

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

Jonathan E Millar¹, Sara Clohisey-Hendry¹, Megan McMannus¹, Marie Zechner¹, Bo Wang¹, Nick Parkinson¹, Melissa Jungnickel¹, Nureen Mohamad Zaki¹, Erola Pairo-Castineira¹, Konrad Rawlik¹, Clark D Russell², Manu Shankar-Hari², Carolyn Calfee³, Daniel F McAuley⁴, and J Kenneth Baillie¹

1. Roslin Institute, University of Edinburgh, Edinburgh, United Kingdom.
2. Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom.
3. Division of Pulmonary, Critical Care, Allergy & Sleep Medicine, Department of Medicine, University of California San Francisco, San Francisco, USA.
4. Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom.

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). Of these, we retrieved 74 studies for full-text evaluation and ultimately included 40 in our meta-analysis^{9,10,15–52}. These 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 lists (40%) were from lung or airway samples, and 21 (60%) from blood. We could not retrieve one gene list²⁷, and no whole-genome sequencing GWAS were found. Only 36% (n=8) of transcriptomic lists used next-generation sequencing. The earliest study was published in 2004¹⁹, while almost half (n=19, 47.5%) were published in the last 5 years.

Most studies aimed to identify genes/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 the 43 available gene lists using MAIC. Lists were categorized 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 a maximum of 5 categories (Figure 1). Similarly, few genes (n=362, 5.1%) were identified by > 1 method, with only *AKR1B10*, *HINT1*, *HSPG2*, *S100A11*, and *SLC18A1* present in transcriptomic, proteomic, and GWAS based lists. To prioritise genes, 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 > 1 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 showed 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, this provides an alternative perspective, with several proteomic lists ranking highly (Figure 2).

Comparison with existing ARDS sources and COVID-19

To contextualise the results of our meta-analysis, we evaluated the degree of 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 in our analysis. Almost half of the overlapping genes (n = 63, 44.4%) were ranked within our prioritized 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 some unsupported gene associations.

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	Survival	Berlin	24	Proteomics	Other	Blood	
	Mirchandani ³⁹	Susceptibility	Berlin	22	Proteomics	Mass Spec	Blood	Monocytes
Sarma ¹⁰	Sub-phenotype	Berlin	41	Transcriptomics	Microarray	Blood	Monocytes	Monocytes
Zhang ⁵¹	AECC	Transcriptomics	RNA-seq	TA	scRNA-Seq	TA	Immune cells	
Liao ³⁴	Either	GWAS	RNA-Seq	Blood	Blood	Blood	Exosomes	
Martucci ³⁶	None	Transcriptomics	Microarray	Blood	Blood	Blood	PBMCS	
Xu ⁴⁹	Survival	GWAS	WES	Blood	Blood	Blood	Blood	
Zhang ⁵⁰	AECC	Transcriptomics	RNA-seq	Blood	Blood	Blood	PBMCS	
Guillen-Guio ²⁸	AECC	Transcriptomics	Microarray	Blood	Blood	Blood	Blood	
Jiang ³⁰	AECC	Transcriptomics	RNA-seq	Blood	Blood	Blood	Blood	
Bos ⁹	AECC	Transcriptomics	Microarray	Blood	Blood	Blood	Blood	
Englert ²⁶	AECC	Transcriptomics	RNA-seq	Blood	Blood	Blood	Blood	
Morrell ⁴¹	AECC	Transcriptomics	Microarray	BALF	BALF	AMs	EVs	
Scheller ⁴⁵	AECC	Transcriptomics	RNA-seq	Blood	Blood	Blood	Blood	
Bime ¹⁸	AECC	Transcriptomics	Microarray	BALF	BALF	BALF	BALF	
Morrell ⁴⁰	AECC	Transcriptomics	Microarray	Blood	Blood	Blood	Blood	
Bhargava ¹⁷	AECC	Transcriptomics	Microarray	Blood	Blood	Blood	Blood	
Lu ³⁵	AECC	Transcriptomics	Microarray	Blood	Blood	Blood	Blood	
Zhu ⁵²	AECC	Transcriptomics	Microarray	Blood	Blood	Blood	Blood	

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	
6	Nguyen ⁴³ Christie ²³	Progression Susceptibility	None Berlin	14 661	Proteomics GWAS	Mass Spec Genotyping	BALF Blood	AMs
2012	Dolinay ²⁴ Tejera ⁴⁸	Susceptibility Susceptibility	AECC AECC	30 812	Proteomics GWAS	Mass Spec Genotyping	BALF Blood	
2011	Frenzel ²⁷ Meyer ³⁷	Susceptibility Survival Susceptibility	AECC AECC AECC	35 46 1241	Transcriptomics Proteomics GWAS	Microarray Mass Spec Genotyping	BALF Blood	
2009	Howrylak ²⁹ Chang ²⁰	Susceptibility Susceptibility	AECC None	13 20	Transcriptomics Proteomics	Microarray 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.

For the BioLitMine search, we identified 4 such genes not initially found in the ARDS MAIC set after correcting historical gene symbol aliases. A further 104 were supported by a single publication. For the remaining 21, we obtained their 100 most co-expressed genes using ARCHS4⁵⁶ (returning data for 18) and assessed the overlap with ARDS MAIC (Fig. S2). Two-thirds exhibited <50% overlap. Finally, we compared the overlap between the genes ranked by MAIC for ARDS 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 prioritized by both analyses (Fig. S2).

Tissue and cell-specific expression

Despite the dominance of blood sampling, the majority of 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, here most were also identified in blood (n=818, 62.6%) (Fig. S3). For the genes solely found in blood sampling lists (n=1,238), almost three-quarters are known to be expressed in the lung using scRNA-seq data (≥ 5 normalised transcripts per million (nTPM)), with a quarter highly-expressed (≥ 100 nTPM) (Fig S2).

Functional enrichment

In-silico perturbation

Sub-groups

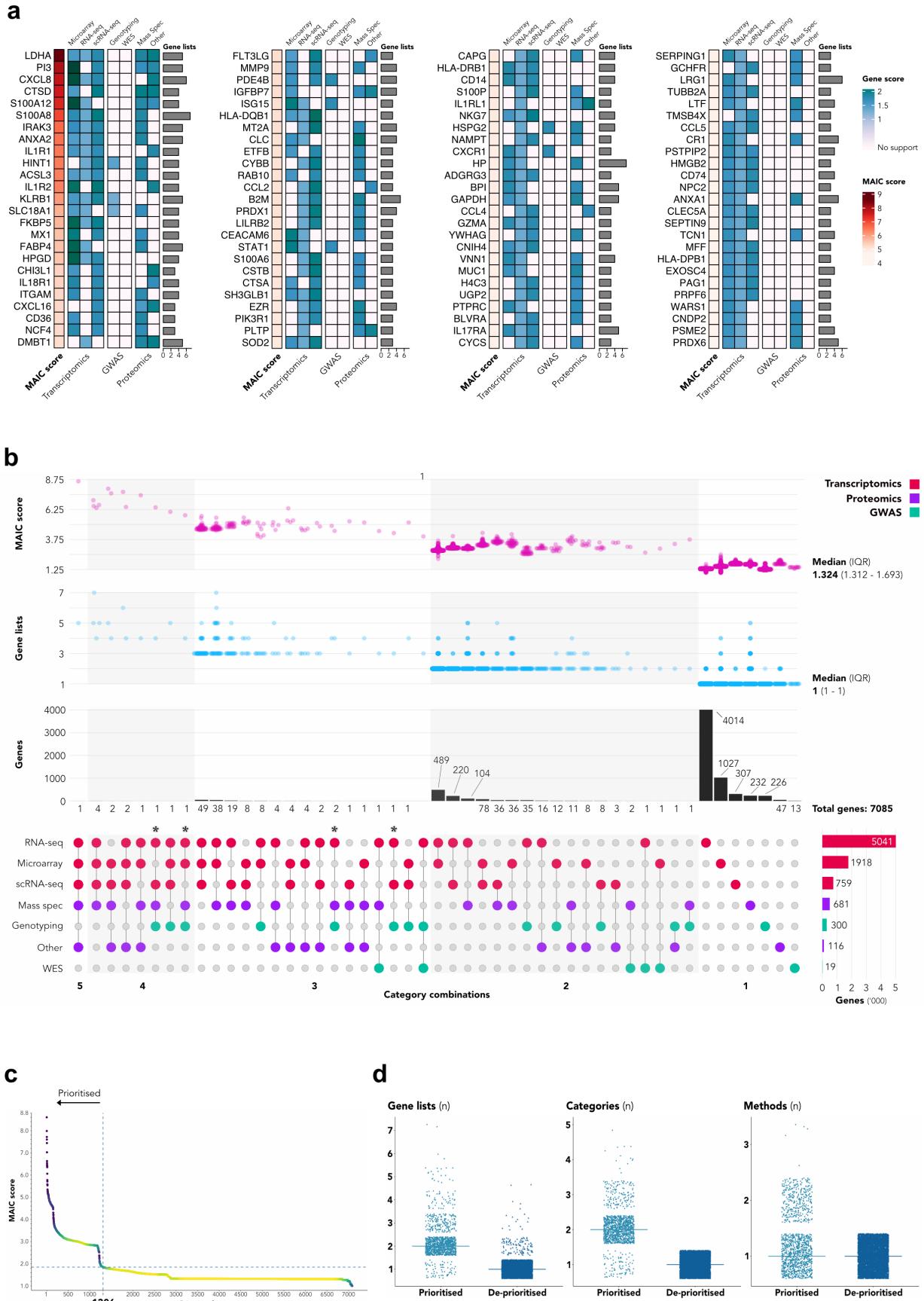


Figure 1: Meta-analysis by information content. (a) Heatmap of top 100 ranked genes showing MAIC score, highest score per category, and number of supporting lists. (b) UpSet plot of MAIC genes showing total numbers for each category combination, MAIC score distribution, and supporting lists. (b) Gene 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 de-prioritized sets.

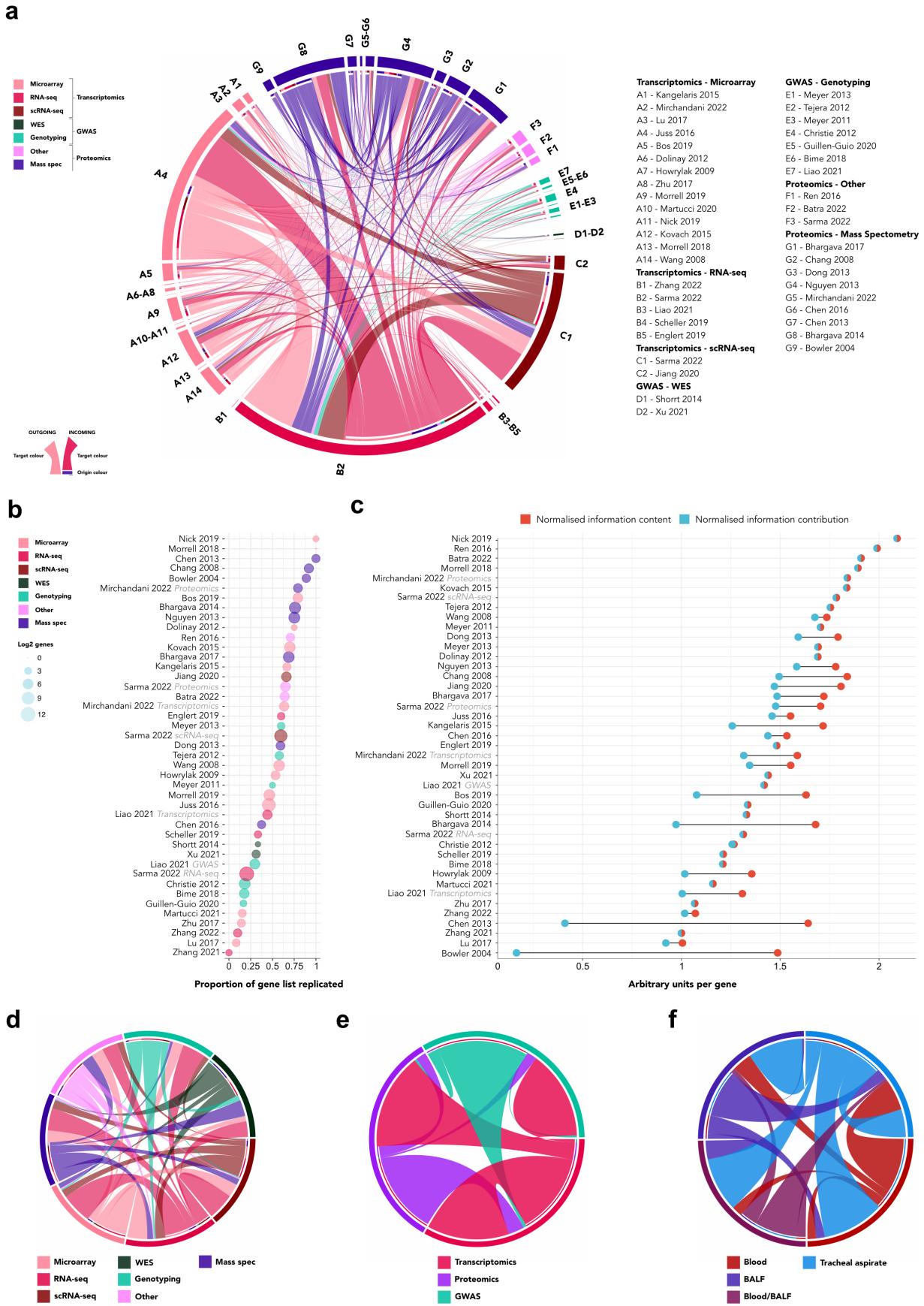


Figure 2: Attributing information in MAIC. (a) Shared information content (IC) between gene lists. Links indicate absolute IC (sum of common gene scores) between studies. (b) Proportion of replicated genes. Circle diameter is logarithm (base 2) of gene number per list. (c) IC normalized by number of 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.

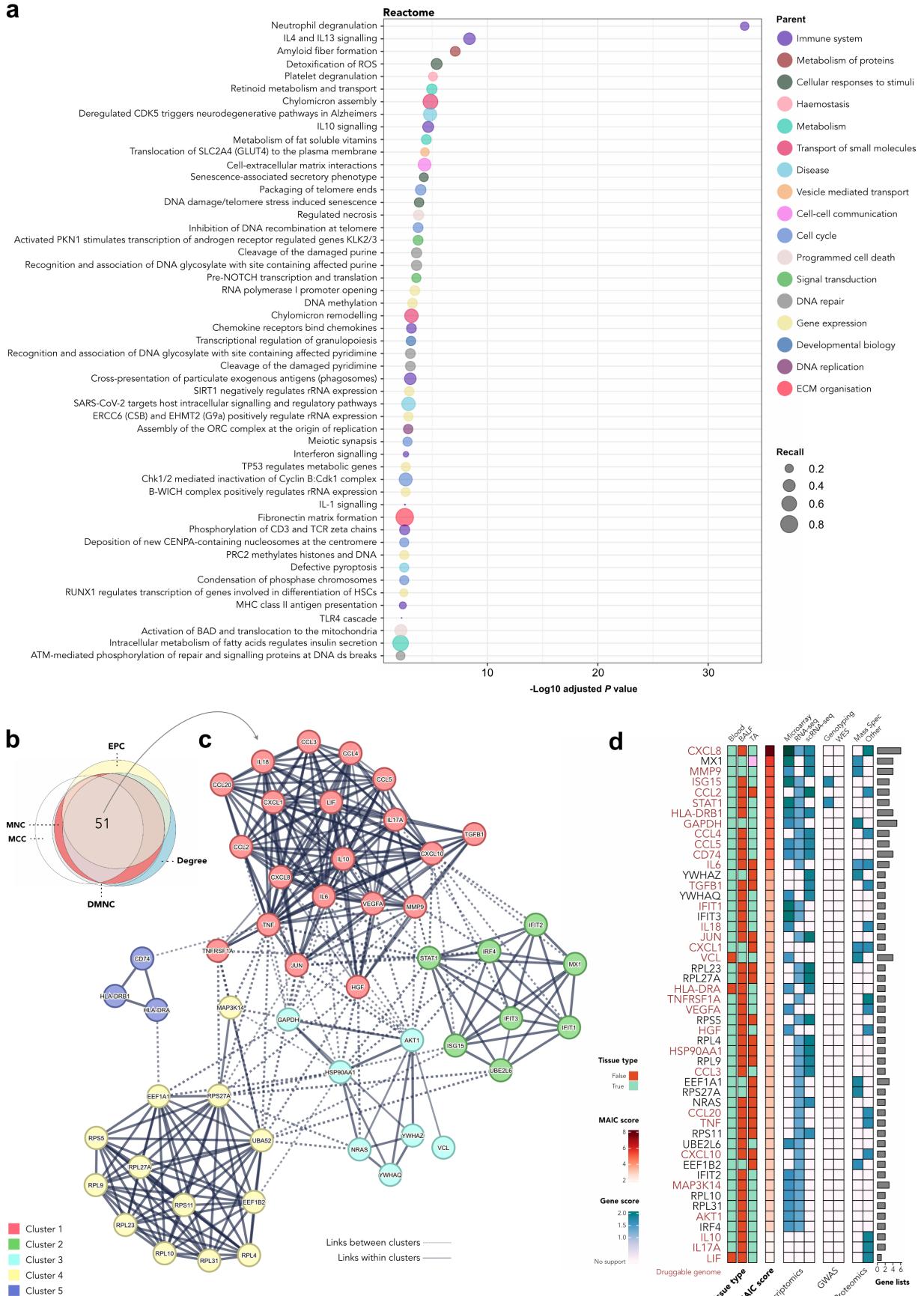


Figure 3: Functional enrichment of prioritised genes. (a) Significantly enriched Reactome terms ($P < 0.01$). Terms colored by parent class and size proportional to recall. (b) Euler diagram of the overlap of hub genes identified by five methods. MNC - Maximum Neighbourhood Component, MCC - Maximal Clique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

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).

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 prioritised genes were retrieved from the Human Protein Atlas (HPA, version 21.0)⁶⁴. We investigated transcript expression in a consensus RNA-seq dataset of 55 tissues, combining data from GTEx^{65,66} (RSEMv1.3.0 v8) and the HPA⁶⁷, and in the HPA RNA-seq blood dataset⁶⁸, containing expression levels in 18 immune cell types and total peripheral blood mononuclear cells. We calculated tissue enrichment scores, using the R package *TissueEnrich*⁶⁹, for genes in comparison to all genes present in GTEx^{65,66} (RSEMv1.3.0 v8) and corrected for multiple comparisons using the Benjamini-Hochberg method⁶⁹. To investigate protein expression, we retrieved tissue-specific expression scores from the HPA⁶⁷.

Functional enrichment

We performed functional enrichment of prioritised genes against the universe of all annotated genes using g:Profiler⁷⁰. The following data sources were used; Gene Ontology (GO) Biological Process⁷¹, Kyoto Encyclopaedia of Genes and Genomes (KEGG)⁷², Reactome⁷³, and WikiPathways⁷⁴. Multiple testing was corrected for using the g:SCS algorithm⁷⁰, with a threshold of $P < 0.01$. The input list was ordered by MAIC score. To address pathway redundancy, we used the output of the functional enrichment analysis as an input to Enrichment Map⁷⁵. We created networks based on a Jaccard similarity cutoff of 0.25 for each of; GO:Molecular Function, GO:Cellular Component, GO:Biological

Process, Reactome, and Wiki Pathways. We then repeated this for all combined. Protein-protein interaction enrichment was performed using STRING v11⁷⁶. We included all possible interaction sources but specified a minimum interaction score of 0.9. 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 with the Reactome pathway with the smallest False Discovery Rate.

In-silico perturbation

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). All code required to reproduce the analyses is available at [Github link].

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