

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

Introduction

The acute respiratory distress syndrome (ARDS) is clinically defined as acute hypoxaemic respiratory failure due to non-cardiogenic pulmonary oedema¹. 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 death², it overlooks the underlying biology and masks heterogeneity³. Arguably, this has contributed to limited success in developing therapeutics⁴. In contrast, a biological definition of ARDS, based on mechanistically distinct sub-phenotypes, may provide the lever necessary for future drug discovery⁵.

Functional genomics technologies enable disease characterisation at unprecedented resolution. The emergence of coronavirus disease 2019 (COVID-19) has provided an opportunity to test their usefulness for drug discovery. A notable success has been the finding that baricitinib, a Janus kinase inhibitor, reduces mortality in patients hospitalised with COVID-19⁶. *A priori* support for baricitinib 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)^{7,8}. The availability of omics data for non-COVID ARDS is limited by comparison, although recent studies have used these techniques to examine signatures of non-COVID ARDS sub-phenotypes^{9,10}.

An unresolved challenge is how large omics data can be effectively exploited¹¹. Specifically, how can we combine data from heterogeneous sources to derive new insights or recalibrate our current 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 sources¹². 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 A¹² and SARS-CoV-2^{7,13}, and shown that it out-performs existing algorithms when combining ranked and un-ranked lists obtained from heterogeneous sources¹⁴.

Here we present a living meta-analysis by information content of ARDS host genomics studies as an open-source resource for gene prioritisation, translational genomics, and drug target discovery. A comprehensive, interactive interface is available at <https://baillielab.net/maic/ards>.

Results

Systematic review

Our search yielded 8,937 unique citations (Fig. S1). We retrieved 74 for full-text evaluation and ultimately included 40 in our meta-analysis^{9,10,15–52}. 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^{10,34,39}, and several used more than one tissue type^{19,22,33}. Excluding GWAS, 14 gene lists (40%) were derived from lung or airway samples, and 21 (60%) from blood. We could not retrieve one gene list²⁷. No whole-genome sequencing GWAS were found, and only 36% (n=8) of transcriptomic lists used next-generation sequencing. The earliest included study was published in 2004¹⁹, 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 ARDS patients. Supplementary Table 1 provides detailed study designs, demographics, and ARDS aetiology.

Meta-analysis by information content (MAIC)

First, we analysed all 43 available gene lists using MAIC. Lists were categorised by method (GWAS, transcriptomics, 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 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 ≥ 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 method⁵³ 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 ≥ 2 lists or categories and by more than one method (Figure 1).

To assess the influence of individual lists, we calculated the information content (IC), reflecting the sum of gene scores across all lists (Figure 2), and the information contribution (ICtb), measuring the sum of gene scores contributing to a gene's overall MAIC score. To obtain relative values, we divided the IC/ICtb for each list by the total. This demonstrated that only 10 lists (from 9 studies) contributed >1% of total information by either metric (Tab. S2). Notably, the RNA-seq list from Sarma et al.¹⁰ accounts for >50% of the total IC and ICtb, a function of its length. To account for this, we normalised relative IC/ICtb 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 (Figure 2).

Comparison with existing ARDS sources and COVID-19

To contextualise the results of our meta-analysis, we evaluated the overlap between the genes prioritised by MAIC and those from two established resources: BioLitMine⁵⁴, using an ARDS MeSH search, and the ARDS Database of Genes⁵⁵ (Fig. S2). BioLitMine identified 271 ARDS-associated genes, of which 142 (52.4%) were found in our analysis. Almost half of the overlapping genes (n = 63, 44.4%) were ranked within our prioritised set (Tab. S3). Of the 239 genes catalogued in the ARDS Database, 177 (74.1%) were also present in our study. However, both sources contain gene associations which lack genome-wide support.

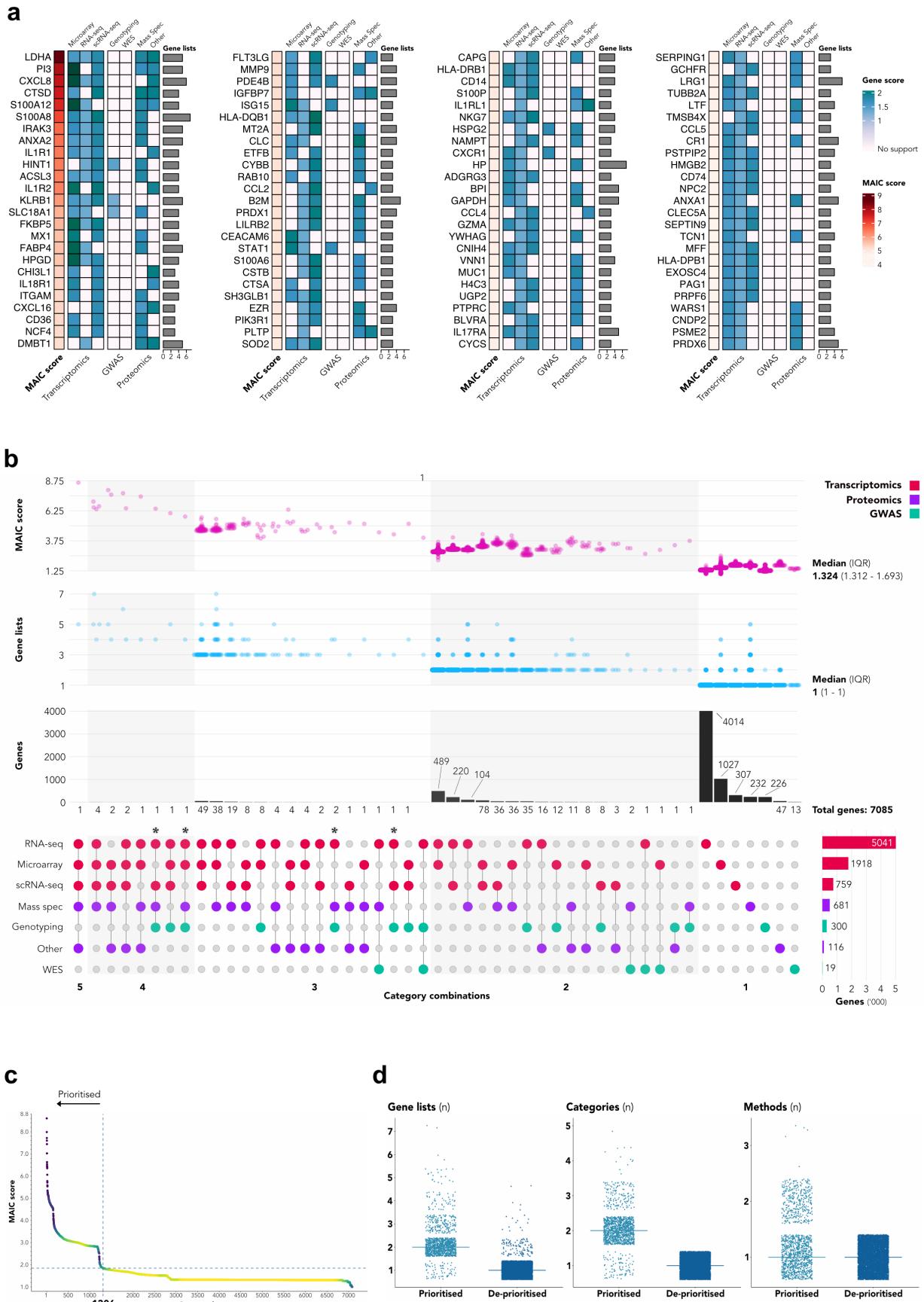


Figure 1: Meta-analysis by information content. (a) Heatmap of top 100 ranked genes showing MAIC score, highest score per category, and number of supporting lists. (b) UpSet plot of MAIC genes showing total numbers for each category combination, MAIC score distribution, and supporting lists. (b) Gene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

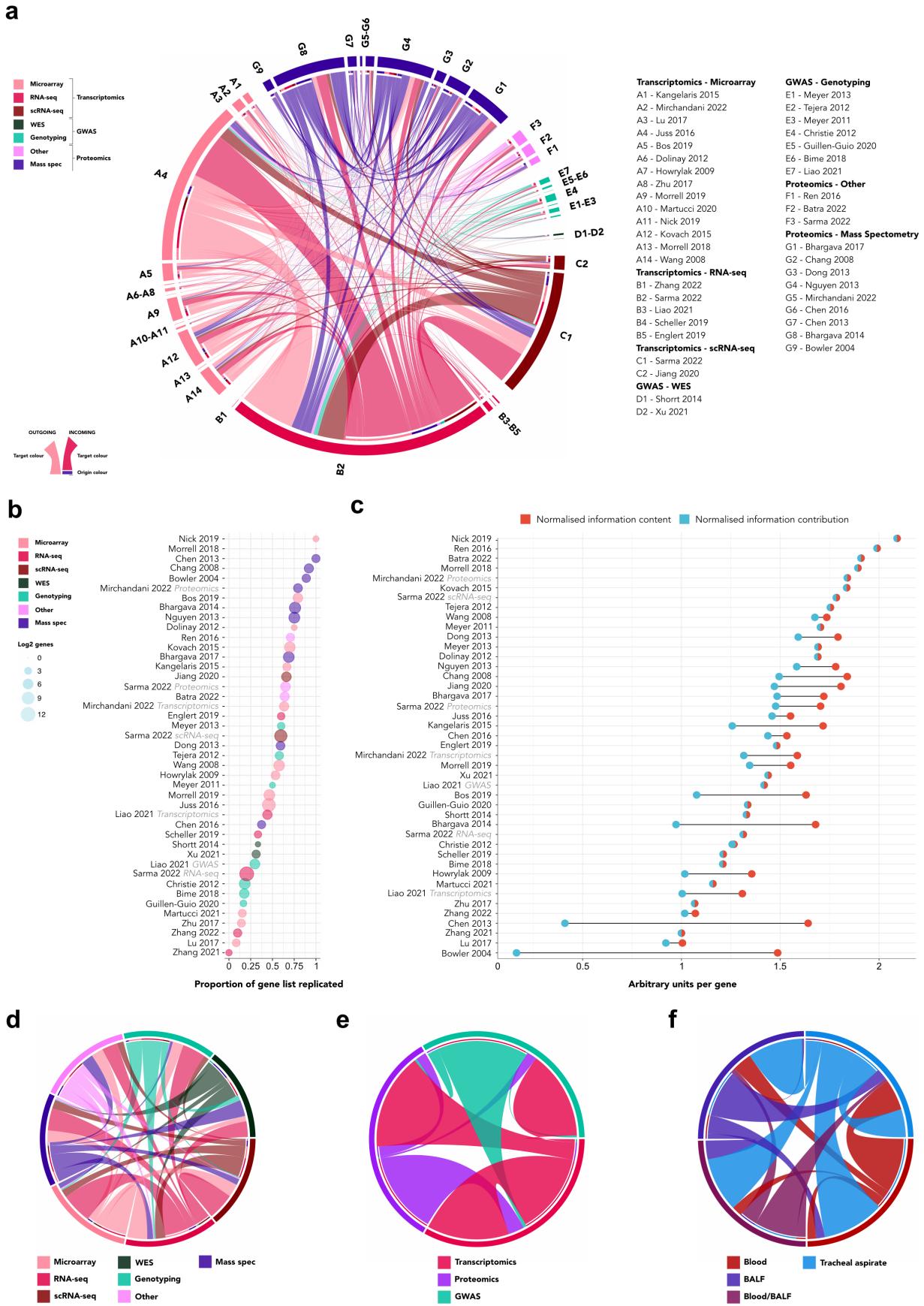


Figure 2: Attributing information in MAIC. (a) Shared information content (IC) between gene lists. Links indicate absolute IC (sum of common gene scores) between studies. (b) Proportion of replicated genes. Circle diameter is logarithm (base 2) of gene number per list. (c) IC normalized by number of genes. Overlapping circles denote equal normalized IC and contribution (IC_{tb} - sum of common gene scores contributing to MAIC), indicating all gene scores contributed to MAIC. (d) Shared IC between categories, scaled so links show fraction of total IC. (e) Shared IC between methods, scaled. (f) Shared IC between tissue types, scaled.

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

Year	Study	Focus	Definition	N ^a	Method	Technique	Tissue	Cell type
2022	Batra ¹⁵ Mirchandani ³⁹	Survival Susceptibility	Berlin	24	Proteomics Proteomics	Other Mass Spec	Blood	Monocytes
	Sarma ¹⁰	Sub-phenotype	Berlin	41	Transcriptomics Proteomics	Microarray Other	Blood	Monocytes
	Zhang ⁵¹ Liao ³⁴	Susceptibility Survival	AECC Either	11 390	Transcriptomics Transcriptomics GWAS	RNA-seq scRNA-Seq RNA-Seq	TA Blood	Immune cells Exosomes
2021	Martucci ³⁶ Xu ⁴⁹	Sub-phenotype Survival	None Berlin	11 105	Transcriptomics Transcriptomics GWAS	Microarray RNA-seq WES	Blood	PBMCs
	Zhang ⁵⁰	Susceptibility	Berlin	5	Transcriptomics	RNA-seq	Blood	Blood
2020	Guillen-Guio ²⁸ Jiang ³⁰	Susceptibility Sub-phenotype Susceptibility	Berlin Berlin	633 3	GWAS Transcriptomics	Genotyping scRNA-seq	Blood Blood	Blood
	Bos ⁹	Survival	Berlin	210	Transcriptomics	Microarray	BALF	PBMCs
2019	Englert ²⁶ Morrell ⁴¹	Susceptibility Susceptibility Survival	AECC None Either	36 6 232	Transcriptomics Transcriptomics GWAS	RNA-seq Microarray Genotyping	BALF EVs	AMs
2018	Scheller ⁴⁵ Bime ¹⁸	Susceptibility	Berlin	35	Transcriptomics	Microarray	BALF	BALF
	Morrell ⁴⁰	Susceptibility	AECC	36	Proteomics	Mass Spec	BALF	BALF
2017	Bhargava ¹⁷ Lu ³⁵	Survival Susceptibility	AECC Berlin	12 199	Transcriptomics Transcriptomics	Microarray Microarray	Blood	Blood
	Zhu ⁵²	Susceptibility						

Year	Study	Focus	Definition	N ^a	Method	Technique	Tissue	Cell type
2016	Chen ²² Juss ³¹	Severity Susceptibility	AECC Berlin	7 23	Proteomics Transcriptomics	Mass Spec Microarray	BALF/Blood	Neutrophils
	Nick ⁴² Ren ⁴⁴	Sub-phenotype Susceptibility	AECC Berlin	121 14	Transcriptomics Proteomics	Microarray Other	Blood	Neutrophils
2015	Kangellaris ³² Kovach ³³	Susceptibility Susceptibility	Berlin	29	Transcriptomics	Microarray	Blood	
2014	Bhargava ¹⁶ Shortt ⁴⁶	Progression Susceptibility	AECC AECC	18 22	Transcriptomics Proteomics	Microarray Mass Spec	BALF/Blood	AMs
2013	Chen ²¹ Dong ²⁵ Meyer ³⁸	Susceptibility Progression Susceptibility	Berlin	11	GWAS Proteomics	WES Mass Spec	BALF Blood	
8	Nguyen ⁴³ Christie ²³	Progression Susceptibility	None Berlin	14 661	Proteomics GWAS	Mass Spec Genotyping	BALF Blood	AMs
	Dolinay ²⁴ Tejera ⁴⁸	Susceptibility Susceptibility	AECC AECC	30 812	Proteomics GWAS	Mass Spec Genotyping	BALF Blood	
2011	Frenzel ²⁷ Meyer ³⁷	Susceptibility Survival	AECC AECC	35 46	Transcriptomics Proteomics	Microarray Mass Spec	BALF Blood	
2009	Howrylak ²⁹ Chang ²⁰	Susceptibility Susceptibility	AECC None	1241 20	GWAS Proteomics	Genotyping Mass Spec	BALF Blood	
2008	Wang ⁴⁷	Susceptibility	AECC	8	Transcriptomics	Microarray	Blood	
2004	Bowler ¹⁹	Susceptibility	AECC	16	Proteomics	Mass Spec	BALF/Blood	

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 historical gene symbol aliases, we matched 4 additional genes from the BioLitMine search not initially found in the ARDS MAIC set. A further 104 genes from this search were supported by a single publication. For each of the remaining 21 genes, we obtained the 100 most co-expressed genes using ARCHS4⁵⁶ (returning data for 18) and assessed the overlap of these sets with ARDS MAIC; two-thirds exhibited <50% overlap (Fig. S2). Finally, we compared the overlap between the genes ranked by ARDS MAIC and by a previous MAIC of the host response to COVID-19¹³ (Fig. S2). In total, 2,606 ARDS genes (36.8%) were also found in COVID-19, of which 143 were prioritised by both analyses (Fig. S2).

Tissue and cell-specific expression

Despite the majority of gene lists being derived from blood samples, most genes included in the meta-analysis were identified in airways samples (n=5,847, 82.5%) (Fig. S3). This was true for the prioritised set of genes, however, most of these were also identified in blood (n=818, 62.6%) (Fig. S3). For the genes uniquely identified in lists derived 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 highly-expressed (\geq 100 nTPM) (Fig. S3).

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). Expectably, neutrophil degranulation and several innate immune pathways (e.g., IL-10 signalling, interferon signalling, MHC II antigen presentation, TLR4 cascade) feature 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 observed to be over-represented. Similarly, lipid and cholesterol metabolism, as well as hyperlipidaemia, were over-represented in KEGG and WikiPathways (Fig. S4). 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. S4).

Next, we used the prioritised set of genes to create a protein-protein interaction (PPI) network. We then graph-clustered this network, identifying 48 clusters with \geq 5 members. Amongst the 10 largest clusters, we found programs associated with the proteasome, cholesterol metabolism, interferon signalling, IL-6 signalling, and the complement cascade (Fig. S5). We then sought to use the PPI network to identify hub genes using an ensemble of topological methods. This analysis suggested 51 genes central to the wider network (Figure 3). 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 3). 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 source of tension in our approach is the balance between disparity in study designs (e.g., susceptibility, sub-phenotype) and the requirement for sufficient data to make meaningful inferences. To partially resolve this, we undertook MAIC on subsets of included gene lists, stratified by study focus. There were sufficient lists to make this tractable for studies focused on susceptibility to ARDS (n=28) and studies of ARDS survival and severity (n=7) (Figure 4).

For susceptibility, MAIC ranked 2,096 genes (Figure 4). The majority of these (n=1,222, 58%) were unique to susceptibility-based lists (Figure 4). Most were identified in blood, with a small fraction found solely in airways

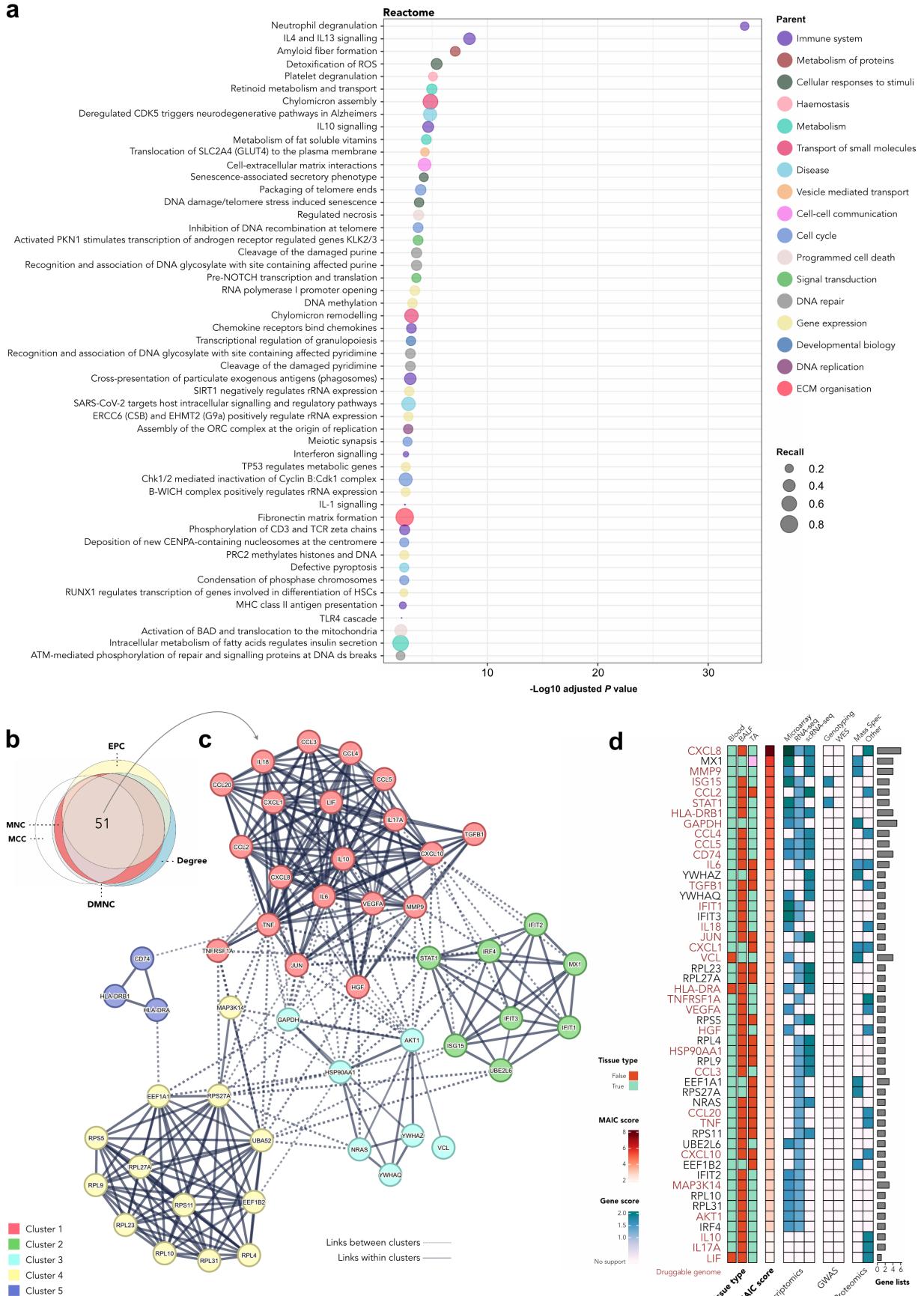


Figure 3: Functional enrichment of prioritised genes. (a) Significantly enriched Reactome terms ($P < 0.01$). Terms colored by parent class and size proportional to recall. (b) Euler diagram of the overlap of hub genes identified by five methods. MNC - Maximum Neighbourhood Component, MCC - Maximal Clique 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 druggable genome.

samples. The inflection point method prioritised the top ranked 130 genes, which were subject to functional enrichment. ORA . 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 by several pathway databases.

For survival, MAIC ranked 463 genes (Figure 4). Approximately half of these (n=238, 51%) were unique to survival-based lists. In contrast to the susceptibility analysis, most survival genes were found in airways samples. Thirty-three genes were prioritised. IL-10 and IL-18 signalling pathways were both significantly enriched in ORA.

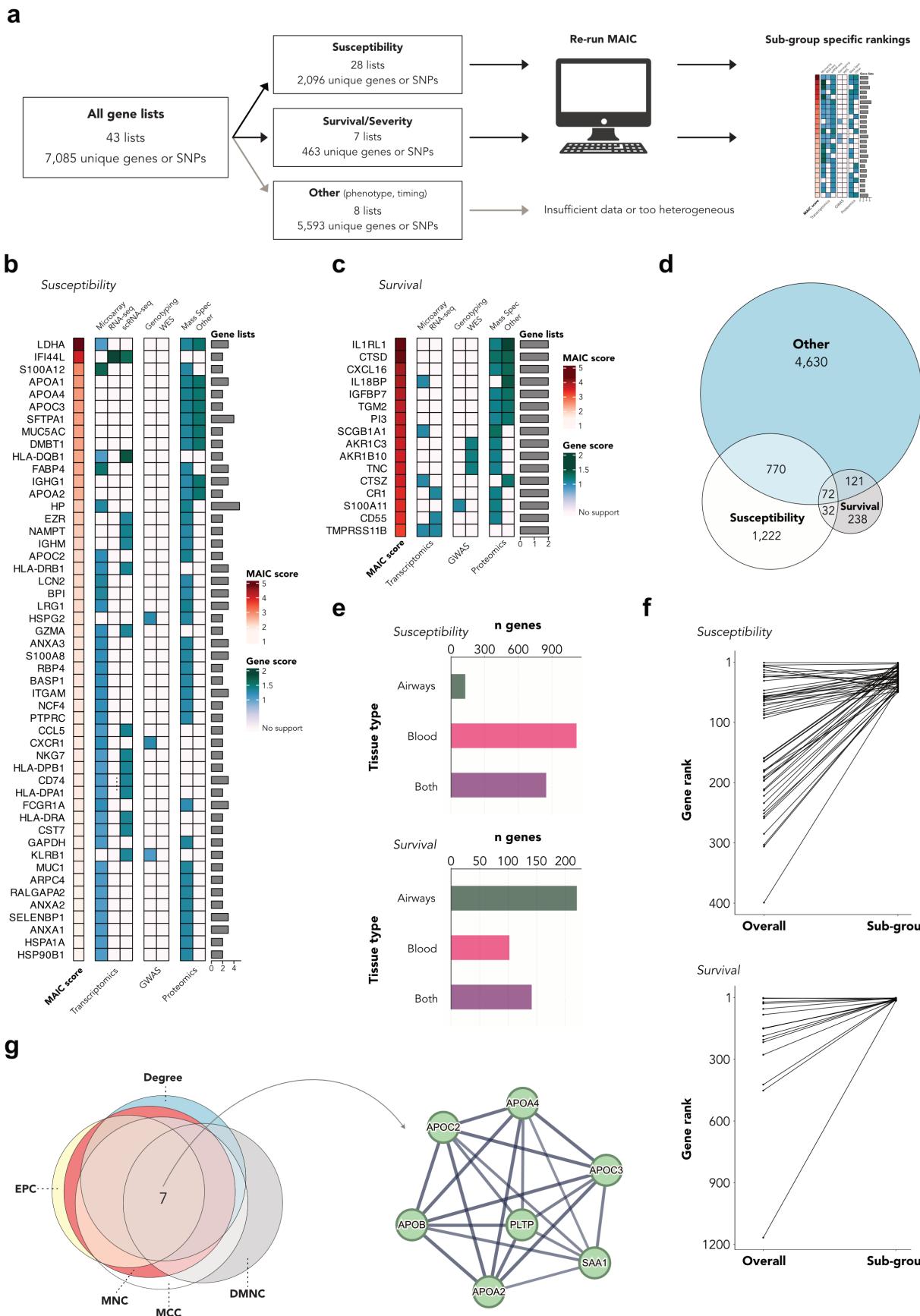


Figure 4: MAIC of sub-groups.

Discussion

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) guidelines⁵⁷.

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 Genes⁵⁵, and the NCBI Gene Expression Omnibus from inception to December 1st, 2022 without language restrictions. We also performed single-level backwards and forwards citation searches using SpiderCite⁵⁸ and hand-searched recent review articles^{59–62}.

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 Screenatron⁵⁸. 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^{7,12–14}. 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 data¹⁴.

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 susceptibility to ARDS or ARDS survival/severity.

For each MAIC iteration, we prioritised genes with sufficient evidentiary 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^{53,63} 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 BioLitMine⁵⁴ 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 Genes⁵⁵ and a prior MAIC of SARS-CoV-2 host genomics¹³.

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)⁶⁴. 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) and in the HPA RNA-seq blood dataset⁶⁵, 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 HPA⁶⁶. We conducted cell-type specific enrichment analysis using WebCSEA⁶⁷ 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:Profiler⁶⁸. The following data sources were used; Kyoto Encyclopaedia of Genes and Genomes (KEGG)⁶⁹, Reactome⁷⁰, WikiPathways⁷¹, and Gene Ontology⁷². Multiple testing was corrected for using the g:SCS algorithm⁶⁸, with a threshold of $P < 0.01$. Input lists were ordered by MAIC score were appropriate. Enrichment was also performed against the National Human Genome Research Institute GWAS Catalog⁷³ using the Enrichr web-interface⁷⁴. Protein-protein interaction enrichment

was performed using STRING v11⁷⁵. We included all possible interaction sources but specified a minimum interaction score of 0.7. We used 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 cytoHubba⁷⁶ and Cytoscape⁷⁷. 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 Database⁷⁸ to identify if they were present in the druggable genome.

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. 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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