

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

Supplementary Material

Supplementary Methods

Search strategy

Inclusion criteria

Glossary

Search Strategy

We used the following strategy to search MEDLINE and a direct translation to search Embase.

1 exp Respiratory Distress Syndrome, Adult/

2 “acute lung injury*”.ti,ab,kf,kw

3 1 OR 2

4 “gene*”.mp

5 “genome*”.mp

6 “transcript*”.mp

7 “protein*”.mp

8 4 OR 5 OR 6 OR 7

9 3 AND 8

10 (“COVID-19*” OR “COVID19*” OR “COVID-2019*” OR “covid”).ti,ab,kf,kw

11 (“SARS-CoV-2*” OR “SARSCov-2*” OR “SARSCoV2*” OR “SARS-CoV2”).ti,sh,kf,kw

12 (“2019-nCoV*” OR “2019nCoV*” OR “19- nCoV*” OR “19nCoV*” OR “nCoV2019*” OR “nCoV-2019*” OR “nCoV19*” OR “nCoV- 19*”).ti,ab,kf,kw

13 10 OR 11 OR 12

14 9 NOT 13

15 Letter.pt OR Conference Abstract.pt OR Conference Paper.pt OR Conference Review.pt OR Editorial.pt OR Erratum.pt OR Review.pt OR Note.pt OR Tombstone.pt

16 14 NOT 15

17 exp *adolescence/ or exp *adolescent/ or exp *child/ or exp *childhood disease/ or exp *infant disease/ or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child or child* or child*3 or children* or girl? or infan* or juvenil* or juvenile* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,kw

18 16 NOT 17

19 ((exp animal/ or nonhuman/) NOT exp human/)

20 18 NOT 19

21 limit 20 to yr=“1967-Current”

Inclusion criteria

Inclusion:

- Human studies: *in-vivo* or *in-vitro*
- Adults (age \geq 18 years)
- Acute Respiratory Distress Syndrome (ARDS)
 - by any contemporaneous definition
- Accepted methodologies:
 - CRISPR screen
 - RNAi screen
 - Protein-protein interaction study
 - Host proteins incorporated into virion or virus-like particle
 - Genome wide association study
 - Transcriptomic study
 - Proteomic study

Exclusion:

- Children (age < 18 years)
- Animal studies
- Meta-analyses, *in-silico* analyses, or re-analysis of previously published data
- Excluded methodologies:
 - *In-vitro* human studies simulating ARDS
 - Candidate *in-vivo* or *in-vitro* transcriptomic or proteomic studies (defined as those investigating < 50 genes)
 - Candidate gene association studies
 - Studies including fewer than 5 individuals in either the control or ARDS arm

Glossary

MAIC score - the score assigned by MAIC to a given gene considering all lists.

Gene score - the score assigned by MAIC to a given gene in a given list.

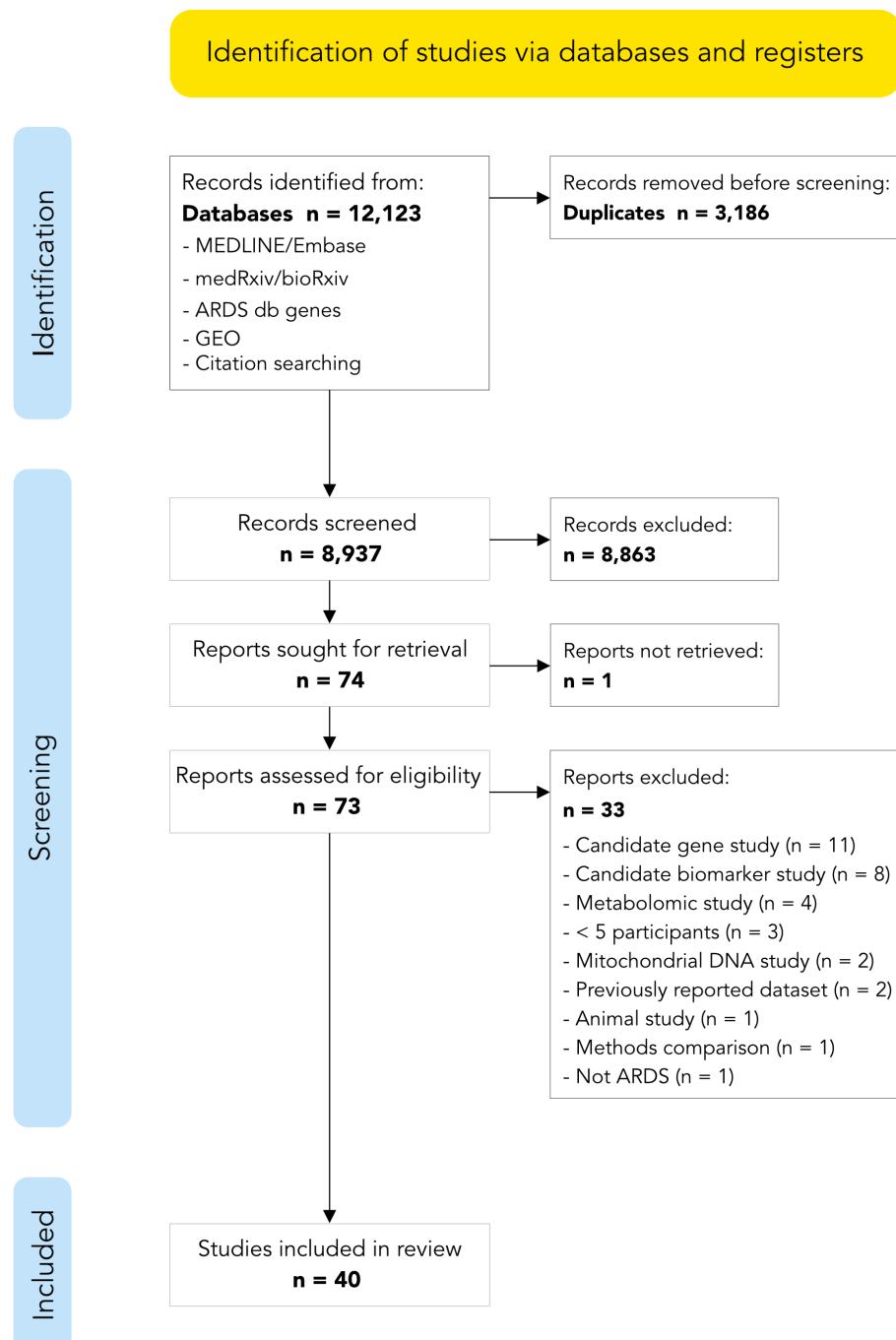
Total MAIC score - the sum of all scores assigned by MAIC to a genes in a given list.

Contributing total MAIC score - the sum of all scores assigned by MAIC to a genes in a given list where that score contributes to the MAIC score for that gene (i.e., excluding those gene scores that are not used because a gene score from another list in the same category is greater).

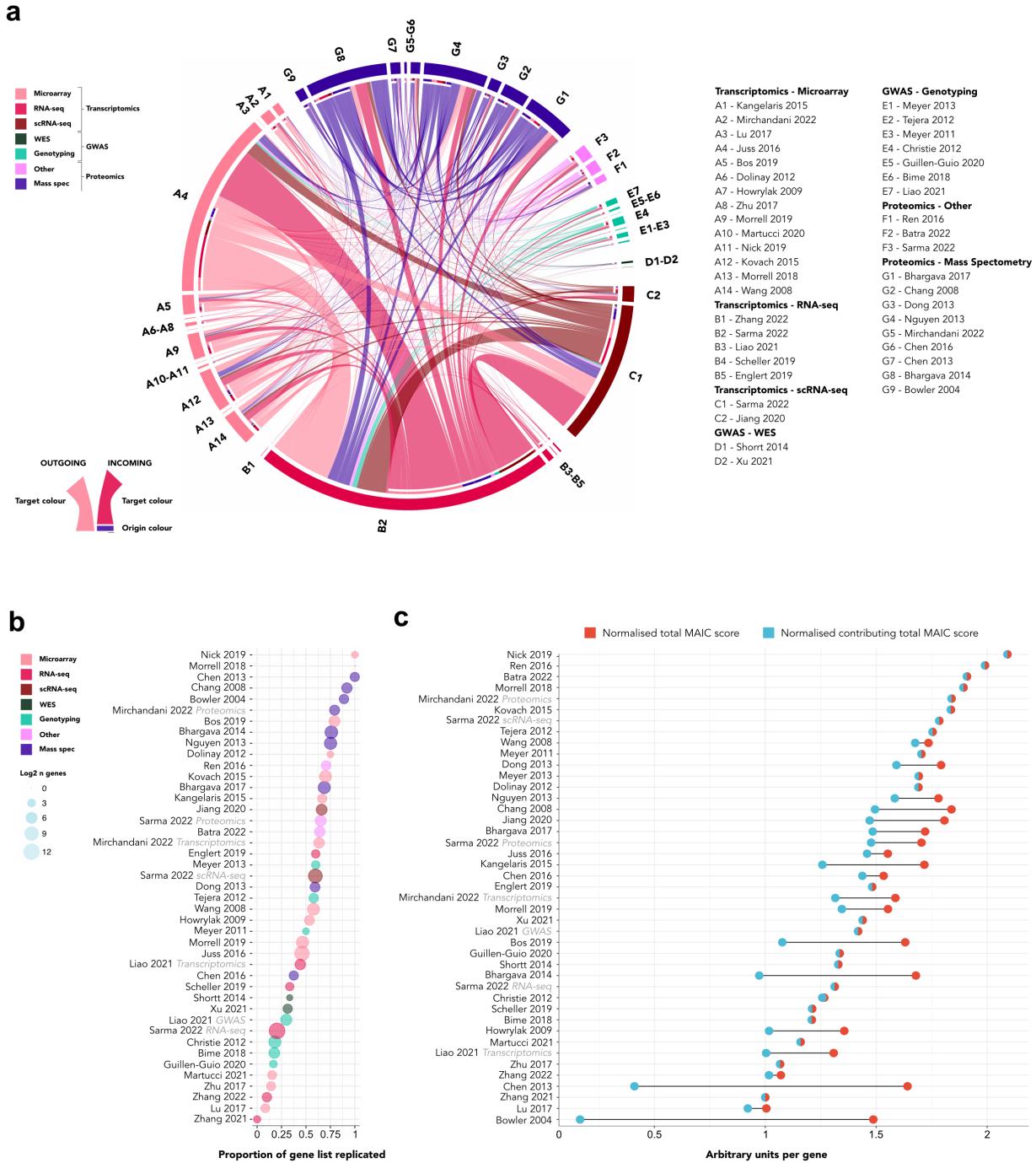
Supplementary Results

Supplementary Figures 1-7

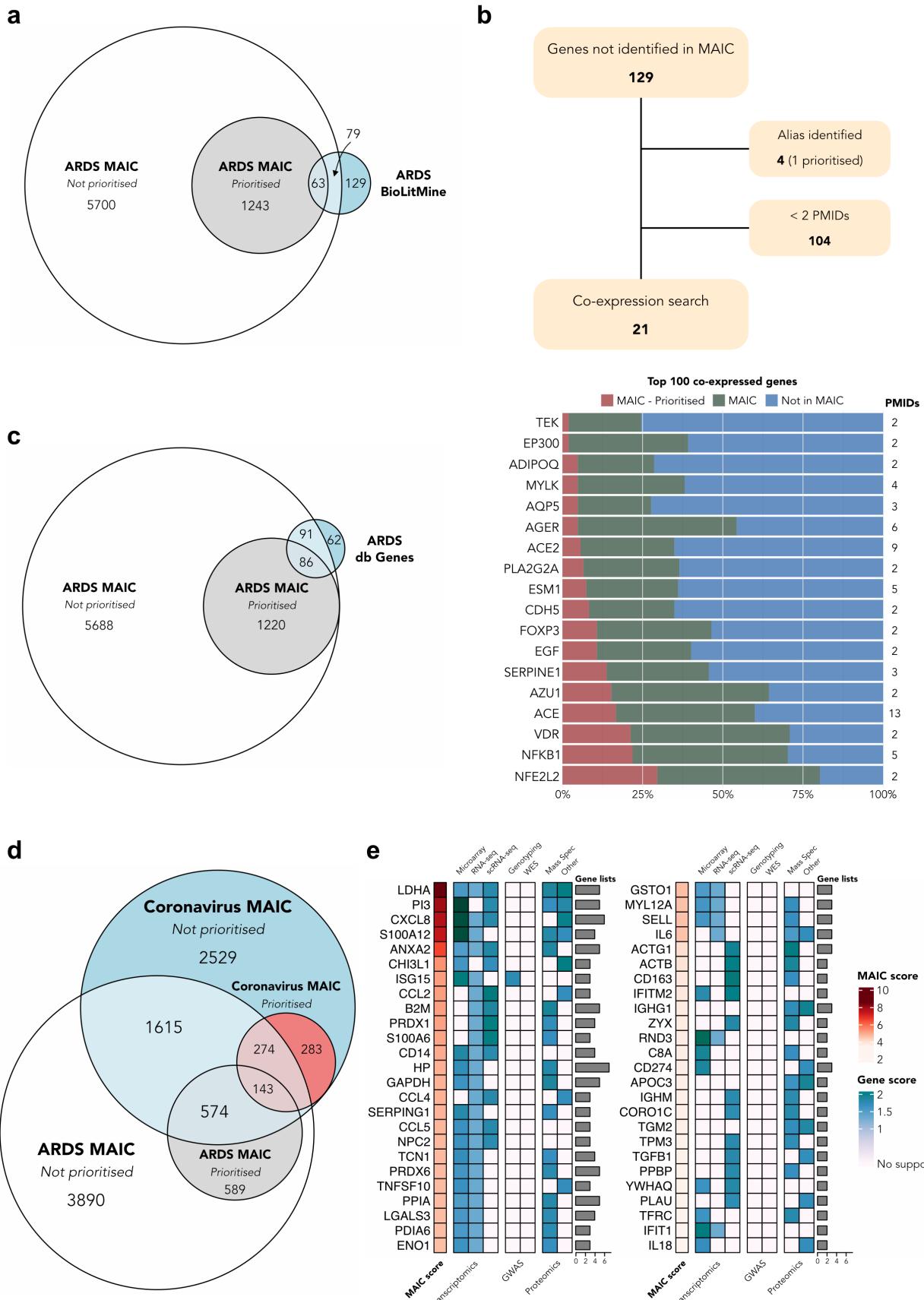
Supplementary Tables 1-4



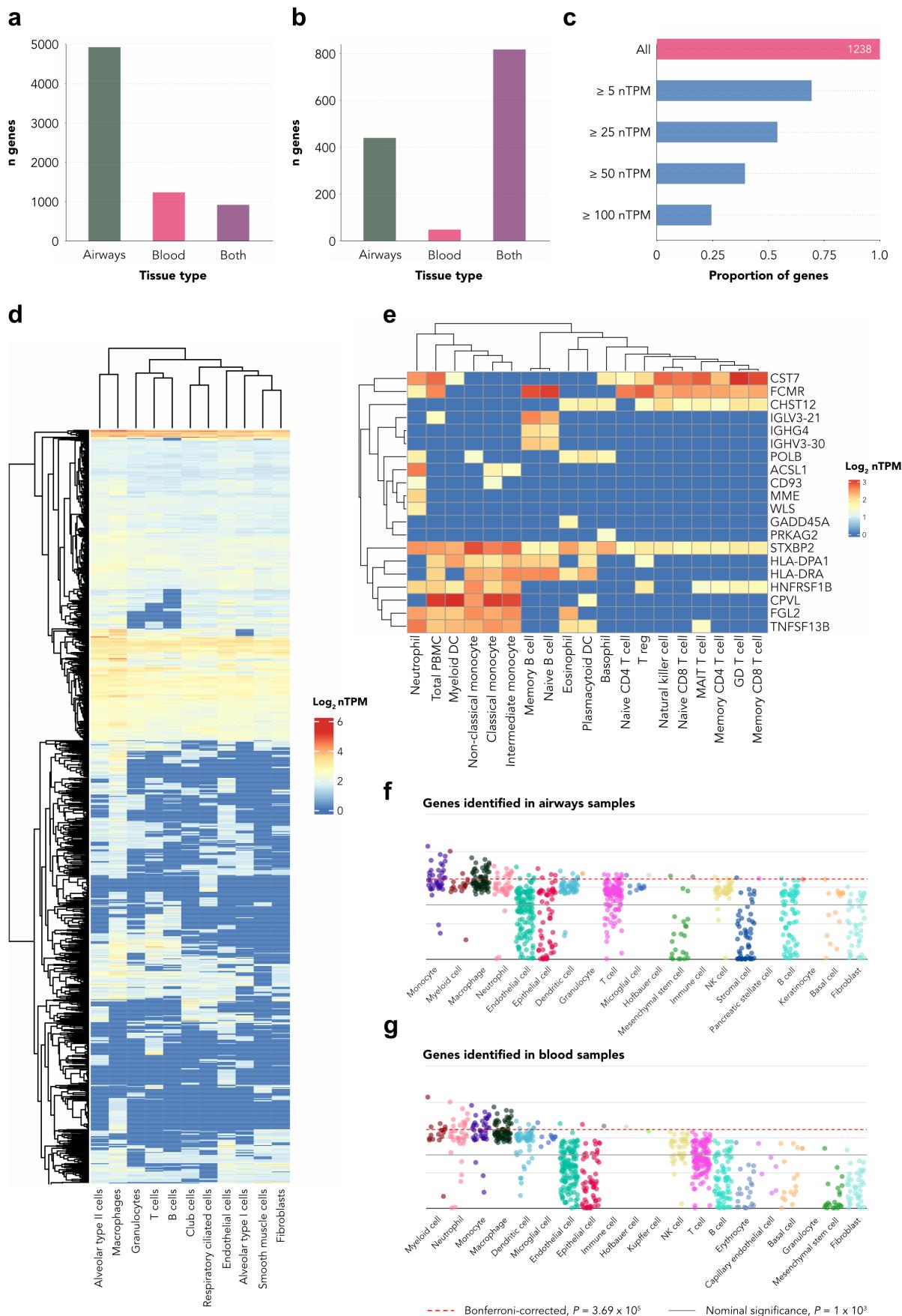
Supplementary-Figure 1: **Systematic review inclusion diagram.** Abbreviations: db - data base; GEO - NCBI Gene Expression Omnibus.



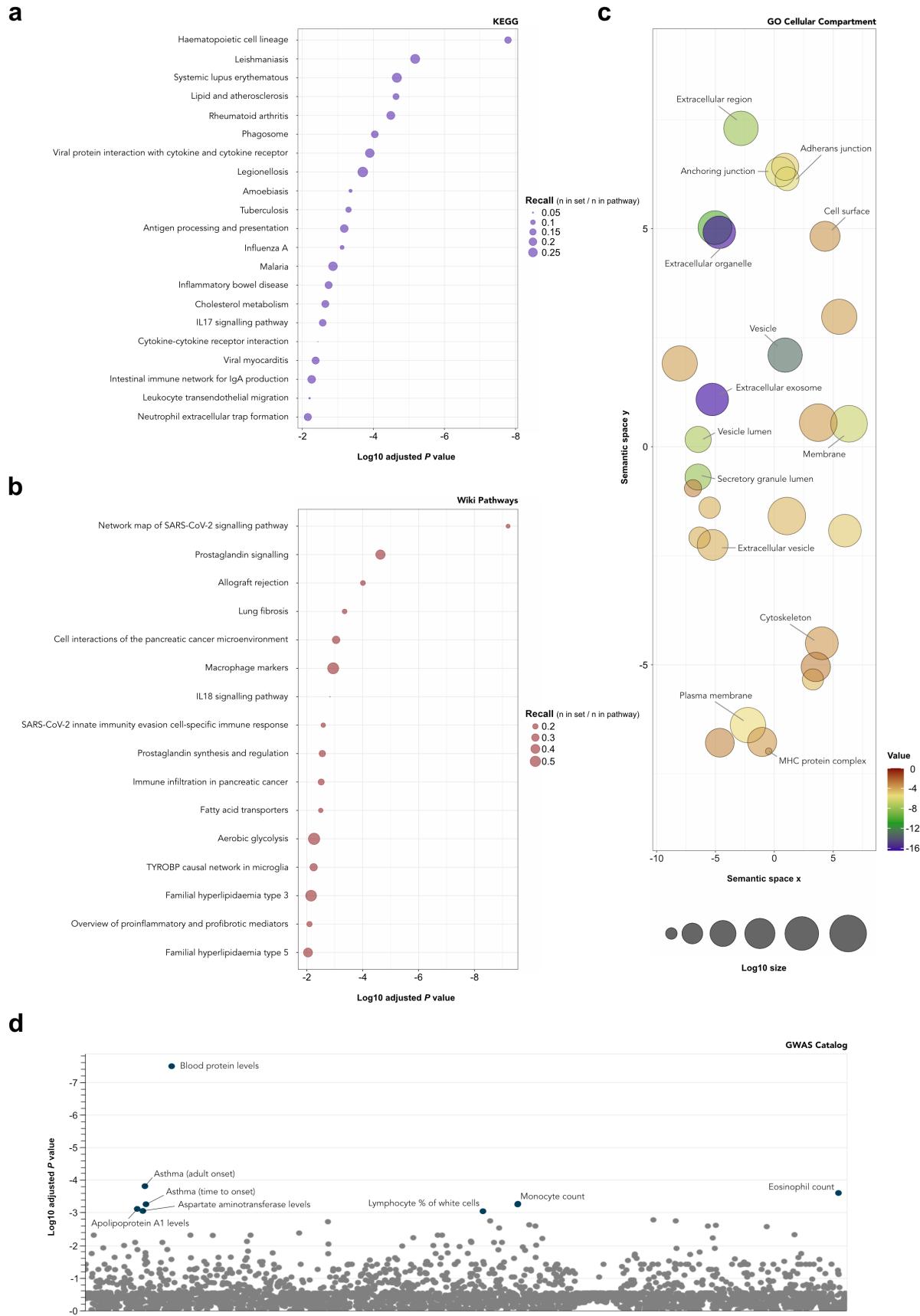
Supplementary-Figure 2: Attributing information in MAIC. (a) Shared information between gene lists. Links indicate shared summed common gene scores between studies. (b) Proportion of replicated genes. Circle diameter is equal to logarithm (base 2) of gene number per list. (c) Total MAIC score (totMS) normalised by number of genes. Overlapping circles denote equal normalised totMS and contribution (ctotMS - sum of common gene scores contributing to MAIC score for a gene), indicating all gene scores contributed to MAIC.



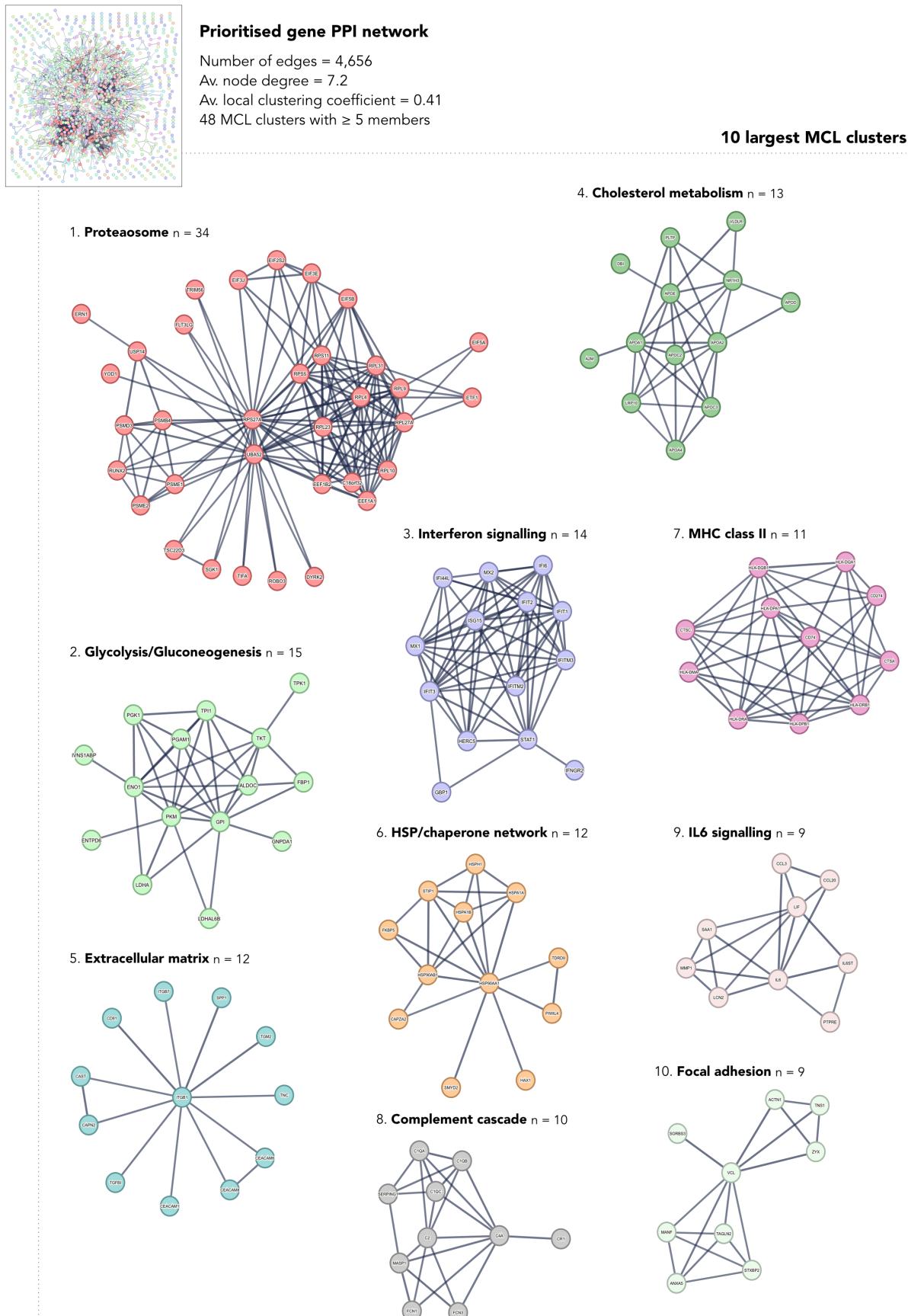
Supplementary-Figure 3: Overlap between ARDS MAIC and ARDS-associated genes and ARDS MAIC and coronavirus MAIC. (a) Euler diagram of gene overlap between ARDS MAIC and a BioLitMine search using the ARDS MeSH term. (b) Schematic overview of a co-expression search for genes identified in the BioLitMine search but not present in ARDS MAIC and a stacked bar plot of the proportion of the 100 most co-expressed genes of this group and ARDS MAIC. (c) Euler diagram of gene overlap between ARDS MAIC and the ARDS Database of Genes. (d) Euler diagram of gene overlap between ARDS MAIC and a MAIC of COVID-19 host-response studies. (e) Heatmap of the 50 top ranked ARDS MAIC genes also prioritised by the coronavirus MAIC, displaying the ARDS MAIC score for each gene, highest gene score in each category, and the number of supporting gene lists.



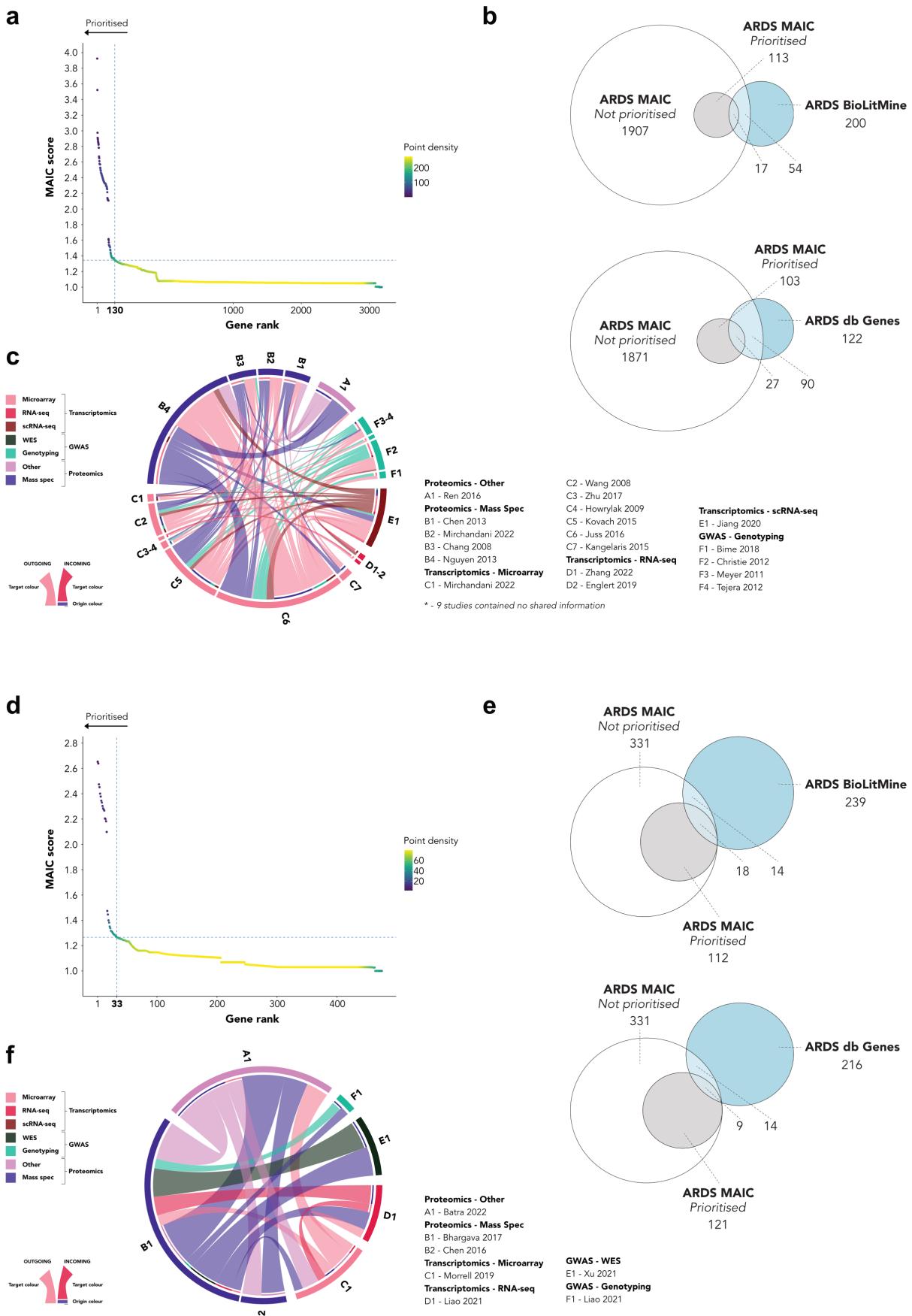
Supplementary-Figure 4: Tissue and cell-specific expression. (a) Bar plot of the tissue type in which genes are identified - all genes ($n=7,085$). (b) Bar plot of the tissue type in which genes are identified - prioritised genes ($n=1,306$). (c) Bar plot of the proportion of genes identified solely in blood meeting mRNA expression thresholds in bulk lung tissue. nTPM - normalised transcripts per million. (d) Heatmap of mRNA expression in lung cell-types for genes identified in studies based on airways sampling. (e) Heatmap of mRNA expression in blood cell-types for genes identified solely in studies based on blood sampling. (f) Manhattan plot of the top 20 cell types overenriched for expression of genes identified by studies based on airways sampling. (g) Manhattan plot of the top 20 cell types overenriched for expression of genes identified by studies based on blood sampling.



Supplementary-Figure 5: Functional enrichment. (a) Significantly enriched KEGG terms ($P < 0.01$) for prioritised genes. Terms size proportional to recall. (b) Significantly enriched WikiPathways terms ($P < 0.01$) for prioritised genes. Terms size proportional to recall. (c) Scatter plot of the semantic similarity between significantly enriched GO cellular component terms for prioritised genes (d) Manhattan plot of the overenrichment of prioritised genes against the GWAS catalog.



Supplementary-Figure 6: **PPI clusters**. A protein-protein interaction network of prioritised genes and the 10 largest graph-based clusters. Functional annotation by hand based on a concensus of enriched Reactome, KEGG, WikiPathways, and GO Biological Process terms.



Supplementary-Figure 7: Details of MAIC on sub-groups. (a) Gene prioritisation for the ARDS MAIC ARDS vs. non-ARDS controls sub-group using the Unit Invariant Knee method. Intersection of lines identifies elbow point of best-fit curve. 130 genes in upper left quadrant were prioritised. (b) Euler diagrams of gene overlap between the ARDS vs. non-ARDS controls sub-group and a BioLitMine search using the ARDS MeSH term and the ARDS Database of Genes. (c) Shared information between ARDS vs. non-ARDS controls gene lists. Links indicate shared summed common gene scores between studies. (d) Gene prioritisation for the ARDS MAIC survival sub-group using the Unit Invariant Knee method. Intersection of lines identifies elbow point of best-fit curve. 33 genes in upper left quadrant were prioritised. (e) Euler diagrams of gene overlap between the survival sub-group and a BioLitMine search using the ARDS MeSH term and the ARDS Database of Genes. (f) Shared information between survival gene lists. Links indicate shared summed common gene scores between studies.

Supplementary Table 1. Gene list information content and contribution.

| Study | Method | Category | N genes | totMS (% sum) | ctotMS (% sum) |
|----------------------------|-----------------|------------|---------|---------------|----------------|
| Sarma ¹ | Transcriptomics | RNA-seq | 4954 | 50.8 | 53.1 |
| Juss ² | Transcriptomics | Microarray | 1318 | 16 | 15.7 |
| Sarma ¹ | Transcriptomics | scRNA-seq | 706 | 9.8 | 10.3 |
| Nguyen ³ | Proteomics | Mass Spec | 161 | 2.2 | 2.1 |
| Wang ⁴ | Transcriptomics | Microarray | 137 | 1.9 | 1.9 |
| Bhargava ⁵ | Proteomics | Mass Spec | 233 | 3.1 | 1.9 |
| Kovach ⁶ | Transcriptomics | Microarray | 123 | 1.8 | 1.9 |
| Bhargava ⁷ | Proteomics | Mass Spec | 144 | 1.9 | 1.8 |
| Morrell ⁸ | Transcriptomics | Microarray | 155 | 1.9 | 1.7 |
| Christie ⁹ | GWAS | Genotyping | 143 | 1.4 | 1.5 |
| Liao ¹⁰ | GWAS | Genotyping | 67 | 0.7 | 0.8 |
| Sarma ¹ | Proteomics | Other | 60 | 0.8 | 0.7 |
| Jiang ¹¹ | Transcriptomics | scRNA-seq | 53 | 0.7 | 0.6 |
| Batra ¹² | Proteomics | Other | 39 | 0.6 | 0.6 |
| Bime ¹³ | GWAS | Genotyping | 51 | 0.5 | 0.5 |
| Bos ¹⁴ | Transcriptomics | Microarray | 53 | 0.7 | 0.5 |
| Chang ¹⁵ | Proteomics | Mass Spec | 37 | 0.5 | 0.5 |
| Mirchandani ¹⁶ | Transcriptomics | Microarray | 41 | 0.5 | 0.4 |
| Mirchandani ¹⁶ | Proteomics | Mass Spec | 29 | 0.4 | 0.4 |
| Liao ¹⁰ | Transcriptomics | RNA-seq | 43 | 0.4 | 0.4 |
| Dong ¹⁷ | Proteomics | Mass Spec | 27 | 0.4 | 0.4 |
| Ren ¹⁸ | Proteomics | Other | 17 | 0.3 | 0.3 |
| Tejera ¹⁹ | GWAS | Genotyping | 19 | 0.3 | 0.3 |
| Howrylak ²⁰ | Transcriptomics | Microarray | 28 | 0.3 | 0.2 |
| Xu ²¹ | GWAS | WES | 16 | 0.2 | 0.2 |
| Chen ²² | Proteomics | Mass Spec | 16 | 0.2 | 0.2 |
| Zhang ²³ | Transcriptomics | RNA-seq | 20 | 0.2 | 0.2 |
| Kangelaris ²⁴ | Transcriptomics | Microarray | 15 | 0.2 | 0.2 |
| Meyer ²⁵ | GWAS | Genotyping | 10 | 0.1 | 0.1 |
| Martucci ²⁶ | Transcriptomics | Microarray | 13 | 0.1 | 0.1 |
| Zhu ²⁷ | Transcriptomics | Microarray | 14 | 0.1 | 0.1 |
| Englert ²⁸ | Transcriptomics | RNA-seq | 10 | 0.1 | 0.1 |
| Lu ²⁹ | Transcriptomics | Microarray | 12 | < 0.1 | < 0.1 |
| Scheller ³⁰ | Transcriptomics | RNA-seq | 9 | < 0.1 | < 0.1 |
| Nick ³¹ | Transcriptomics | Microarray | 4 | < 0.1 | < 0.1 |
| Guillen-Guio ³² | GWAS | Genotyping | 6 | < 0.1 | < 0.1 |
| Meyer ³³ | GWAS | Genotyping | 4 | < 0.1 | < 0.1 |
| Dolinay ³⁴ | Transcriptomics | Microarray | 4 | < 0.1 | < 0.1 |
| Chen ³⁵ | Proteomics | Mass Spec | 16 | < 0.1 | < 0.1 |

| Study | Method | Category | N genes | totMS (% sum) | ctotMS (% sum) |
|-----------------------|-----------------|-----------------|----------------|----------------------|-----------------------|
| Zhang ³⁶ | Transcriptomics | RNA-seq | 5 | < 0.1 | < 0.1 |
| Shortt ³⁷ | GWAS | WES | 3 | < 0.1 | < 0.1 |
| Bowler ³⁸ | Proteomics | Mass Spec | 18 | < 0.1 | < 0.1 |
| Morrell ³⁹ | Transcriptomics | Microarray | 1 | < 0.1 | < 0.1 |

Abbreviations: GWAS - Genome-wide association study; Mass Spec - Mass spectometry; totMS - Total MAIC score; ctotMS - Contributing total MAIC score; WES - Whole-exome sequencing. totMS and ctotMS are reported as the percentage of the sum of totMS/ctotMS for all lists included in the analysis.

Supplementary Table 2. ARDS MAIC prioritised genes found in common by BioLitMine with >= 2 associated publications.

| Publication | | | MAIC |
|-------------|-------|---|------|
| Gene | count | PubMed IDs | rank |
| TGFB1 | 8 | 30395619, 29083412, 28188225, 27309347, 22034170, 20142324, 16100012, 12654639 | 225 |
| VEGFA | 8 | 24356493, 23542734, 21797753, 19543148, 19349383, 17289863, 15920019, 15741444 | 320 |
| IL10 | 8 | 32217834, 31936183, 30280795, 28432351, 22033829, 21138342, 18242340, 16585075 | 1268 |
| SFTPB | 6 | 21128671, 18679120, 16100012, 15190959, 14718442, 12490037 | 177 |
| IL17A | 6 | 34239039, 32795834, 32651218, 30655311, 26709006, 26002979 | 1294 |
| PI3 | 5 | 28187039, 24617927, 19251943, 19197381, 18203972 | 2 |
| CXCL8 | 5 | 22897124, 22080750, 21348591, 17498967, 14729508 | 3 |
| IL6 | 5 | 34757857, 33250487, 32826331, 31261506, 18593632 | 144 |
| TNF | 5 | 31261506, 22507624, 21784970, 17034639, 16135717 | 651 |
| NAMPT | 4 | 24821571, 24053186, 18486613, 17392604 | 58 |
| IL1RN | 4 | 30095747, 29943912, 23449693, 18838927 | 175 |
| SCGB1A1 | 4 | 32787812, 28548310, 18521628, 16215398 | 187 |
| NPPB | 4 | 28322314, 26359292, 21696613, 19830720 | 1239 |
| HGF | 3 | 18065658, 17702746, 11943656 | 343 |
| IL33 | 3 | 33936076, 31147742, 23000728 | 385 |
| CXCL10 | 3 | 31651197, 23542734, 23144331 | 671 |
| S100A12 | 2 | 26274928, 24887223 | 5 |
| MUC1 | 2 | 21418654, 17565019 | 69 |
| PLAU | 2 | 23064953, 17994220 | 244 |
| EPAS1 | 2 | 28613249, 25574837 | 425 |
| FASLG | 2 | 30385692, 12414525 | 503 |
| EDN1 | 2 | 27765761, 17875064 | 643 |
| AKT1 | 2 | 27607575, 15961723 | 950 |
| MMP8 | 2 | 24651234, 15187163 | 1223 |

Supplementary Table 3. ARDS susceptibility gene list information content and contribution.

| Study | Method | Category | N genes | totMS (% sum) | ctotMS (% sum) |
|----------------------------|-----------------|------------|---------|---------------|----------------|
| Juss ² | Transcriptomics | Microarray | 1318 | 54.7 | 54.7 |
| Nguyen ³ | Proteomics | Mass Spec | 161 | 8.1 | 7.7 |
| Christie ⁹ | GWAS | Genotyping | 143 | 6 | 6.3 |
| Kovach ⁶ | Transcriptomics | Microarray | 123 | 5.8 | 6.1 |
| Wang ⁴ | Transcriptomics | Microarray | 137 | 5.8 | 6 |
| Jiang ¹¹ | Transcriptomics | scRNA-seq | 53 | 2.9 | 3 |
| Bime ¹³ | GWAS | Genotyping | 51 | 2.2 | 2.3 |
| Mirchandani ¹⁶ | Transcriptomics | Microarray | 41 | 1.7 | 1.6 |
| Chang ¹⁵ | Proteomics | Mass Spec | 37 | 1.9 | 1.5 |
| Mirchandani ¹⁶ | Proteomics | Mass Spec | 29 | 1.4 | 1.3 |
| Howrylak ²⁰ | Transcriptomics | Microarray | 28 | 1.2 | 1.3 |
| Ren ¹⁸ | Proteomics | Other | 17 | 1 | 1.1 |
| Tejera ¹⁹ | GWAS | Genotyping | 19 | 0.9 | 1 |
| Chen ³⁵ | Proteomics | Mass Spec | 16 | 0.9 | 0.9 |
| Zhang ²³ | Transcriptomics | RNA-seq | 20 | 0.8 | 0.9 |
| Zhu ²⁷ | Transcriptomics | Microarray | 14 | 0.6 | 0.6 |
| Kangelaris ²⁴ | Transcriptomics | Microarray | 15 | 0.7 | 0.6 |
| Englert ²⁸ | Transcriptomics | RNA-seq | 10 | 0.6 | 0.6 |
| Lu ²⁹ | Transcriptomics | Microarray | 12 | 0.5 | 0.5 |
| Meyer ²⁵ | GWAS | Genotyping | 10 | 0.4 | 0.4 |
| Bowler ³⁸ | Proteomics | Mass Spec | 18 | 0.9 | 0.4 |
| Scheller ³⁰ | Transcriptomics | RNA-seq | 9 | 0.4 | 0.3 |
| Guillen-Guio ³² | GWAS | Genotyping | 6 | 0.2 | 0.2 |
| Zhang ³⁶ | Transcriptomics | RNA-seq | 5 | 0.2 | 0.2 |
| Dolinay ³⁴ | Transcriptomics | Microarray | 4 | 0.2 | 0.2 |
| Shortt ³⁷ | GWAS | WES | 3 | 0.1 | 0.1 |
| Meyer ³³ | GWAS | Genotyping | 4 | < 0.1 | 0.1 |
| Morrell ³⁹ | Transcriptomics | Microarray | 1 | < 0.1 | < 0.1 |

Abbreviations: GWAS - Genome-wide association study; Mass Spec - Mass spectrometry; totMS - Total MAIC score; ctotMS - Contributing total MAIC score; WES -

Whole-exome sequencing. totMS and ctotMS are reported as the percentage of the sum of totMS/ctotMS for all lists included in the analysis.

Supplementary Table 4. ARDS survival/severity gene list information content and contribution.

| Study | Method | Category | N genes | totMS (% sum) | ctotMS (% sum) |
|-----------------------|-----------------|-----------------|----------------|----------------------|-----------------------|
| Bhargava ⁷ | Proteomics | Mass Spec | 144 | 30.4 | 30.3 |
| Morrell ⁸ | Transcriptomics | Microarray | 155 | 29.7 | 29.7 |
| Liao ¹⁰ | GWAS | Genotyping | 67 | 12.9 | 13 |
| Batra ¹² | Proteomics | Other | 39 | 9.4 | 9.4 |
| Liao ¹⁰ | Transcriptomics | RNA-seq | 43 | 8.5 | 8.5 |
| Xu ²¹ | GWAS | WES | 16 | 3.5 | 3.5 |
| Chen ²² | Proteomics | Mass Spec | 16 | 3.4 | 3.4 |
| Lu ²⁹ | Transcriptomics | Microarray | 12 | 2.2 | 2.2 |

Abbreviations: GWAS - Genome-wide association study; Mass Spec - Mass spectrometry; totMS - Total MAIC score; ctotMS - Contributing total MAIC score; WES - Whole-exome sequencing. totMS and ctotMS are reported as the percentage of the sum of totMS/ctotMS for all lists included in the analysis.

Supplementary Data

Supplementary Data Files 1-8

Supplementary Data File 1. Raw gene list input to MAIC.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_1.csv

Supplementary Data File 2. MAIC output - overall.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_2.csv

Supplementary Data File 3. BioLitMine and ARDS Database of Genes results.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_3.csv

Supplementary Data File 4. MAIC output - ARDS vs. non-ARDS controls sub-group.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_4.csv

Supplementary Data File 5. MAIC output - survival sub-group.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_5.csv

Supplementary Data File 6. Functional enrichment results - overall.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_6.csv

Supplementary Data File 7. Functional enrichment results - ARDS vs. non-ARDS controls sub-group.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_7.csv

Supplementary Data File 8. Functional enrichment results - survival sub-group.

https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_8.csv

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