 [60] Prospective observational cohort PGD 3 *versus* PGD <3 128 (68, 53%)	ICAM-1	ELISA (R&D Systems, Inc., Minneapolis, MN, USA)	358.4 (314–405) ng·mL^{-1} 378 (341–416) ng·mL^{-1} 362.2 (319–406) ng·mL^{-1}	261.7 (245–278) ng·mL^{-1} 246.4 (235–257) ng·mL^{-1} 249.8 (237–263) ng·mL^{-1}	0.05 0.0001 0.001	6 24 48	26/128 (20)
Diamond 2011 [61] Prospective observational cohort PGD 3 *versus* PGD <3 104 (72, 69%)	CC-16	ELISA (Biovendor, Candler, NC, USA)	13.8 (7.9–30.4) ng·mL^{-1}	8.2 (4.5–19.1) ng·mL^{-1}	0.02	6	29/104 (27)

Continued

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TABLE 3 Continued

Author and year/cohort N (n, % double LUTX)	Biomarker	Methods	Biomarker concentration in PGD patients	Biomarker concentration in non-PGD patients	p-value	Time point h	PGD incidence, n/N (%)
Diamond 2011 [39] Nested case-control studytive observational cohort PGD 3 *versus* PGD <3 119 (96, 81%)	PTX3[#]	ELISA (Alexis Biochemicals, Switzerland)	45.7 ng·mL^{-1} (n/a) 88.9 ng·mL^{-1} (n/a)	18.0 ng·mL^{-1} (n/a) 22.7 ng·mL^{-1} (n/a)	0.02 0.007	6 24	40/119 (33)
Diamond 2012 [38] Nested case-control study (matched for diagnosis) PGD 3 *versus* PGD <3 119 (96, 81%)	Angiopoietin-2	ELISA (R&D Systems, Inc., Minneapolis, MN, USA)	3749 (3204–5840) pg·mL^{-1} 6272 (4386–9659) pg·mL^{-1}	3218 (2204–4477) pg·mL^{-1} 4886 (3431–8181) pg·mL^{-1}	0.03 0.03	6 24	40/119 (33)
Hashimoto 2016 [52] Prospective observational cohort (PGD 3 *versus* PGD <3) 60 (60, 100%)	M30	ELISA (PREVIVA AB, Nacka, Sweden)	325. 0 (142.8–3727.6) U·L^{-1} 348.1 (163.8–585.9) U·L^{-1}	100 (58.6–161) U·L^{-1} 97.3 (58.9–142) U·L^{-1}	0.0013 0.0004	24 48	10/60 (17)
	M65	ELISA (PREVIVA AB, Nacka, Sweden)	2439 (1214–4666) U·L^{-1} 3718 (784–5578) U·L^{-1}	321 (188–759) U·L^{-1} 311 (145–576) U·L^{-1}	0.0002 0.0001	24 48	10/60 (17)
Hoffman 2009 [54] Nested case-control study (no matching) PGD 3 *versus* PGD 0 50 (33, 66%)	CCL-2	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	725±54 pg·mL^{-1} 356±300 pg·mL^{-1} 579±585 pg·mL^{-1}	410±435 pg·mL^{-1} 195±65 pg·mL^{-1} 216±90 pg·mL^{-1}	<0.05 <0.05 <0.05	6 24 48	25/50 (50)
	IP-10	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	450±1080 pg·mL^{-1} 413±885 pg·mL^{-1}	42±35 pg·mL^{-1} 36±10 pg·mL^{-1}	<0.05 <0.05	24 48	25/50 (50)
	IL-2R	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	21 955±22 640 pg·mL^{-1}	10 038±15 480 pg·mL^{-1}	<0.05	48	25/50 (50)
	IL-6	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	179±360 pg·mL^{-1}	37±45 pg·mL^{-1}	<0.05	48	25/50 (50)
	INF-α	Multiplex bead array (Luminex, R&D Systems, Inc., MN, USA)	37±25 pg·mL^{-1} 38±30 pg·mL^{-1}	59±40 pg·mL^{-1} 57±20 pg·mL^{-1}	<0.05 <0.05	24 48	25/50 (50)
Lederer 2011 [62] Nested case-control study (diagnosis and procedure matching) PGD 3 *versus* n/a 120 (62, 52%)	Leptin	ELISA (R&D Systems, Inc., Minneapolis, MN, USA)	23.4 (10.0–53.5) ng·mL^{-1}	16.4 (7.6–37.2) ng·mL^{-1}	0.049	24	40/120 (33)
Mazo 2018 [47] Prospective observational cohort PGD 3 *versus* PGD <3 100 (51, 51%)	Procalcitonin	Fluoroimmunoassay (KRYPTOR compact)	2.83 ng·mL^{-1} 2.02 ng·mL^{-1}	1.47 ng·mL^{-1} 1.12 ng·mL^{-1}	0.002 0.01	24 48	22/100 (22)
Moreno 2007 [32] Prospective observational cohort PGD ⩾ 2 *versus* PGD<2 31 (22, 71%)	IL-6	ELISA	310.50±140.36 pg·mL^{-1}	177.13±111.86 pg·mL^{-1}	0.016	12	11/31 (39)

Continued

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TABLE 3 Continued

Author and year/cohort N (n, % double LUTX)	Biomarker	Methods	Biomarker concentration in PGD patients	Biomarker concentration in non-PGD patients	p-value	Time point h	PGD incidence, n/N (%)
Riera 2016 [58] **Prospective observational cohort** **PGD 3 *versus* PGD <3** **100 (51, 51%)**	proADM	Fluoroimmunoassay (MR-proADM Kryptor; Brahms GmbH, Hennigsdorf, Germany)	3.25 (1.5–4.27) nmol·L^{-1}	1.61 (1.13–2.33) nmol·L^{-1}	0.016	24	22/100 (22)
Scozzi 2019 [43] **Prospective observational cohort** **PGD ⩾ 2 *versus* PGD<2** **62 (62, 100%)**	mtDNA	Real-time PCR (Bio-Rad CFX-Connect)	9.78 (9.86–9.88) Log10 copy·mL^{-1}	9.66 (9.5–9.78) Log10 copy·mL^{-1}	0.05	6	9/60 (14)
Shah 2012 [42] **Prospective observational cohort** **PGD 3 *versus* PGD <3** **108 (72, 67%)**	CCL-2	ELISA (R&D, Minneapolis, MN, USA)	167.95 (94.8–346.7) pg·mL^{-1}	103.5 (51.1–229.9) pg·mL^{-1}	0.04	24	30/108 (28)
Sims 2011 [37] **Prospective observational cohort** **PGD 3 *versus* PGD <3** **38 (20, 53%)**	SP-D	ELISA (Yamasa Corporation, Tokyo, Japan)	111.3 (77.4–157.2) ng·mL^{-1} 78.9 (56.9–88.7) ng·mL^{-1} 67.1 (46.8–86.4) ng·mL^{-1}	103.2 (103.2–156.4) ng·mL^{-1} 87.3 (67.7–139.7) ng·mL^{-1} 66.8 (27.0–104.1) ng·mL^{-1}	<0.05 <0.05 <0.05	6 24 48	11/38 (29)
Suberviola 2017 [51] **Prospective observational cohort** **PGD 3 *versus* PGD <3** **233 (125, 54%)**	Procalcitonin	Fluoroimmunoassay (Brahms GmbH, Hennigsdorf, Germany)	4.57 (0.25–11.82) ng·mL^{-1} 4.9 (1.46–14.16) ng·mL^{-1} 2.61 (0.84–9.31) ng·mL^{-1}	0.47 (0.05–1.93) ng·mL^{-1} 1.07 (0.32–2.97) ng·mL^{-1} 1.01 (0.43–2.47) ng·mL^{-1}	0.0001 0.0001 0.006	6 24 48	28/233 (12)

Biomarker concentration data are presented as median (IQR) or mean±SD. LUTX: lung transplant; PGD: primary graft dysfunction. IL: interleukin; CCL: chemokine (C-C motif) ligand; IL-1Ra: interleukin-1 receptor; IP-10: interferon gamma-induced protein 10; sRAGE: serum receptor for advanced glycation end products; PAI-1: plasminogen activator inhibitor-1; ICAM-1: intracellular adhesion molecule-1; SYN-1: syndecan-1; CC-16: club cell secretory protein; PTX3: plasma long pentraxin-3; IL-2R: interleukin-2 receptor; INF: interferon; proADM: proAdrenomedullin; mtDNA: mitochondrial DNA; SP-D: surfactant protein D. #: only for IPF patients.

aimed to map the available evidence with a scoping review through a structured, deductive, predetermined framework and basic numerical and graphical extraction.

Our exploration identified 26 candidate biomarkers for potential PGD phenotyping. However, only five of these (sRAGE, ICAM-1, PA1-1, SP-D and FSTL-1) had their test performance in predicting PGD described, and this was limited to just three studies and only 276 double LUTX unique cases. Among these, only sRAGE had confirmatory analyses in more than one study. Given the nature of our study, integrating the biomarkers predicting performance across the included studies was deemed inappropriate and was not attempted. Nevertheless, given the scarcity and heterogeneity of data, a possible meta-analysis on the topic appears unfeasible.

Still, the available evidence collected in this scoping review shows that several biomarkers could be attractive targets for future studies aiming at phenotyping LUTX recipients. Those biomarkers might represent the pathogenic mediators of the multifaceted multiorgan molecular events that characterise PGD: recognition of oxidant stress, endothelial damage and activation of cell-mediated inflammation, monocyte recruitment, microangiopathy and lung epithelial injury (see figure 3). While direct inferences cannot be taken from these results, it is notable that some of those biomarkers have already been shown to be possible targets for the biological phenotyping of ARDS [10, 64, 65], sepsis [12], trauma [66] and other inflammatory disease.

On the one hand, some of these biomarkers (*i.e.*, PCT and PTX3) might just be epiphenomena of activation of inflammation and thus are employable only as unspecific, and not pathogenetic, markers, much less as possible therapeutic targets. On the other hand, some of the markers above may also be involved in the causal physiopathological pathway initiated by ischaemia–reperfusion and leading to PGD. Moreover, several treatment approaches are available for some of those pathogenic markers, potentially opening avenues for repurposing such treatments for PGD.

Receptor for advanced glycation end (RAGE) is a ubiquitous transmembrane immunoglobulin receptor for nonenzymatically glycated adducts that form in the presence of oxidant stress and once activated, leads to the activation of the nuclear factor kappa B (NF-κB) pathway and the release of adhesion molecules (*e.g.*, ICAM-1) and pro-inflammatory cytokines [67]. Several pieces of evidence suggest that the RAGE/NF-κB pathway activation has a pathogenetic role in acute lung injury and that the measurement of RAGE soluble isoform (sRAGE) might be used as a potential type 1 cell injury plasma marker. Moreover, RAGE modulation has been posited as a therapeutic target [68, 69].

ICAM-1 is an immunoglobin-like protein primarily expressed by leukocytes and endothelial cells [70], is upregulated in response to pro-inflammatory stimuli – comprising sRAGE – and favours the adhesion and activation of antigen-presenting and cytotoxic T-cells, thus leading to endothelial damage. The upregulation of ICAM-1 has been documented in several inflammatory conditions (*e.g.*, COVID-19 [71], sepsis-induced acute kidney injury [72]), and since soluble ICAM-1 is not specific to lung endothelium may represent a possible pathogenic pathway of the widespread endothelial damage observed during PGD, leading to vasoplegia and acute kidney injury. Interestingly, short-term ICAM-1 modulation through anti-ICAM-1 monoclonal antibody is feasible and could prevent solid organ transplant rejection in nonhuman primates free of calcineurin inhibitors [73].

PAI-1 is a member of the serine protease superfamily that is the principal inhibitor of the plasminogen activators [74]. Several pro-inflammatory cytokines enhance PAI-1 synthesis, leading to hypofibrinolytic and thrombotic complications. In fact, PAI-1 is a significant predictor of disease severity and all-cause mortality in sepsis [75]. In the context of LUTX, PAI-1 may be the physiopathological link between endothelial activation and microangiopathy, leading to multiorgan dysfunction occurring during PGD. Again, several PAI-1 inhibitors have been produced to study the pharmacological effect of PAI-1 inhibition *in vitro* and *in vivo* [76] and may find a role in the targeted management of PGD.

SP-D is a pattern-recognition molecule of the collectins family involved in innate immune defence, expressed in pulmonary and non-pulmonary epithelial cells [77]. SP-D modulates immune cells, epithelial cells, fibrocytes and smooth muscle cell functions in response to several inflammatory stimuli. Following the loss of air–blood barrier integrity, SP-D leaks into the bloodstream, and thus plasma SP-D levels appear to be an accurate marker of acute lung epithelial injury [78]. Preclinical models demonstrated that local pulmonary treatment with recombinant SP-D might be beneficial in these cases [79].

FSTL1 is a small secreted glycoprotein from mesenchymal cells, exhibiting profibrotic and pro-inflammatory properties [80]. It participates in epithelial–mesenchymal transition and airway remodelling. The emerging

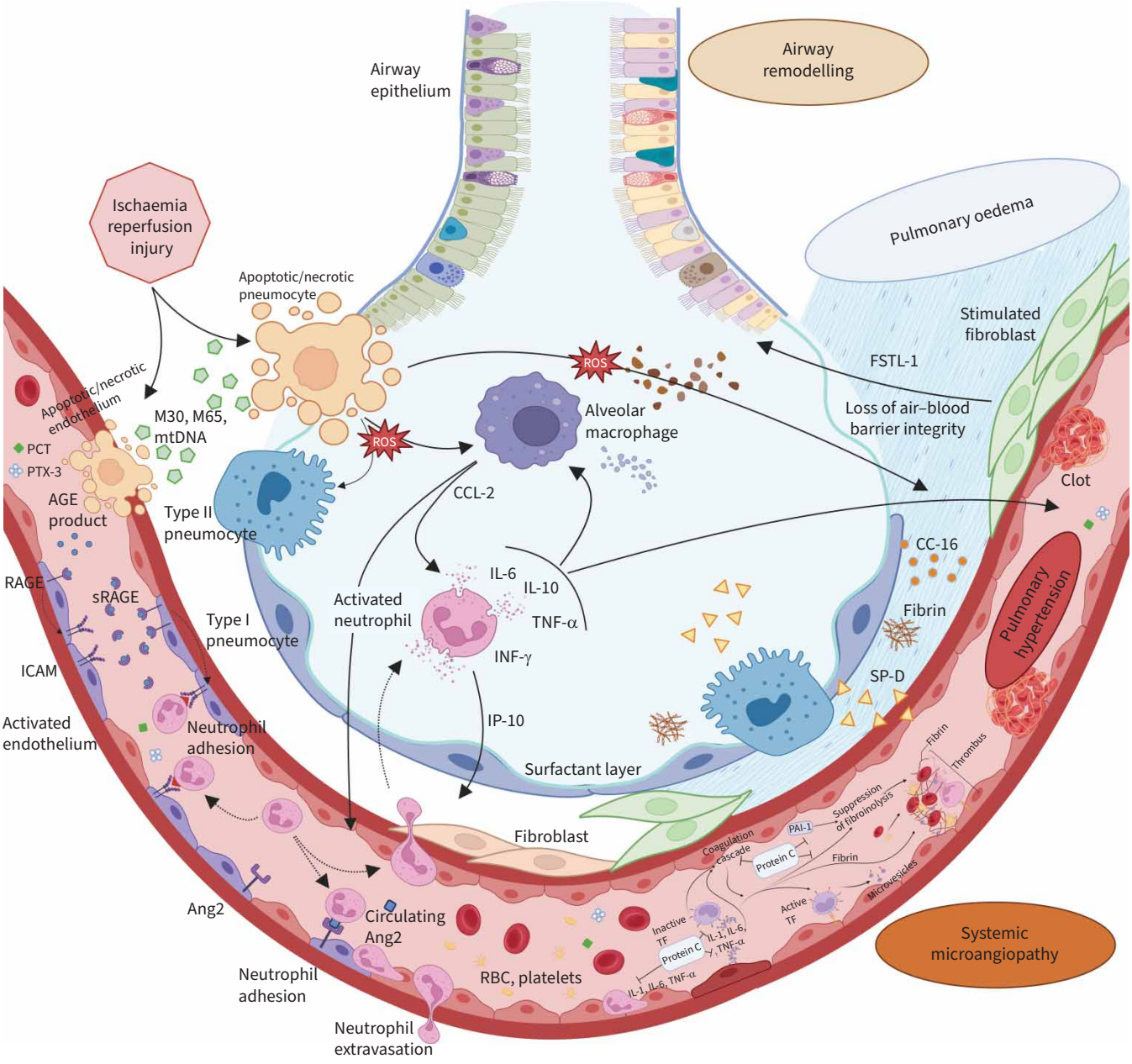

FIGURE 3 Putative pathophysiological pathways of primary graft dysfunction. In this figure, we present the putative pathophysiology of primary graft dysfunction (PGD) and its correlation with serum and alveolar biomarkers. Perioperative ischaemia initiates apoptosis and necrosis in both epithelial and endothelial cells. Upon reperfusion, the release of reactive oxygen species (ROS), advanced glycation end products (AGE) and mitochondrial DNA (mtDNA) into the intravascular and intra-alveolar spaces activates the receptor for advanced glycation end products (RAGE), which is liberated in blood as soluble RAGE (sRAGE). RAGE and sRAGE leads to the expression of the intracellular adhesion molecule-1 (ICAM-1) and angiopoietin-2 (Ang2) receptors promoting the adhesion, activation and extravasation of circulating neutrophils. The activation of intravascular neutrophils facilitates the suppression of fibrinolysis and thrombin generation through activated protein C and plasminogen activator inhibitor-1 (PAI-1). This contributes to pulmonary hypertension and systemic microangiopathy, culminating in distant end-organ damage (*e.g.*, acute kidney injury). Simultaneously, the intra-alveolar release of ROS and cellular debris activates release of surfactant protein D (SP-D) by type II pneumocytes, while alveolar macrophages further activate extravased neutrophils by chemokine (C-C motif) ligand-2 (CCL-2). Intra-alveolar activated neutrophils release several pro-inflammatory cytokines, such as interleukin (IL)-6, IL-10, tumour necrosis factor-α (TNF-α), interferon-γ (INF-γ), interferon gamma-induced protein 10 (IP-10) and club cell secretory protein (CC16), subsequently amplifying the local and systemic inflammatory cascade. Overall, the pro-inflammatory response leads to the disruption of the air–blood barrier integrity, resulting in pulmonary oedema. Additionally, activated fibroblasts release follistatin-like 1 (FSTL-1), promoting epithelial–mesenchymal transition and airway remodelling. PCT: procalcitonin; PTX3: plasma long pentraxin-3; RBC: red blood cell; TF: tissue factor.

understanding of FSTL1 positions it as a novel inflammatory mediator, suggesting its potential involvement in the transition from PGD to chronic lung allograft disease. This would make FSTL1 an interesting candidate for PGD phenotyping and possible immunomodulatory interventions [81].

IP-10 is a chemokine that modulates innate and adaptive immune responses by recruiting inflammatory cells and that, while bound to its receptor CXCR3, can induce chemotaxis, apoptosis, cell growth and epithelial activation. IP-10 (also known as CXCL10) has been shown in animal models [82] as a possible target for ARDS modulation.

IL-1Ra is an anti-inflammatory cytokine released during acute inflammatory responses, which has been associated with ARDS [83], sepsis [84] and mortality [85]. Of note, a recombinant and slightly modified version of IL-1Ra (*i.e.*, anakinra) is approved for immunomodulation during rheumatoid arthritis, and it has been widely employed during the COVID-19 pandemic [86].

Protein C is an anticoagulant and anti-inflammatory zymogen whose lower levels have been independently associated with increased mortality and adverse outcomes in ARDS and used for ARDS phenotyping [87]. Notably, in cases of purpura fulminans, protein C substitution is a promising therapeutic approach [88].

CCL-2 is a monomeric polypeptide that regulates the recruitment and migration of monocytes and macrophages and the induction of vascular activation. Furthermore, growing evidence suggests that CCL-2 might be implicated in pulmonary fibrosis and associated pulmonary hypertension [89]. In the context of LUTX, CCL-2 increases may be concurrent with preoperative pulmonary arterial hypertension or part of a causal pathway in PGD pathogenesis, mediating the infiltration of polymorphonucleates into the implanted graft. Again, several therapeutic agents targeting CCL-2 have been developed in the context of cancer immunochemotherapy.

Overall, the available evidence suggests that several biomarkers can be employed for PGD phenotyping. Nevertheless, the included studies showed several limitations.

The breadth of the collected evidence was limited to small patient cohorts recruited in a few centres and nations, despite we considered for this analysis all the available literature without temporal limits and included studies utilising both the 2005 and 2016 ISHLT definitions. On the one hand, limiting the search to the most recent definition would have provided minimal evidence (*i.e.*, just four studies used the most updated definition); on the other hand, there is no actual difference in the 2005 and 2016 definitions as regards to the possible biological signatures [22]. Thus, we aimed to include the broadest but most coherent literature with our – defined *a priori* – admissibility criteria. Despite this, only a limited number of studies were found, and most of them utilised not uniform and mostly outdated definitions for PGD diagnosis. A vast majority of studies were conducted in the USA and were produced mainly by the same USA-based research team. The number of patients per study ranged around the hundred mark, further underlining the limited breadth of literature available.

As per the resulting study cohorts, most studies included single and double LUTX. Only three studies [41, 43, 52] included only double LUTX. Furthermore, none of the above studies differentiated outcomes or biomarker concentration among single or double LUTX cohorts. This occurrence is very notable, given that formal criteria for diagnosing PGD in single-lung transplant recipients have not been established, and the very same ISHLT consensus conference concluded *verbatim* that “there is sufficient evidence to consider the mechanisms and analyses of PGD in single LUTX separately from those of bilateral LUTX.”

Techniques utilised for biomarker measurement were overall not fitted for clinical use, and no study attempted a comprehensive phenotyping of LUTX recipients by modern statistical techniques (*e.g.*, latent-class analyses). Indeed, measurements of plasma biomarkers were carried out primarily by ELISA and secondarily, in the most recent papers, by MBAA techniques. None utilised point-of-care devices for biomarker measurement. Both ELISA and MBAA are valid for research purposes. Still, long turnaround times make them not applicable to the scope of early, rapid sub-phenotyping of LUTX patients in clinical practice, and prospectively applying those techniques at multiple time points might be prohibitively expensive.

Furthermore, no study assessed the incidence of concurrent systemic manifestations of PGD (*e.g.*, vasoplegia, acute renal injury).

Some limitations apply to our scoping review. First, we focused our search on serum biomarkers of PGD and forgo the inclusion of studies analysing other withdrawal sites (namely BAL). Several reasons guided

this choice. Theoretically, the conception of PGD as a systemic syndrome drove us to search for equally systemic markers capable of elucidating the multilayered manifestations of post-transplantation ischaemia/reperfusion injury. In practical terms, BAL is typically not deemed clinically necessary unless there is a severe presentation of PGD or to exclude other potential causes of respiratory failure, particularly infections. However, the implementation of BAL may pose challenges, particularly in the most severely affected patients. Blood collection is far safer, and its logistical footprint is minimal compared to BAL. Furthermore, we do not know of any point-of-care device – available or under development – capable of on-site biomarker concentration measurement on BAL samples, while several are already commercialised for detecting cytokine panels on blood [90]. In short, due to collection and processing constraints, BAL samples are now unsuitable for early, bedside, noninvasive biological phenotyping of LUTX patients and thus were not considered.

Second, despite the literature search of the most common electronic bibliographic databases, some relevant studies might have been missed due to exclusion of grey and non-English literature. Nevertheless, our literature search was informed by an *a priori*, transparent, prospectively published and reproducible protocol to avoid this selection bias. Third, our study, as any scoping review, lacks a critical appraisal of the included studies, and accordingly, the risk of bias in the evidence or assessment of methodological limitations was not consistent with the purposes of this study. Thus, our results must be considered not as an indication for patient management or policy changes but as an indication for future research. Characterisation and interpretation of the included studies might have been subject to reviewer bias or error. To contrast this possible limitation and increase reliability, the screening and data characterisation forms were pretested and revised prior to implementation by all reviewers. Moreover, each record was reviewed by two independent reviewers, supervised by a third reviewer to solve eventual conflicts, and three different authors assessed each of the included studies.

Conclusions

With this scoping review, we documented a vast knowledge gap and the need for further prospective international studies that utilise uniform diagnostic criteria, modern platforms and statistical approaches to identify early biological signatures of PGD in LUTX patients.

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