

# The genomic landscape of Acute Respiratory Distress Syndrome: a meta-analysis by information content of genome-wide studies of the host response.

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## **Abstract**

Acute respiratory distress syndrome (ARDS) is a clinically defined syndrome of acute hypoxaemic respiratory failure secondary to non-cardiogenic pulmonary oedema. It arises from a diverse set of triggers and encompasses marked biological heterogeneity, complicating efforts to develop effective therapies. An extensive body of recent work (including transcriptomics, proteomics, and genome-wide association studies) has sought to identify proteins/genes implicated in ARDS pathogenesis. These diverse studies have not been systematically collated and interpreted.

To solve this, we performed a systematic review and computational integration of existing omics data implicating host response pathways in ARDS pathogenesis. We identified 40 unbiased studies reporting associations, correlations other links with 7000 named protein-coding genes, from 6,856 ARDS patients.

We used meta-analysis by information content (MAIC) to integrate and evaluate these data, ranking over 7,000 genes and weighting cumulative evidence for association. Functional enrichment of strongly-supported genes revealed cholesterol metabolism, endothelial dysfunction, innate immune activation and neutrophil degranulation as key processes. We identify 51 hub genes, most of which are potential therapeutic targets. To explore biological heterogeneity, we conducted a separate analysis of ARDS severity/outcomes, revealing distinct gene associations and tissue specificity. Our large-scale integration of existing omics data in ARDS enhances understanding of the genomic landscape by synthesising decades of data from diverse sources. The findings will help researchers refine hypotheses, select candidate genes for functional validation, and identify potential therapeutic targets and repurposing opportunities. Our study and the publicly available computational framework represent an open, evolving platform for interpretation of ARDS genomic data.

## Introduction

The acute respiratory distress syndrome (ARDS) is clinically defined as acute hypoxaemic respiratory failure due to non-cardiogenic pulmonary oedema<sup>1</sup>. It occurs following a variety of insults; pulmonary and extra-pulmonary. While this definition has been useful in identifying patients at risk of serious morbidity and death<sup>2</sup>, it overlooks the underlying biology and masks heterogeneity<sup>3</sup>. Arguably, this has contributed to limited success in developing therapeutics<sup>4</sup>. In contrast, a biological definition of ARDS may provide the lever necessary for future drug discovery<sup>5</sup>.

Functional genomics technologies enable hypothesis-free disease characterisation at unprecedented resolution. The emergence of coronavirus disease 2019 (COVID-19) has provided an opportunity to test genetic approaches to drug discovery in a homogeneous subset of ARDS patients. A notable success is the finding that baricitinib, a Janus kinase inhibitor, reduces mortality in patients hospitalised with COVID-19<sup>6</sup>. *A priori* support for baricitinib<sup>7</sup> was greatly enhanced following the discovery of a causal link between elevated tyrosine kinase 2 (TYK2) expression and severe COVID-19 in genome-wide association studies (GWAS)<sup>8</sup>. The availability of comparable omics data for non-COVID ARDS is limited.

An unresolved challenge is how large omics data can be effectively exploited<sup>9</sup>. Specifically, how can we combine data from heterogeneous sources to derive new insights or recalibrate our understanding in the light of new data? We have proposed meta-analysis by information content (MAIC) as a data-driven, algorithmic, method for combining gene lists from diverse sources<sup>10</sup>. MAIC is agnostic to the quality or methodology of the sources and combines ranked or un-ranked gene sets by calculating weights for each list and gene, and iteratively updating them to converge on a ranked meta-list. We have successfully applied MAIC to host-genomics studies of Influenza A<sup>10</sup> and coronavirus infection<sup>8,11</sup>, and shown that it out-performs existing algorithms when combining ranked and un-ranked lists obtained from heterogeneous sources<sup>12</sup>.

In this work, we present a living meta-analysis by information content of ARDS host genomics studies. This serves as an open-source resource for gene prioritisation, functional genomics, and drug target discovery. An interactive interface can be accessed at <https://baillielab.net/maic/ards>, alongside a complementary [R package](#).

## Results

### Systematic review

We first conducted a systematic review of existing genome-wide studies, which reported associations between genes, transcripts, or proteins and ARDS susceptibility, severity, survival, or phenotype. Our search yielded 8,937 unique citations (Fig. S1). We retrieved 74 articles for full-text evaluation and included 40 in our meta-analysis<sup>13–52</sup>. These 40 studies produced 44 unique gene lists (22 transcriptomic, 13 proteomic, and 9 based on genome-wide association studies (GWAS); see Table 1). Three studies reported results from multiple methodologies<sup>33,38,44</sup>, and several used more than one tissue type<sup>18,21,32</sup>. Excluding GWAS, 14 gene lists (40%) were derived from lung or airways samples, and 21 (60%) from blood. We could not retrieve one gene list<sup>26</sup>. No whole-genome sequencing GWAS were found, and only 36% (n=8) of transcriptomic lists used next-generation sequencing techniques. The earliest included study was published in 2004<sup>18</sup>, however, almost half (n=19, 47.5%) were published in the last 5 years.

Most studies aimed to identify genes or proteins associated with ARDS susceptibility (n=27, 67.5%). The remainder examined associations with survival (n=6, 15%), sub-phenotype (n=4, 10%), disease progression (n=2, 5%), or severity (n=1, 2.5%). In total, studies included 6,856 patients with ARDS.

### Meta-analysis by information content (MAIC)

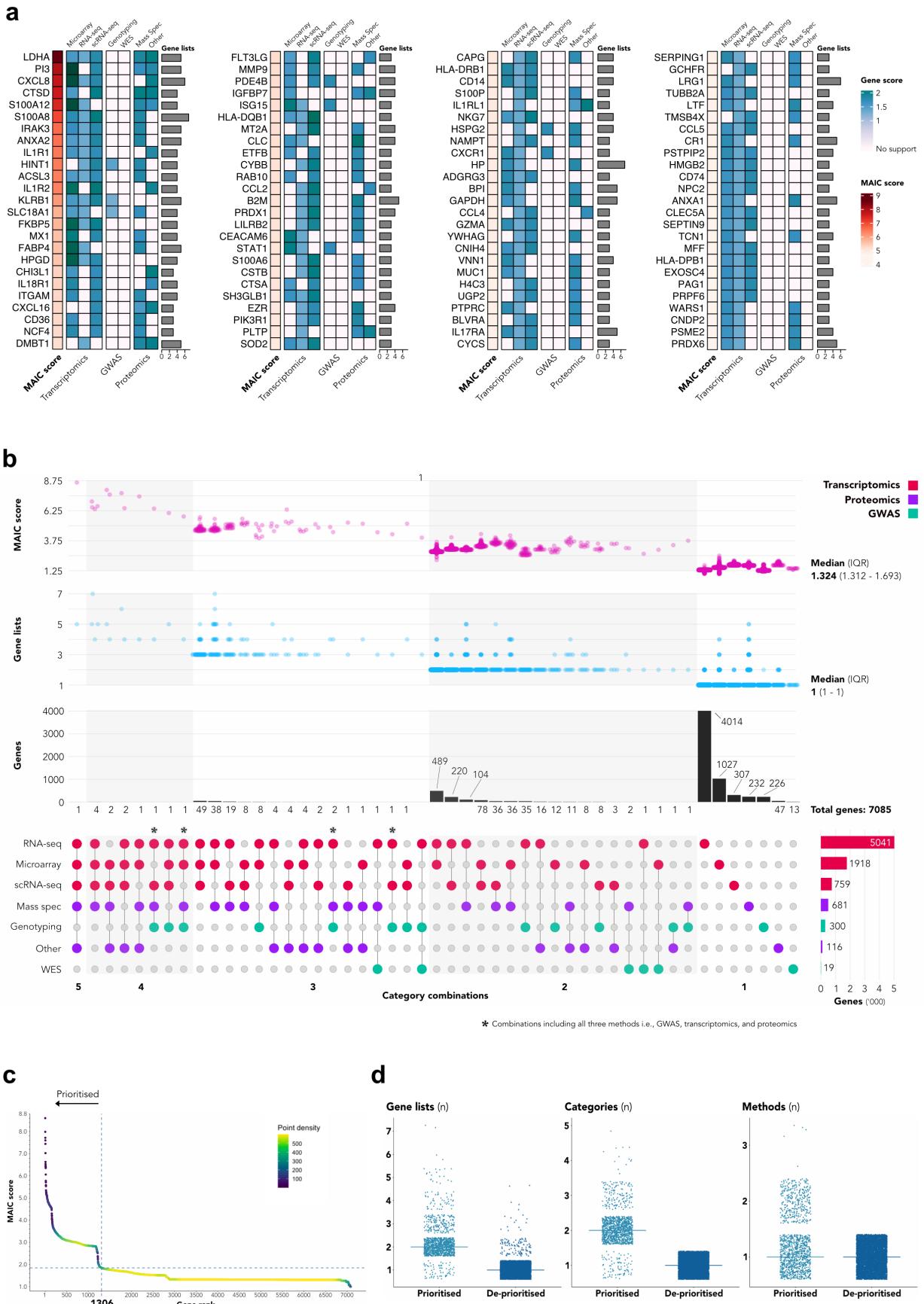
We analysed all 43 available gene lists using MAIC. Lists were categorised by method (i.e., GWAS, transcriptomics, and proteomics) and technique (e.g., RNA-seq, mass spectrometry; see Table 1). In total, we ranked 7,085 unique genes (or SNPs), with a median of 27 genes per gene list (range 1-4,954). The top 100 ranked genes are summarized in Figure 1. Most genes were found in a single category (n=5,866, 82.8%); only 157 (2.2%) were identified in  $\geq 3$  categories, with the maximum number of categories supporting a gene being 5 (Figure 1). Similarly, few genes (n=362, 5.1%) were identified by more than one method, with only *AKR1B10*, *HINT1*, *HSPG2*, *S100A11*, and *SLC18A1* present in transcriptomic, proteomic, and GWAS-based lists.

To prioritise genes for further investigation, we used the unit invariant knee method<sup>53</sup> to identify the inflection point in the MAIC score curve. This prioritised 1,306 genes with scores above this point (Figure 1). These genes were more likely to be found in  $\geq 2$  lists or categories and by more than one method (Figure 1).

To assess the influence of individual lists, we calculated the total MAIC score (totMS), reflecting the sum of gene scores across each list (Fig. S2), and the contributing total MAIC score (ctotMS), measuring the sum of each lists gene scores which contribute to a gene's overall MAIC score. To obtain relative values, we divided the totMS/ctotMS for each list by the total across all included lists. This demonstrated that only 10 lists (from 9 studies) contributed >1% by either metric (Tab. S2). Notably, the RNA-seq list from Sarma et al.<sup>44</sup> accounts for >50%, a function of its length. To account for this, we normalised totMS/ctotMS by the number of genes per list; along with the proportion of replicated genes in each list, this provides an alternative perspective, with several proteomic studies ranking highly (Fig. S2).

### Comparison with existing ARDS sources and COVID-19

To place our meta-analysis results in context, we evaluated the overlap between the genes prioritised by MAIC and those from two established resources: BioLitMine<sup>54</sup>, using an ARDS MeSH search, and the ARDS Database of Genes<sup>55</sup> (Fig. S3a and Fig. S3c). A search using BioLitMine, identified 271 ARDS-associated genes, of which 142 (52.4%) were present in our analysis. Almost half of the overlapping genes (n = 63, 44.4%) ranked within our prioritised set (Tab. S3).



**Figure 1: Meta-analysis by information content.** (a) Heatmap of top 100 ranked genes showing MAIC score, highest score per category, and number of supporting lists. (b) UpSet plot of ranked genes showing total numbers for each category combination, MAIC score distribution, and supporting lists. (c) Gene prioritisation using the Unit Invariant Knee method. Intersection of lines identifies elbow point of best-fit curve. 1,306 genes in the upper left quadrant were prioritised. (d) Strip plots comparing number of lists , categories, and methods per gene between prioritised and deprioritised sets.

Table 1: Summary of studies and gene lists included in the systematic review

Year	Study	Focus	Definition	N <sup>a</sup>	Method	Technique	Tissue	Cell type
2022	Batra <sup>13</sup>	Survival	Berlin	24	Proteomics	Other	Blood	
	Mirchandani <sup>38</sup>	ARDS vs. non-ARDS	Berlin	22	Proteomics	Mass Spec	Blood	Monocytes
	Sarma <sup>44</sup>	Sub-phenotype	Berlin	41	Transcriptomics Proteomics	Microarray Other	Blood	Monocytes
					Transcriptomics	RNA-seq	TA	TA
	Zhang <sup>51</sup>	ARDS vs. non-ARDS	AECC	11	Transcriptomics	scRNA-Seq	TA	Immune cells
2021	Liao <sup>33</sup>	Survival	Either	390	Transcriptomics GWAS	RNA-Seq	Blood	Exosomes
	Martucci <sup>35</sup>	Sub-phenotype	None	11	Transcriptomics	Genotyping	Blood	
	Xu <sup>49</sup>	Survival	Berlin	105	GWAS	RNA-seq	Blood	PBMCs
	Zhang <sup>50</sup>	ARDS vs. non-ARDS	Berlin	5	Transcriptomics	Microarray	Blood	
	Guillen-Guio <sup>27</sup>	ARDS vs. non-ARDS	Berlin	633	GWAS	WES	Blood	
	Jiang <sup>29</sup>	ARDS vs. non-ARDS	Berlin	3	Transcriptomics	RNA-seq	Blood	
	Bos <sup>17</sup>	Sub-phenotype	Berlin	210	Transcriptomics	Genotyping	Blood	PBMCs
	Englert <sup>25</sup>	ARDS vs. non-ARDS	Either	11	Transcriptomics	scRNA-seq	Blood	
	Morrell <sup>40</sup>	Survival	AECC	36	Transcriptomics	Microarray	Blood	
	Scheller <sup>45</sup>	ARDS vs. non-ARDS	None	6	Transcriptomics	RNA-seq	BALF	AMs
	Bime <sup>16</sup>	ARDS vs. non-ARDS	Either	232	GWAS	Genotyping	Blood	EVs
	Morrell <sup>39</sup>	ARDS vs. non-ARDS	Berlin	35	Transcriptomics	Microarray	BALF	
2017	Bhargava <sup>15</sup>	Survival	AECC	36	Proteomics	Mass Spec	BALF	
	Lu <sup>34</sup>	ARDS vs. non-ARDS	AECC	12	Transcriptomics	Microarray	Blood	
	Zhu <sup>52</sup>	ARDS vs. non-ARDS	Berlin	199	Transcriptomics	Microarray	Blood	

Year	Study	Focus	Definition	N <sup>a</sup>	Method	Technique	Tissue	Cell type
2016	Chen <sup>21</sup>	Severity	AECC	7	Proteomics	Mass Spec	BALF/Blood	
	Juss <sup>30</sup>	ARDS vs. non-ARDS	Berlin	23	Transcriptomics	Microarray	Blood	Neutrophils
	Nick <sup>41</sup>	Sub-phenotype	AECC	121	Transcriptomics	Microarray	Blood	Neutrophils
	Ren <sup>43</sup>	ARDS vs. non-ARDS	Berlin	14	Proteomics	Other	Blood	
2015	Kangearis <sup>31</sup>	ARDS vs. non-ARDS	Berlin	29	Transcriptomics	Microarray	Blood	
	Kovach <sup>32</sup>	ARDS vs. non-ARDS	AECC	18	Transcriptomics	Microarray	BALF/Blood	AMs
2014	Bhargava <sup>14</sup>	Progression	AECC	22	Proteomics	Mass Spec	BALF	
	Shortt <sup>46</sup>	ARDS vs. non-ARDS	AECC	213	GWAS	WES	Blood	
	Chen <sup>20</sup>	ARDS vs. non-ARDS	Berlin	11	Proteomics	Mass Spec	Blood	
	Dong <sup>24</sup>	Progression	None	14	Proteomics	Mass Spec	BALF	AMs
	Meyer <sup>37</sup>	ARDS vs. non-ARDS	Berlin	661	GWAS	Genotyping	Blood	
	Nguyen <sup>42</sup>	ARDS vs. non-ARDS	AECC	30	Proteomics	Mass Spec	BALF	
	Christie <sup>22</sup>	ARDS vs. non-ARDS	AECC	812	GWAS	Genotyping	Blood	
	Dolinay <sup>23</sup>	ARDS vs. non-ARDS	AECC	35	Transcriptomics	Microarray	Blood	
	Tejera <sup>48</sup>	ARDS vs. non-ARDS	AECC	1400	GWAS	Genotyping	Blood	
	Frenzel <sup>26</sup>	Survival	AECC	46	Proteomics	Mass Spec	BALF	
	Meyer <sup>36</sup>	ARDS vs. non-ARDS	AECC	1241	GWAS	Genotyping	Blood	
	Howrylak <sup>28</sup>	ARDS vs. non-ARDS	AECC	13	Transcriptomics	Microarray	Blood	
2011		ARDS vs. non-ARDS	None	20	Proteomics	Mass Spec	BALF	
2009	Chang <sup>19</sup>	ARDS vs. non-ARDS	AECC	8	Transcriptomics	Microarray	Blood	
2008	Wang <sup>47</sup>	ARDS vs. non-ARDS	AECC	16	Proteomics	Mass Spec	BALF/Blood	
2004	Bowler <sup>18</sup>	ARDS vs. non-ARDS	AECC					

a - The number of patients with ARDS included in each study. Abbreviations: AECC - American-European Consensus Conference; AMs - Alveolar macrophages; BALF - Bronchoalveolar lavage fluid; EVs - Extracellular vesicles; GWAS - Genome-wide association study; MS - Mass spectrometry; PBMCs - Peripheral blood mononuclear cells; TA - Tracheal aspirate; WES - Whole-exome sequencing.

After correcting for historical gene symbol aliases, we matched 4 additional genes from the BioLitMine search. A further 104 genes were supported by just a single publication (Fig. S3b). For each of the remaining 21 genes, we obtained the 100 most co-expressed genes using ARCHS4<sup>56</sup> (returning data for 18) and assessed the overlap of these sets with the results of ARDS MAIC; two-thirds exhibited <50% overlap (Fig. S3b). Of the 239 genes catalogued in the ARDS Database of Genes, 177 (74.1%) were also found in our study. However, both sources contain gene associations which lack genome-wide support.

Finally, we compared the overlap between genes ranked by ARDS MAIC and those identified in a previous MAIC of the host response to coronaviruses<sup>11</sup> (Fig. S3d). In total, 2,606 genes (36.8%) were shared, of which 143 were prioritised by both analyses (Fig. S3e).

### Tissue and cell-specific expression

While most gene lists were derived from blood sampling, most genes were identified in airways samples ( $n=5,847$ , 82.5%) (Fig. S4a). This was equally the case for the prioritised gene set, however the majority of these genes were also identified in blood samples ( $n=818$ , 62.6%) (Fig. S4b). Among genes uniquely identified in lists obtained from blood samples ( $n=1,238$ ), almost three-quarters are known to be expressed in the lung (HPA scRNA-seq data,  $\geq 5$  normalised transcripts per million (nTPM)), with a quarter being highly-expressed ( $\geq 100$  nTPM) (Fig. S4c).

For prioritised genes found in lists obtained from airways sampling, there was a wide variety of cell-specific expression (Fig. S4d). However, in the smaller set of prioritised genes identified solely in lists employing blood samples, clusters of expression specific to neutrophils, T cells, and monocytes were evident (Fig. S4e). Cell-type specific gene enrichment analysis suggests innate immune as well as epithelial and endothelial cell types are enriched among genes identified in airways samples (Fig. S4f). However, enrichment of epithelial and endothelial cells was not evident for prioritised genes identified from blood sampling alone (Fig. S4g).

### Functional enrichment

Having identified a set of prioritised genes, we undertook several functional enrichment analyses. First, we performed over-representation analysis (ORA). In Reactome, 51 terms were significantly enriched ( $P < 0.001$ ) (Figure 3). Not unexpectedly, neutrophil degranulation and several innate immune pathways (e.g., IL-10 signalling, interferon signalling, MHC II antigen presentation, TLR4 cascade) featured heavily. However, multiple pathways associated with cholesterol biology and metabolism (e.g., chylomicron assembly/remodelling, GLUT4 translocation, TP53 regulation of metabolic genes, insulin regulation) were also over-represented. Similarly, lipid and cholesterol metabolism, as well as hyperlipidaemia, were over-represented in KEGG and WikiPathways (Fig. S5a and Fig. S5b). In an enrichment analysis using the GWAS Catalog, the prioritised set of genes was associated with asthma (adult onset/time to onset), monocyte, lymphocyte, and eosinophil counts, aspartate aminotransferase levels, and levels of apolipoprotein A1 (Fig. S5d).

Next, we used the prioritised set of genes to create a protein-protein interaction (PPI) network. We graph-clustered this network, identifying 48 clusters with  $\geq 5$  members. Among the 10 largest clusters, we found programs associated with the proteasome, cholesterol metabolism, interferon signalling, IL-6 signalling, and the complement cascade (Fig. S6). We then sought to use the PPI network to identify hub genes using an ensemble of topological methods. This analysis suggests 51 genes as being central to the wider network (Figure 2). Clustering these genes alone identified 5 clusters, which may be associated with innate immune cytokine signalling, interferon signalling, MHC class II antigen presentation, PI3K-Akt signalling, and eukaryotic translation elongation (Figure 2). The majority of hub genes ( $n=31$ ,

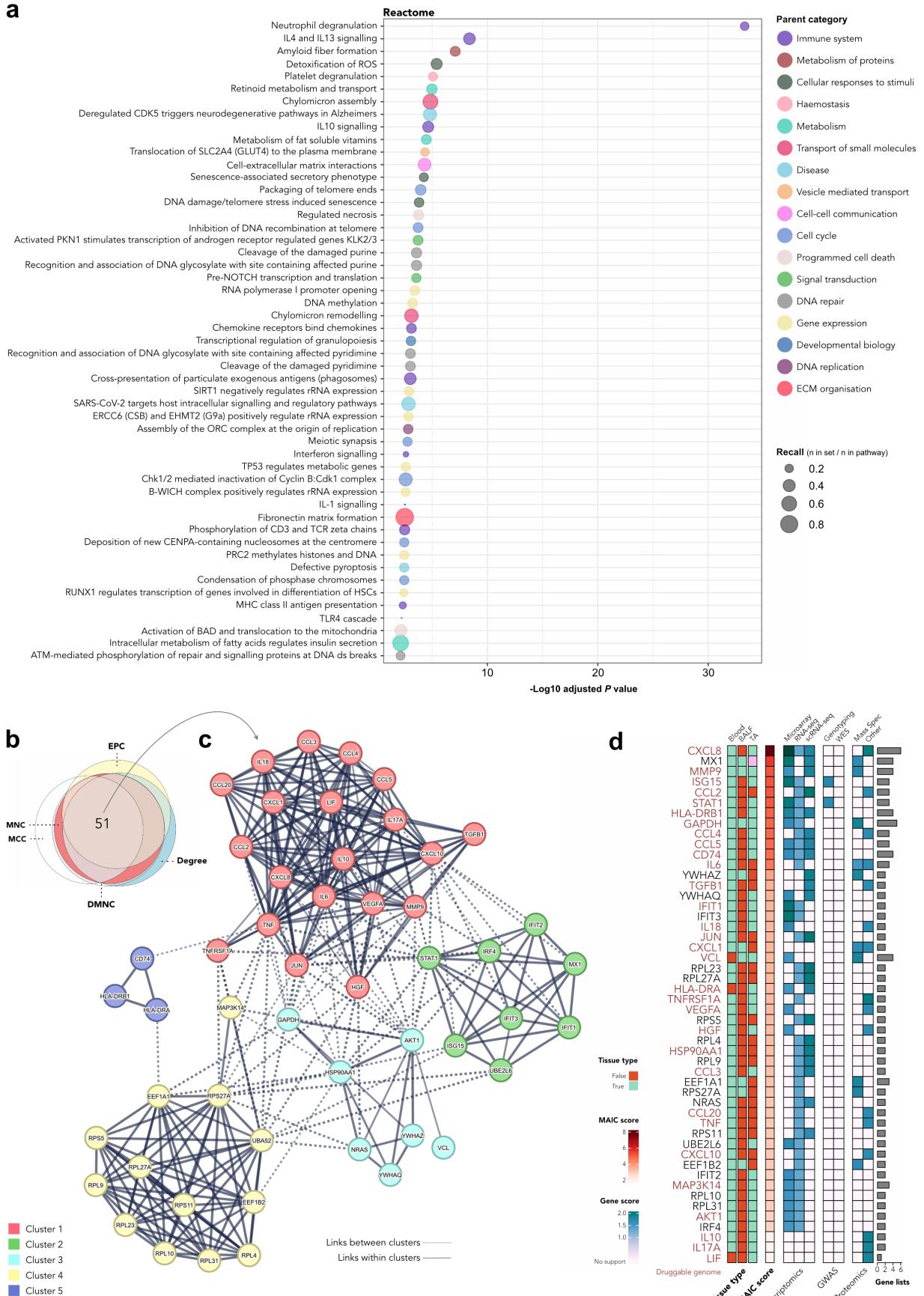
61%) are currently druggable and include targets such as *IL-6*, *IL-17A*, *IL-18*, and *MAP3K14*.

### Sub-groups

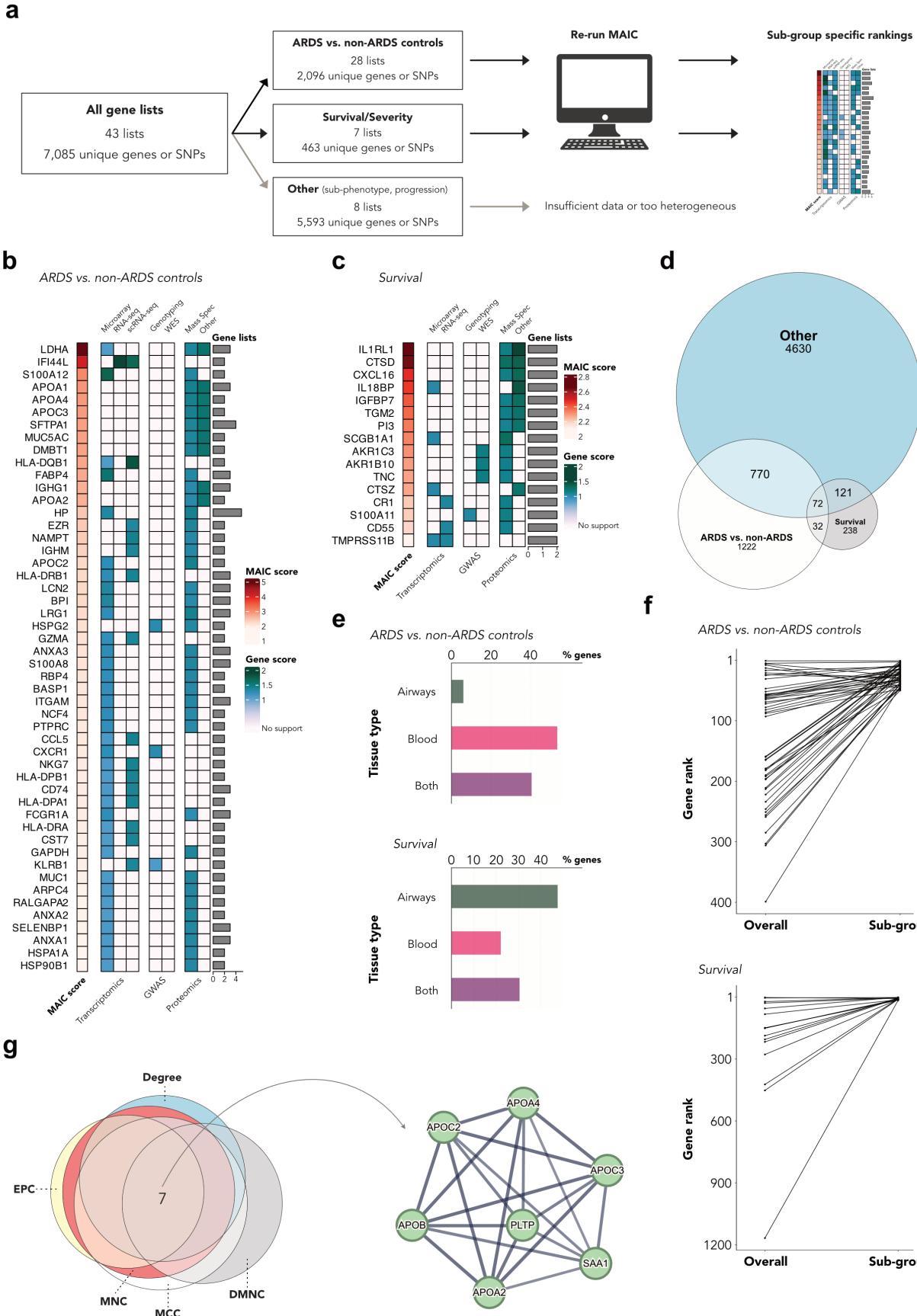
A potential limitation of our approach is the disparity in design of included studies. To address this, we undertook MAIC on subsets of gene lists, stratified by study focus. There were sufficient lists to make this tractable for studies focused on ARDS versus non-ARDS controls (n=28) and studies of ARDS survival and severity (n=7) (Figure 3).

For ARDS vs. non-ARDS controls, there were 15 transcriptomic (54%), 7 GWAS (25%), and 6 proteomic lists (21%). Together, these studies included 5,713 patients with ARDS. MAIC ranked 2,096 genes (Figure 3). The majority of these (n=1,222, 58%) were unique to this sub-group (Figure 3). Most were identified in blood, with a small fraction found solely in airways samples. The inflection point method prioritised the top ranked 130 genes (Fig. S7a). In comparison to the BioLitMine search and the ARDS Database of Genes, 71/271 and 117/239 genes were found among this set, respectively (Fig. S7b). A microarray-based transcriptomic list from Juss *et. al.*<sup>30</sup> accounted for more than half (54.7%) of the relative ICtb, with an additional 12 lists having a relative ICtb  $\geq 1\%$  (Tab. S4). ORA using Reactome, KEGG, and WikiPathways identified 25 significantly enriched pathways, including multiple terms related to cholesterol metabolism and glycolysis (Figure 4). A consensus of topological models identified 7 hub genes within a PPI network of prioritised genes. These genes cluster in a single group, characterised as being related to cholesterol metabolism (Figure 3).

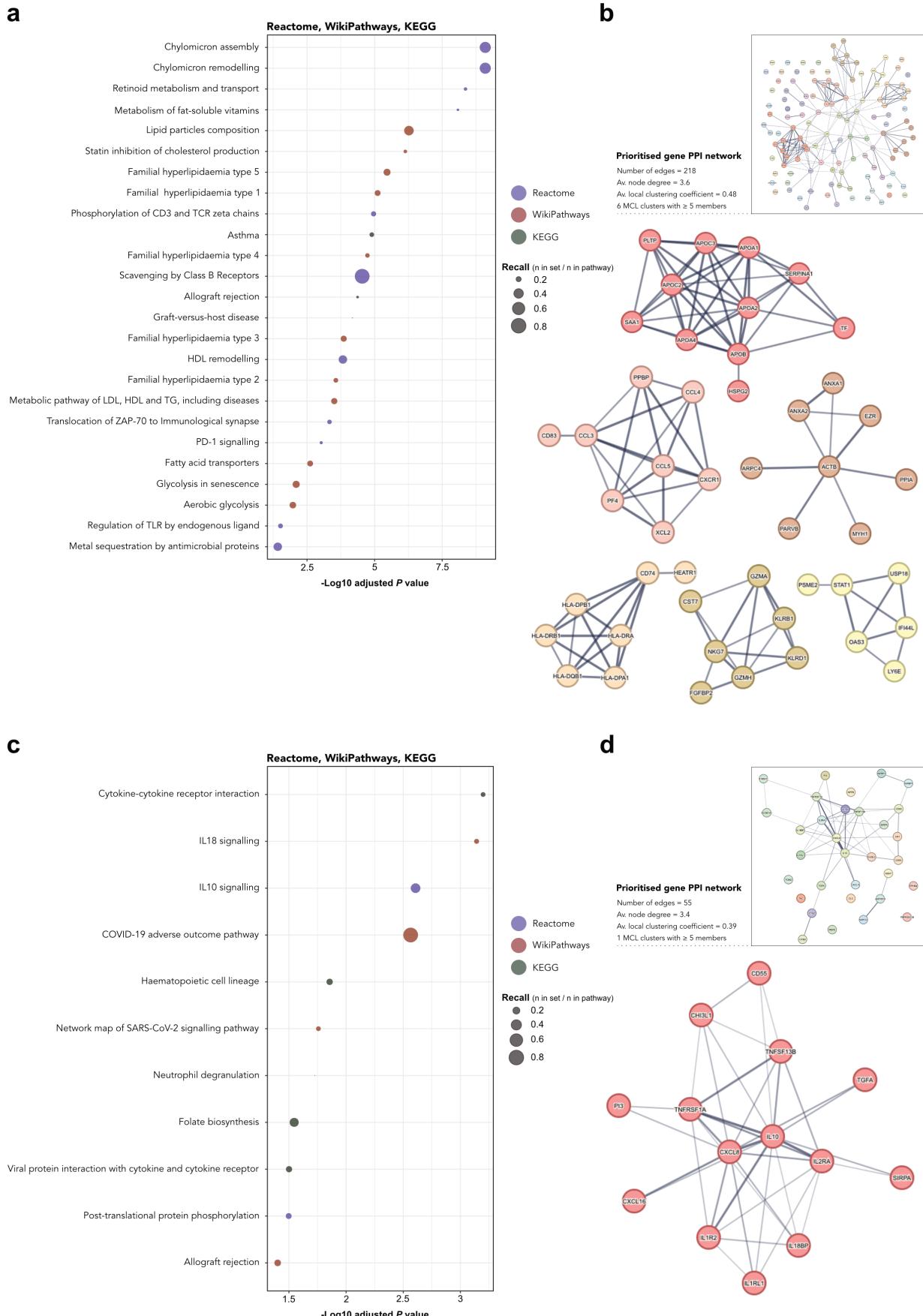
For survival, there were 8 gene lists, consisting of 3 transcriptomic lists (37.5%), 3 proteomic lists (37.5%), and 2 GWAS (25%). Together, these studies included 644 patients with ARDS. MAIC ranked 463 genes (Figure 3). Approximately half of these (n=238, 51%) were unique to survival-based lists. In contrast to the ARDS vs. non-ARDS analysis, most survival genes were found in airways samples. Thirty-three genes were prioritised (Fig. S7d). In total, 32/271 of the BioLitMine ARDS-associated genes and 23/239 of the ARDS Database of Genes genes were found among the ARDS MAIC survival set (Fig. S7e). The proteomic and transcriptomic lists from Bhargava *et.al*<sup>15</sup> and Morrell *et. al*<sup>40</sup> each contributed approximately 30% of the relative ICtb (Tab. S5). IL-10 and IL-18 signalling pathways were both significantly enriched in ORA (Figure 4). Graph-based clustering of the prioritised set of survival genes identified a single large cluster of immune-related genes including, *IL-10*, *CXCL8*, *TNFRSF1A*, and *IL2RA* (Figure 4).



**Figure 2: Functional enrichment of prioritised genes.** (a) Significantly enriched Reactome terms ( $P < 0.01$ ). Terms colored by parent class and size proportional to recall. (b) Euler diagram of the overlap of hub genes identified by five methods. MNC - Maximum Neighbourhood Component, MCC - Maximal Clique Centrality, DMNC - Density of MNC, EPC - Edge Percolated Component. (c) Protein-protein interaction (PPI) network of hub genes, clustered using the Markov Chain Algorithm. (d) Heatmap of common hub genes displaying tissue type(s), MAIC score, highest category score, supporting lists, and presence in the DGIdb druggable genome (indicated in red).



**Figure 3: MAIC of sub-groups.** (a) Schematic of ARDS MAIC sub-group analyses. (b) Heatmap of top 50 ranked genes in the ARDS vs. non-ARDS controls set showing MAIC score, highest score per category, and number of supporting lists. (c) Heatmap of 16 ranked genes in the survival set with multi-list support showing MAIC score, highest score per category, and number of supporting lists. (d) Euler diagram of gene overlap between the ARDS vs. non-ARDS controls and survival sets and the remainder of genes. (e) Bar plots of the tissue type in which genes are identified. (f) Slope plot comparing the ranks of ARDS vs. non-ARDS controls and survival prioritised genes with their ranks in the full iteration of ARDS MAIC. (g) Euler diagram of the overlap of hub genes identified by five methods. MNC - Maximum Neighbourhood Component, MCC - Maximal Clique Centrality, DMNC - Density of MNC, EPC - Edge Percolated Component and a protein-protein interaction (PPI) network of hub genes, clustered using the Markov Chain Algorithm - for ARDS vs. non-ARDS controls.



**Figure 4: Sub-group functional enrichment.** (a) Significantly enriched Reactome, WikiPathways, and KEGG terms ( $P < 0.01$ ) for prioritised genes in the ARDS vs. non-ARDS controls sub-group. Terms are coloured by pathway and size is proportional to recall. (b) A protein-protein interaction network of prioritised genes in the ARDS vs. non-ARDS controls cohort and graph-based clusters with  $\geq 5$  members. (c) Significantly enriched Reactome, WikiPathways, and KEGG terms ( $P < 0.01$ ) for prioritised genes in the survival sub-group. Terms are coloured by pathway and size is proportional to recall. (d) A protein-protein interaction network of prioritised genes in the survival cohort and graph-based clusters with  $\geq 5$  members.

## Discussion

Our systematic integration of more than 20 years of data is the first large-scale meta-analysis of the genomic landscape of ARDS. This implicates over 7,000 genes and prioritises 1,306. The wide inclusion criteria capture a diverse range of study designs and methods; the subsequent application of MAIC establishes the sum of this knowledge, downgrading noisy, irrelevant, or low-quality information. These results have three main applications. First, they can be used to better understand the pathobiology of ARDS, providing a resource to prioritise future *in-vitro* and *in-vivo* studies and permitting comparisons between important sub-groups. Second, they prioritise therapeutic targets, serving as a source against which novel and repurposed treatments can be screened. Third, they serve as a base for quantifying the novelty or additive nature of future omics studies in ARDS.

Our review included 40 studies with genome-wide hypotheses. These studies varied in their aims and methods, however, some key themes are of note. Most obviously, the rate at which this form of study is being published is increasing; half of all studies in the last 5 years and a quarter since 2020. Similarly, there were few studies which employed next-generation sequencing (NGS) techniques or equivalent, and only two single-cell RNA-seq studies. A partial explanation may be the emergence of COVID-19, which is likely to have consumed the attention of many research teams active in this field. It is not unreasonable to conclude that an increasing number of non-COVID ARDS single-cell and NGS studies will emerge in the coming years. This reinforces the requirement for methods capable of meta-analysing multi-omic data<sup>57</sup>. Less obviously, a minority of studies have sampled the lung in ARDS, with only four examining the bulk transcriptome in the distal airspace. Reliance on information derived from blood samples may present a skewed picture of the pathobiology of ARDS and represents a missed opportunity to identify novel targets in the lung<sup>58</sup>.

A key advantage of the MAIC approach is its ability to integrate diverse data sources. Traditional methods of gene list meta-analysis rely on simple vote counting or robust rank aggregation<sup>59</sup>. Instead, MAIC applies a data-derived weighting to each gene list, allows the investigator to define granular categorisation (preventing any one particular method from overwhelming the analysis), and permits the inclusion of both ranked and unranked lists. We have previously used MAIC to identify anti-viral genes in response to Influenza A infection, showing that it outperforms other available methods<sup>10</sup>. We have since validated the superiority of MAIC in similar circumstances in a comprehensive simulation<sup>12</sup>.

Our prioritisation of genes simultaneously validates existing concepts of ARDS pathobiology and provides novel insights. The functional prominence of innate immunity and cytokine signalling - in particular neutrophil-related activity - is unsurprising<sup>60</sup>. As is the high ranking of genes such as *CXCL8*<sup>61</sup>, *IL-18*<sup>62</sup>, *MMP9*<sup>63</sup>, and *MUC1*<sup>64</sup>. However, other findings are intriguing. A single gene example is histidine triad nucleotide binding protein 1 (*HINT1*), ranked 10<sup>th</sup> and one of only 5 genes to have support from GWAS, transcriptomics, and proteomics methods. To our knowledge, no plausible role for *HINT1* has previously been suggested in ARDS<sup>65</sup>. However, *HINT1* has been implicated in T-cell response<sup>66</sup>, immunoregulation<sup>67</sup>, and apoptosis<sup>65</sup>. Another notable finding is the significant enrichment of cholesterol uptake, efflux, and esterification pathways among prioritised genes<sup>68,69</sup>. Stratification by sub-group offered further insights. The observation of a tight cluster of genes important in cholesterol metabolism at the hub of those prioritised in ARDS vs. non-ARDS controls is of therapeutic relevance<sup>70,71</sup>. However, other programs were observed in the setting of ARDS vs. non-ARDS controls including, type I interferon signalling<sup>72</sup>, MHC class II<sup>73</sup>, cell-cell adhesion<sup>74</sup>, and natural killer cell cytotoxicity<sup>75</sup>. In contrast, genes prioritised for outcome are functionally more homogeneous and related to cytokine signalling, in particular IL-10 and IL-18 signalling, indicating that shared pathways dictate mortality/severity once ARDS is established.

Our approach has limitations. We purposefully sought studies with genome-wide hypotheses, excluding single-gene or candidate genetics studies. In the case of a gene with extensive evidence from the latter, our methodology may underestimate its association with ARDS. However, these study designs are subject to other limitations, such as publication and investigator biases<sup>76</sup>. In our iteration of MAIC, we did not account for direction of expression or effect. For a given gene, if the direction of expression differs between studies, MAIC may overestimate the strength of evidence associated with that gene. The inability to account for directionality also limits the scope of functional enrichment analyses which can be performed. Similarly, the use of an unsupervised prioritisation threshold may influence the outcomes of downstream analyses, however principled the approach. Finally, the general paucity of data, and in particular the limited number of single-cell transcriptomics (or proteomics) studies, limits the depth of inference that can be made. It is likely that many pathological perturbations occur with cell-specificity, which may not be apparent in bulk analyses of heterogeneous tissues<sup>77</sup>. In future, the addition of data from these modalities may reveal precision targets.

Crucially, we provide an open platform and associated tools to enable deeper mining of the output. This allows others to re-analyse the data based on alternative sub-group divisions or to integrate unseen information. Ongoing multi-omic data integration with this initial study will further enhance the resolution of the data and increase our confidence in the results.

In summary, by systematically integrating decades of ARDS genomics, this study improves the scope for gene prioritisation and enhances molecular pathophysiological clarity. Our results strongly implicate interferon signalling and cholesterol metabolism dysregulation, providing a specific therapeutic targets. Enrichment patterns and sub-group differences also give clues to genomic drivers of susceptibility, outcomes, and mortality. This substantially improves our conceptualisation of the genomic landscape of ARDS, setting the stage for functional validation.

## Methods

The systematic review and meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022306270). The review is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>78</sup>.

### Search strategy and selection criteria

A detailed description of our search strategy and eligibility criteria is provided in the Supplementary Methods. Briefly, we searched MEDLINE, Embase, bioRxiv, medRxiv, the ARDS Database of Genes<sup>55</sup>, and the NCBI Gene Expression Omnibus from inception to April 1<sup>st</sup>, 2023 without language restrictions. We also performed single-level backwards and forwards citation searches using SpiderCite<sup>79</sup> and hand-searched recent review articles<sup>80–83</sup>.

We included human genome-wide studies reporting associations between genes, transcripts, or proteins and ARDS susceptibility, severity, survival, or phenotype, accepting any contemporaneous ARDS definition. We excluded paediatric studies (age < 18 years), animal studies, *in-vitro* human ARDS models, candidate *in-vivo* or *in-vitro* studies (< 50 genes/proteins), candidate gene associations, and studies with < 5 patients per arm (except scRNA-seq).

### Outcomes

We retrieved ranked lists of genes associated with the ARDS host response, preferring measures of significance and adjusted *P* values over raw *P* values when multiple ranking measures were used. We obtained both summary lists (all implicated genes) and author-defined subgroup lists. To combine subgroup lists into summary lists, we took the minimum *P* value or maximum effect size. We excluded genes below the author-defined threshold for significance/effect magnitude. If unavailable, we excluded genes with *P* > 0.05, z-score < 1.96, or log fold change < 1.5.

### Study selection and data extraction

Article titles and abstracts from our search were stored in Zotero v6.0-beta (Corporation for Digital Scholarship, United States). Titles were initially screened by one author using Screenatron<sup>79</sup>. Two authors then independently screened abstracts against eligibility criteria, with a third resolving inconsistencies. Full texts and supplements of eligible studies were retrieved and inclusion adjudicated by consensus.

Data were extracted by one author and cross-checked by a second. Gene, transcript, or protein identifiers were mapped to HGNC symbols or Ensembl/RefSeq equivalents if no HGNC symbol was available. Unannotated SNPs were searched in NCBI dbSNP. miRBase (University of Manchester, United Kingdom) provided miRNA symbols. For microarray probes without symbols, we used the DAVID Gene Accession Conversion tool (Laboratory of Human Retrovirology and Immunoinformatics, Frederick National Laboratory for Cancer Research, United States) to map them to HGNC symbols. We extracted information relating to study design, methodology, tissue/cell type, demographics, ARDS aetiology, risk factors, severity, and outcomes.

### Meta-analysis by information content (MAIC)

The MAIC algorithm has been described in detail<sup>8,10,11,84</sup>. Full documentation and the source code are available at <https://github.com/baillielab/maic>. Briefly, MAIC combines ranked and unranked lists of related named entities, such as genes, from heterogeneous experimental categories, without prior regard to the quality of each source. The algorithm makes four key assumptions; (1) genes associated with ARDS exist as true positives, (2) a gene is more likely to be a true positive if it is found in more than one source, (3) the probability of being a true positive is enhanced if the gene

appears in a list that contains a higher proportion of replicated genes, and (4) the probability is further enhanced if it is found in more than one category of experiment. Based on these assumptions, MAIC compares lists with each other, forming a weighting for each source based on its information content, which is then used to calculate a score for each gene. The output is a ranked list summarizing the total information supporting each gene's association with ARDS. We have shown MAIC outperforms available algorithms, especially with ranked and unranked heterogeneous data<sup>84</sup>.

As our primary analysis, we performed MAIC on all summary gene lists, regardless of study focus. Lists were assigned categories based on their methodology and experimental technique: genome-wide association study (GWAS) - genotyping, GWAS - whole exome sequencing, transcriptomics - microarray, transcriptomics - RNA-sequencing (RNA-seq), transcriptomics - single cell RNA-seq (scRNA-seq), proteomics - mass spectrometry, and proteomics - other. For secondary analyses, we performed MAIC on subsets of lists based on study focus (i.e., susceptibility to ARDS or survival/severity).

In secondary analyses, we repeated this pipeline for gene lists arising from studies in which the focus was ARDS vs. non-ARDS controls or ARDS survival/severity.

For each MAIC iteration, we prioritised genes with sufficient evidential support for further study (i.e., the gene set before which information content diminished such that there was little/no corroboration for the remainder's ARDS association). We used the unit invariant knee method<sup>53,85</sup> to identify the elbow point in the best-fit curve of MAIC scores. Genes with values above this point were prioritized for downstream analyses.

### **ARDS literature and SARS-CoV-2 associations**

We used BioLitMine<sup>54</sup> to query the NCBI Gene database for genes associated with the Medical Subject Heading (MeSH) term "Respiratory Distress Syndrome, Acute", generating a list of genes and publications. We descriptively compared the overlap between this list and the MAIC-ranked gene list. Similar comparisons were made between the ARDS MAIC results and the gene set in the ARDS Database of Genes<sup>55</sup> and a prior MAIC of SARS-CoV-2 host genomics<sup>11</sup>.

### **Tissue expression and enrichment**

Transcript and protein expression data for genes included in ARDS MAIC were retrieved from the Human Protein Atlas (HPA, version 21.0)<sup>86</sup>. We investigated mRNA expression in a consensus scRNA-seq dataset of 81 cells from 31 sources ([https://www.proteinatlas.org/about/assays+annotation#singlecell\\_rna](https://www.proteinatlas.org/about/assays+annotation#singlecell_rna)) and in the HPA RNA-seq blood dataset<sup>87</sup>, containing expression levels in 18 immune cell types and total peripheral blood mononuclear cells. To investigate protein expression, we retrieved tissue-specific expression scores from the HPA<sup>88</sup>. We conducted cell-type specific enrichment analysis using WebCSEA<sup>89</sup> and extracted the top 20 general cell types for each query.

### **Functional enrichment**

We performed functional enrichment of genes against the universe of all annotated genes using g:Profiler<sup>90</sup>. The following data sources were used; Kyoto Encyclopaedia of Genes and Genomes (KEGG)<sup>91</sup>, Reactome<sup>92</sup>, WikiPathways<sup>93</sup>, and Gene Ontology<sup>94</sup>. Multiple testing was corrected for using the g:SCS algorithm<sup>90</sup>, with a threshold of  $P < 0.01$ . Input lists were ordered by MAIC score were appropriate. In the case of GO cellular component terms, we used the REVIGO tool to perform multi-dimensional scaling of the matrix of all pairwise semantic similarities<sup>95</sup>. Enrichment was also performed against the National Human Genome Research Institute GWAS Catalog<sup>96</sup> using the Enrichr web-interface<sup>97</sup>. Protein-protein interaction enrichment was performed using STRING v11<sup>98</sup>. We included all possible

interaction sources but specified a minimum interaction score of 0.7. We used the the whole annotated genome as the statistical background. Markov Clustering Analysis (MCL) was applied to the resulting network with an inflation parameter of 3. Clusters were annotated by hand having considered enrichment against KEGG, Reactome, and WikiPathways. To identify hub genes within the PPI network, we used cytoHubba<sup>99</sup> and Cytoscape<sup>100</sup>. The highest ranked genes by Maximum Neighbourhood Component (MNC), Maximal Clique Centrality (MCC), Density of MNC (DMNC), Edge Percolated Component (EPC), and node degree were retrieved. The intersecting genes of these methods were deemed hub genes. Hub genes were searched for in the Drug Gene Interaction Database<sup>101</sup> to identify if they were present in the druggable genome. The Drug Gene Interaction Database (DGIdb) was queried for each ranked gene<sup>102</sup>.

### **Software and code availability**

MAIC is implemented in Python v3.9.7 (Python Software Foundation, Wilmington, United States). All other analyses were performed with R v4.2.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Code required to reproduce the analyses is available at [https://github.com/JonathanEMillar/ards\\_maic\\_analysis](https://github.com/JonathanEMillar/ards_maic_analysis). An R package (ARDSMAICR) containing the data used in this manuscript and several functions helpful in analyses is available at <https://github.com/baillielab/ARDSMAICr>.

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