

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

## 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

## **Supplementary Results**

Supplementary Figures 1-7

Supplementary Tables 1-4

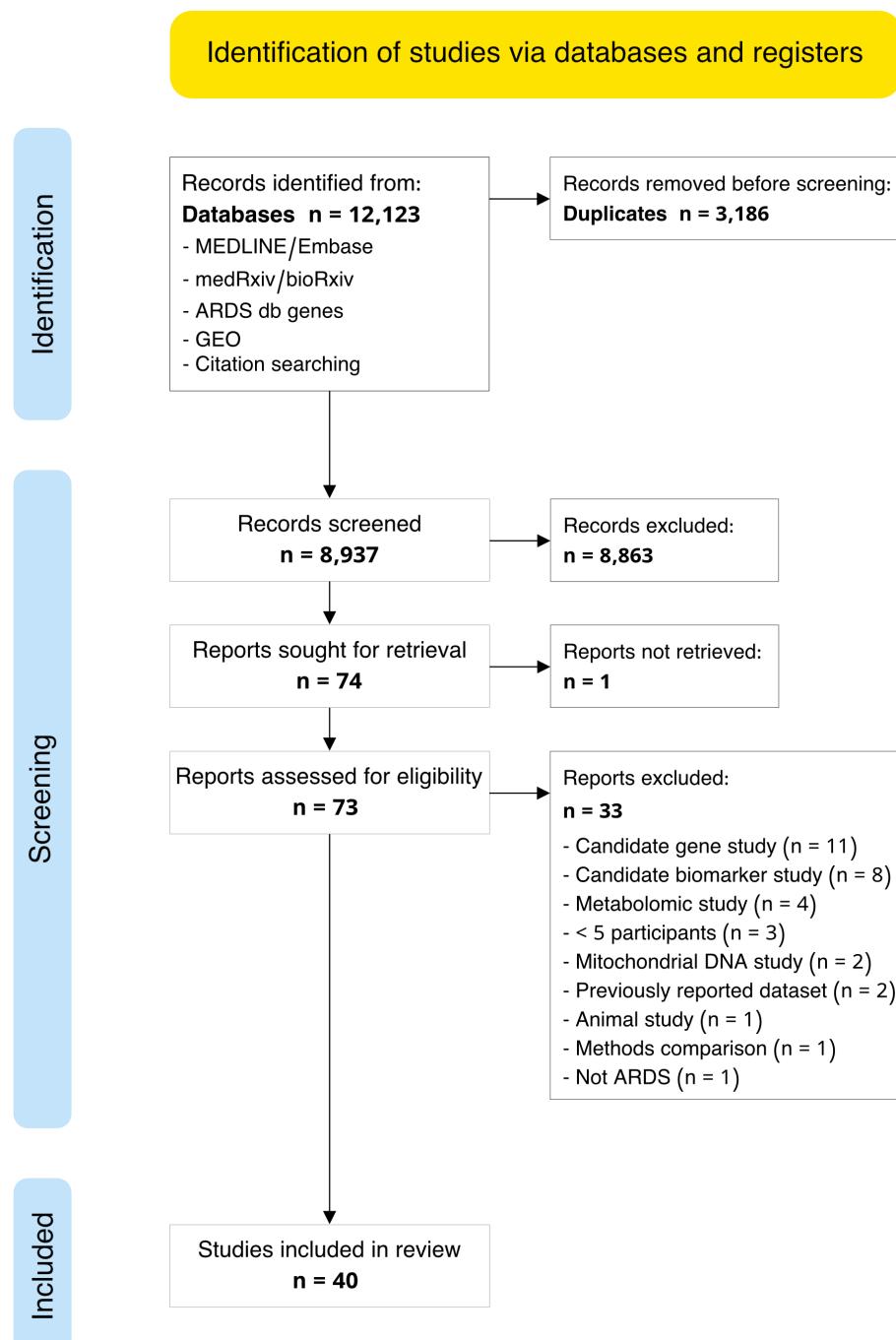
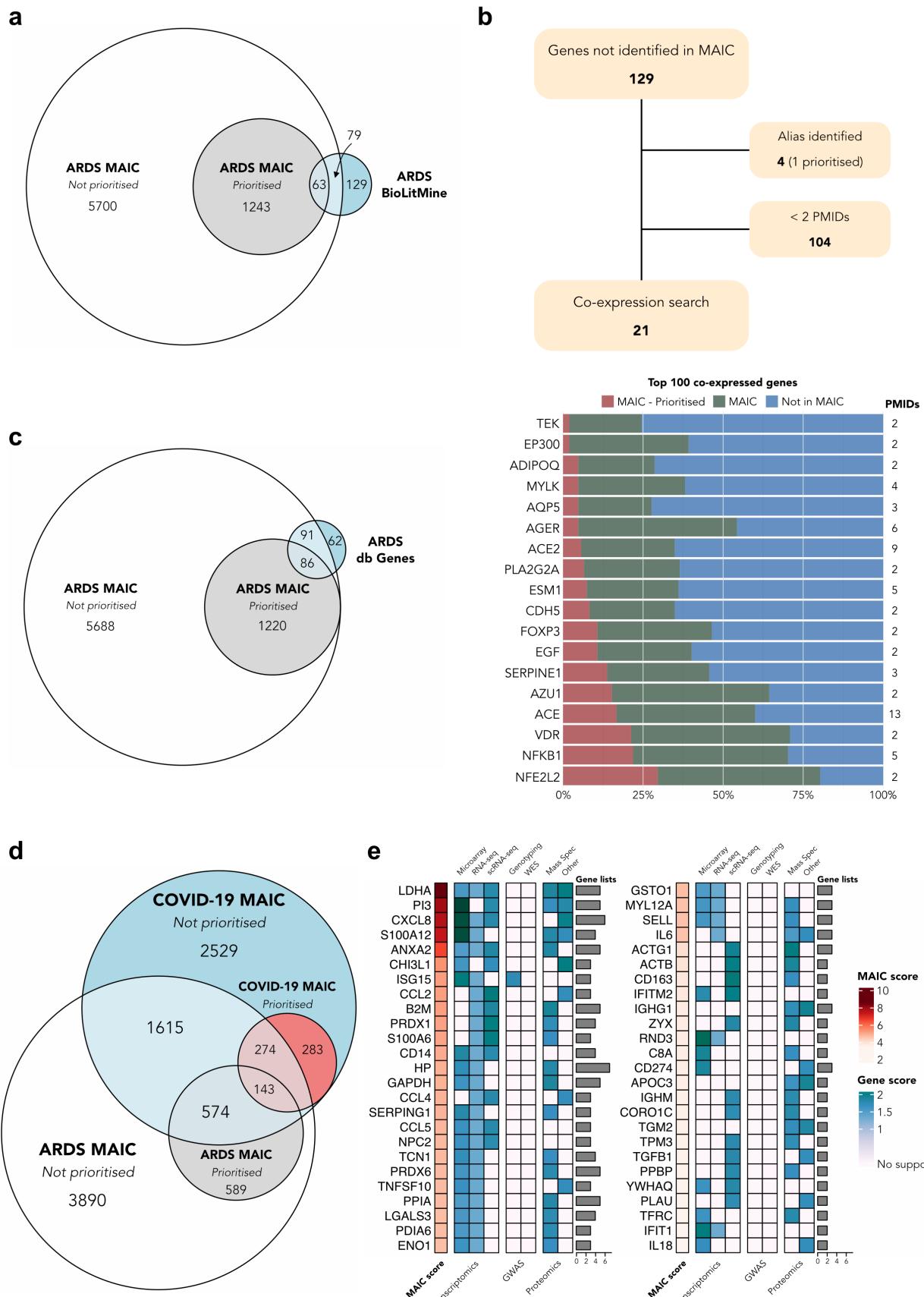
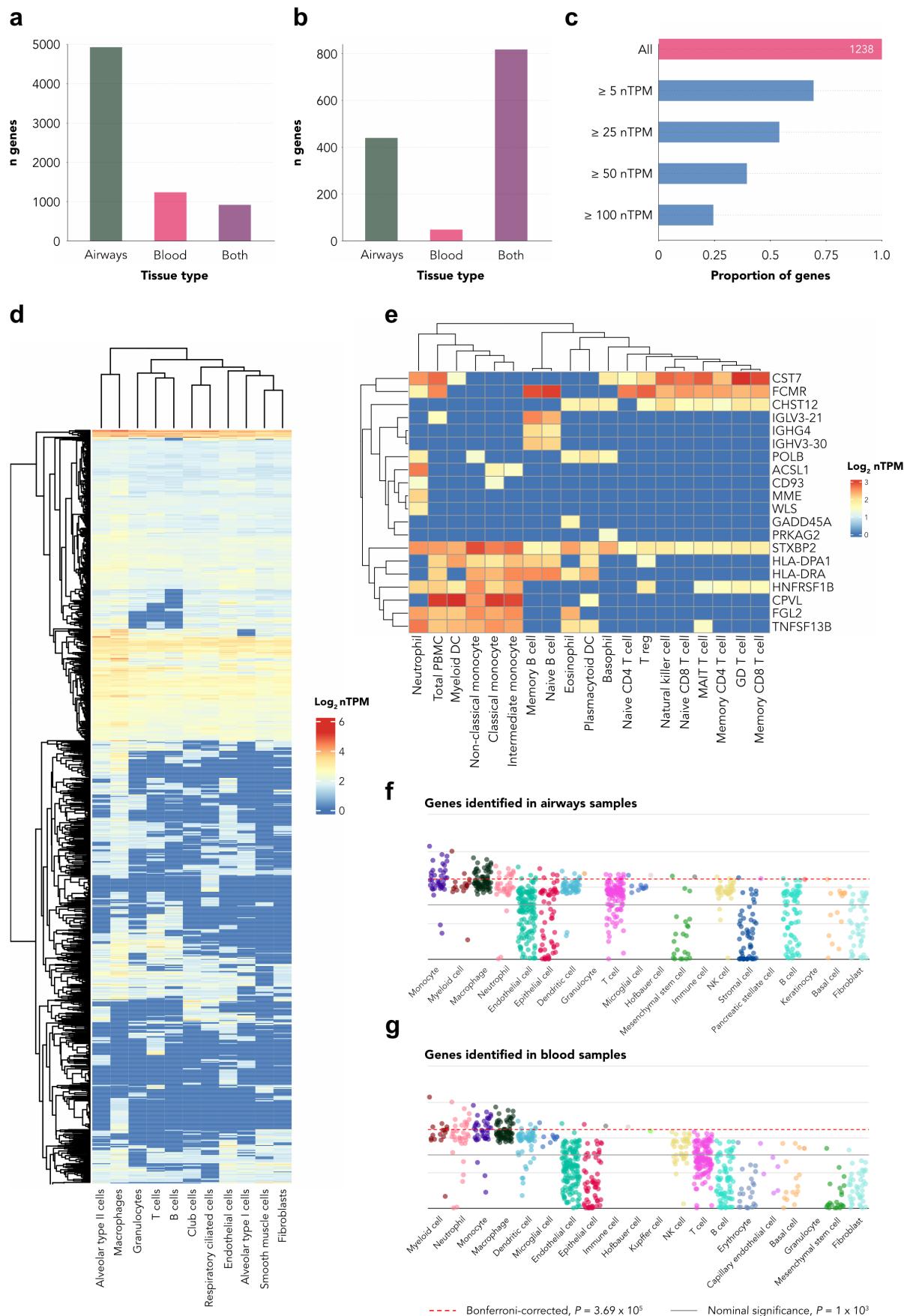


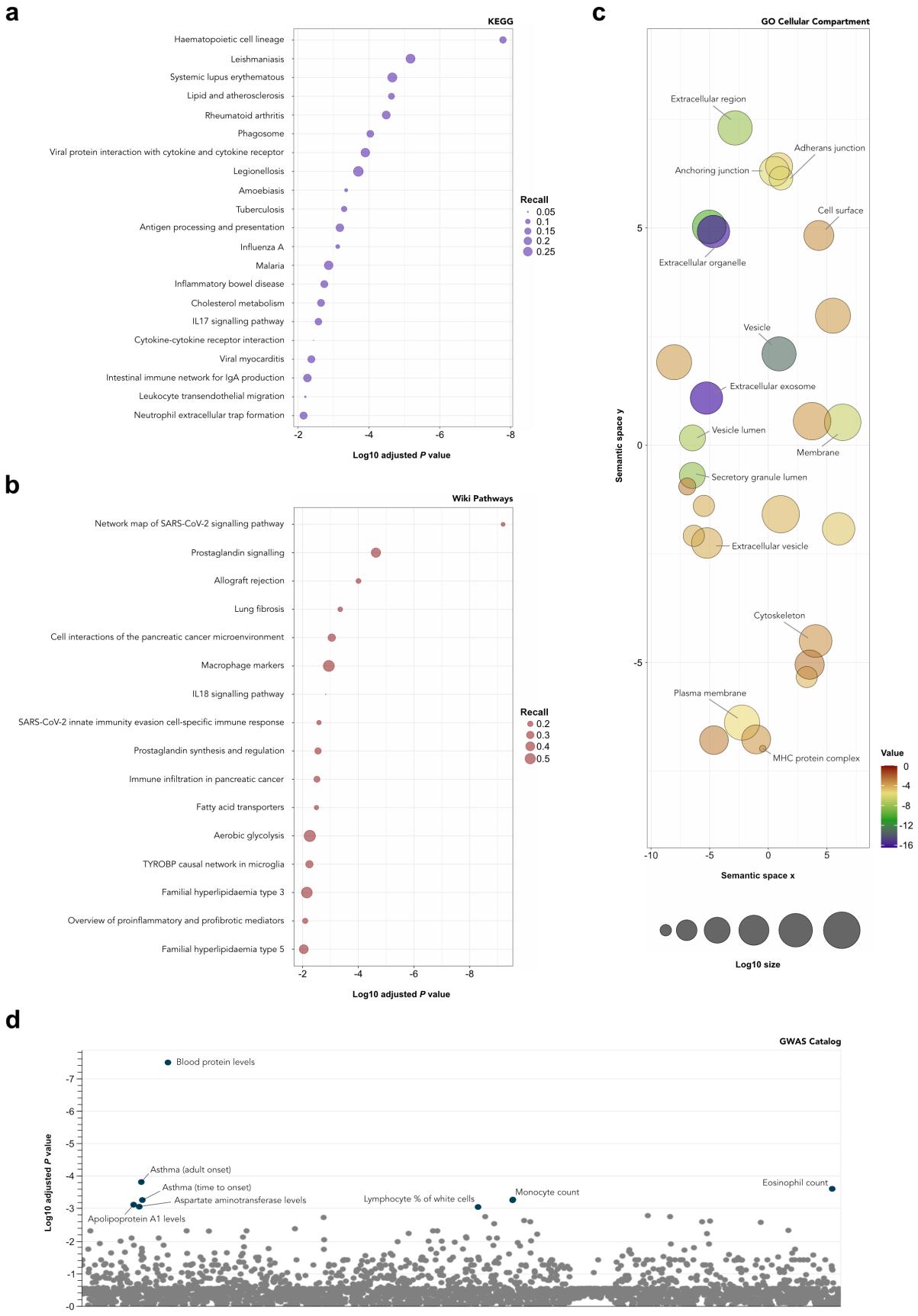
Figure 1: **Systematic review inclusion diagram.** Abbreviations: db - data base; GEO - NCBI Gene Expression Omnibus.



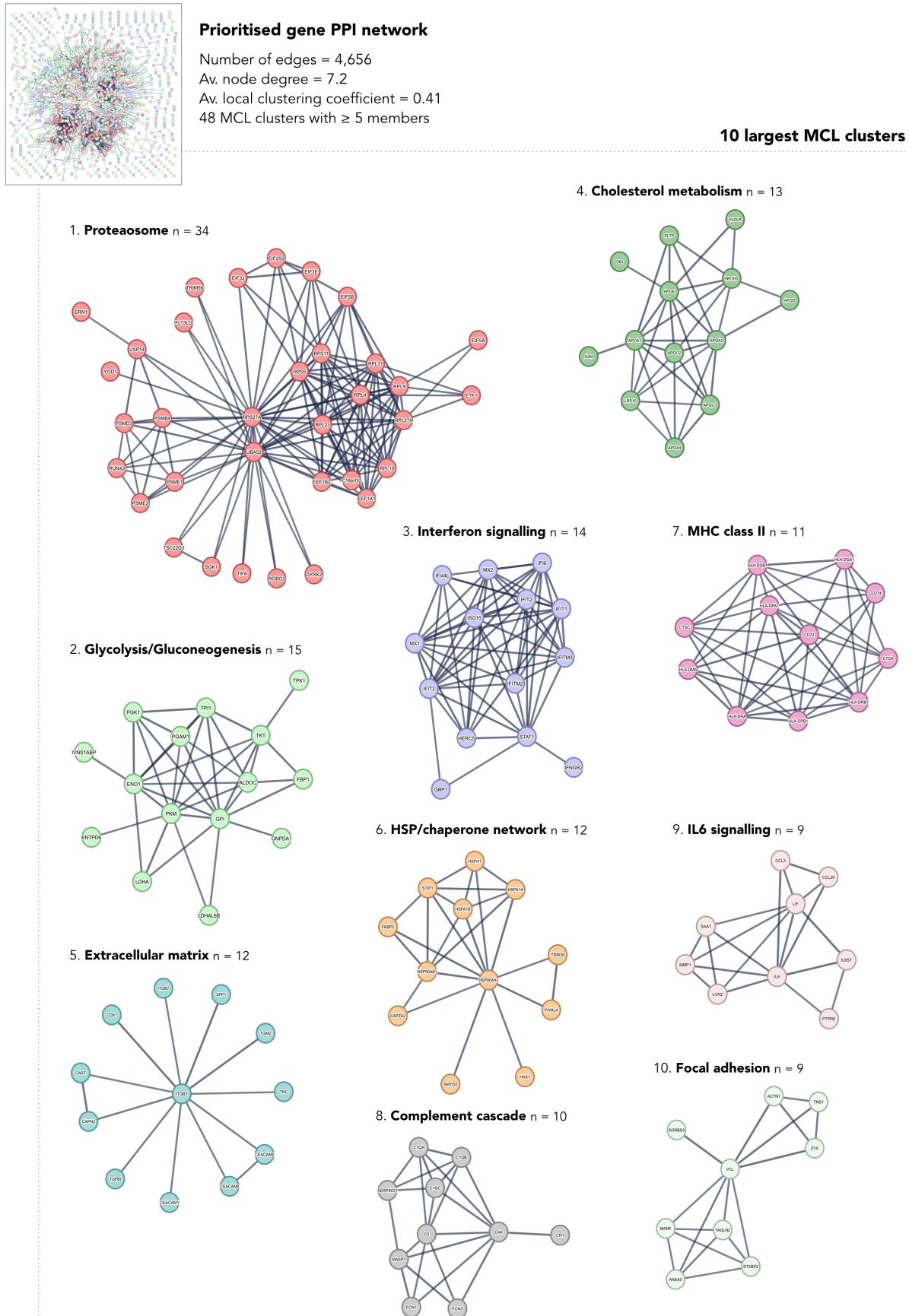
**Figure 2: Overlap between ARDS MAIC and ARDS-associated genes and ARDS MAIC and COVID-19 MAIC.**  
 (a) Eular diagram of gene overlap between ARDS MAIC and a BioLitMine search using the ARDS MeSH term. (b) Schematic overview of a co-expression search for genes identified in the BioLitMine search but 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) Eular diagram of gene overlap between ARDS MAIC and the ARDS Database of Genes. (d) Eular 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 COVID-19 MAIC, displaying the ARDS MAIC score for each gene, highest gene score in each category, and the number of supporting gene lists.



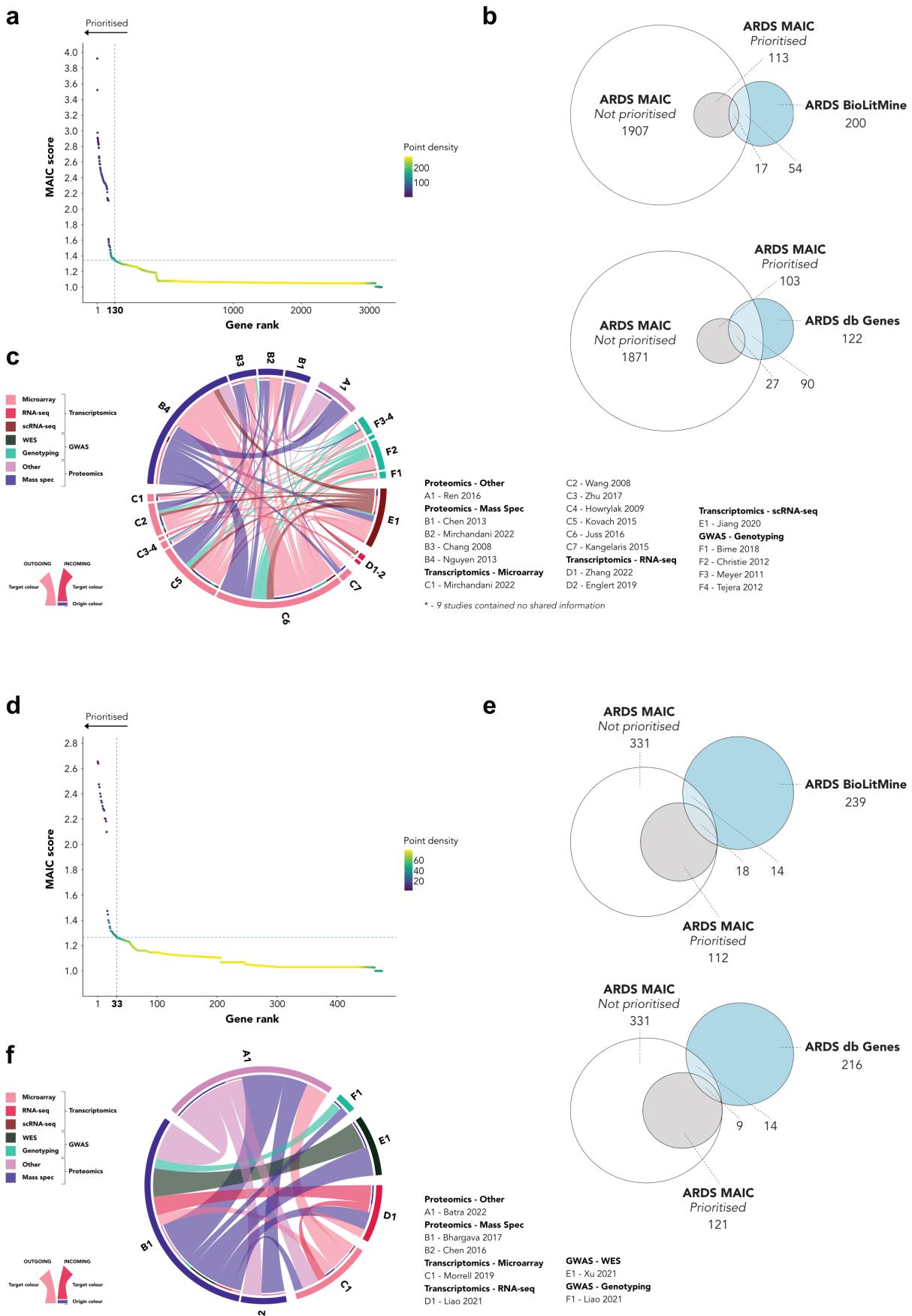
**Figure 3: Tissue and cell-specific expression.** (a) Bar plot of the tissue type in which genes are identified - all genes ( $n=7,085$ ). (b) Bar plot of the tissue type in which genes are identified - prioritised genes ( $n=1,306$ ). (c) Bar plot of the proportion of genes identified solely in blood 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.



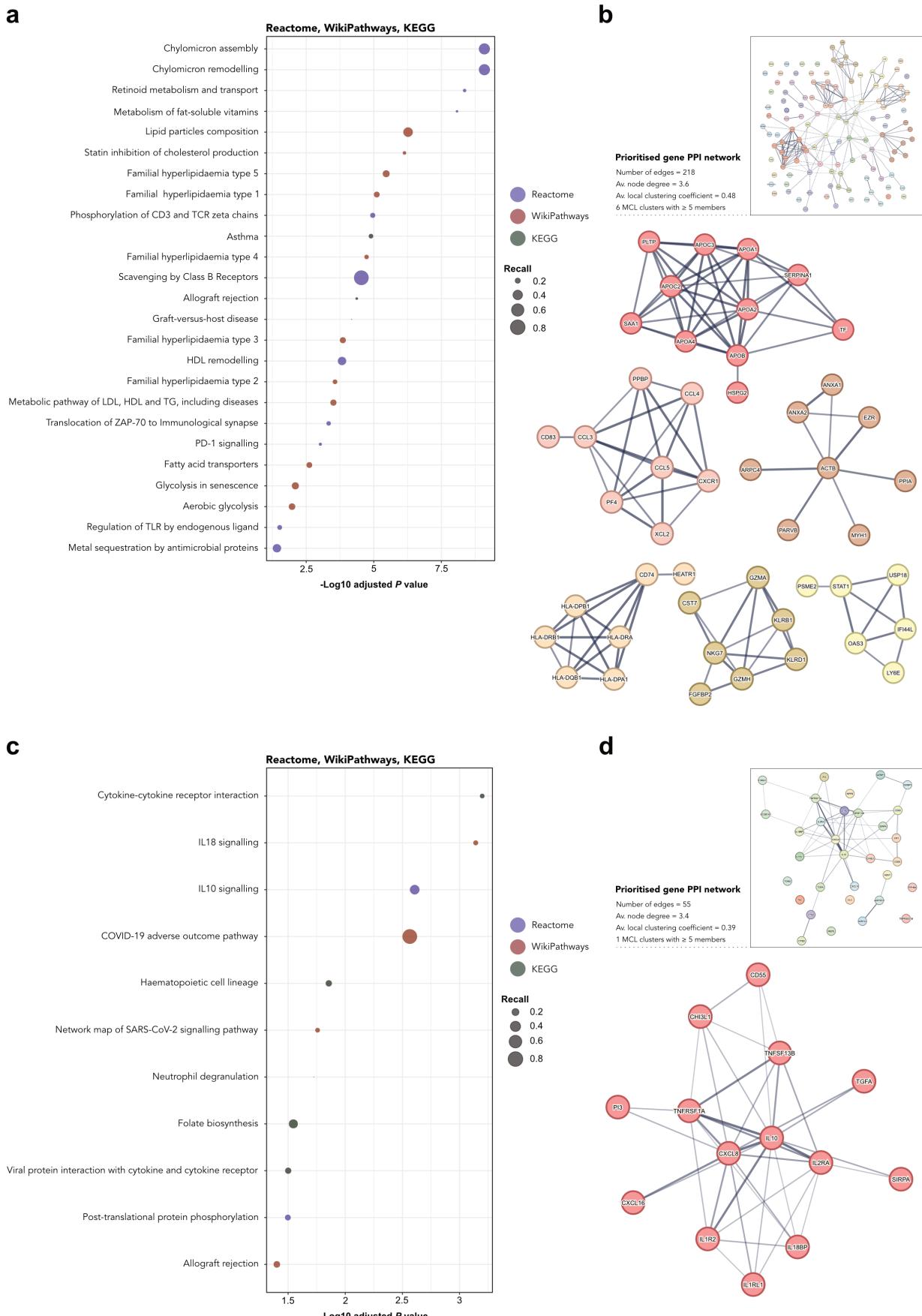
**Figure 4: Functional enrichment.** (a) Significantly enriched KEGG terms ( $P < 0.01$ ) for prioritised genes. Terms size proportional to recall. (b) Significantly enriched WikiPathways terms ( $P < 0.01$ ) for prioritised genes. Terms size proportional to recall. (c) Scatter plot of the semantic similarity between significantly enriched GO cellular component terms for prioritised genes (d) Manhattan plot of the overenrichment of prioritised genes against the GWAS catalog.



**Figure 5: 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.



**Figure 6: Details of MAIC on sub-groups.** (a) Gene prioritization for the ARDS MAIC susceptibility 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 prioritized. (b) Euler diagrams of gene overlap between the ARDS MAIC susceptibility sub-group and a BioLitMine search using the ARDS MeSH term and the ARDS Database of Genes. (c) Shared information content (IC) between susceptibility gene lists. Links indicate absolute IC (sum of common gene scores) between studies. (d) Gene prioritization 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 prioritized. (e) Euler diagrams of gene overlap between the ARDS MAIC survival sub-group and a BioLitMine search using the ARDS MeSH term and the ARDS Database of Genes. (f) Shared information content (IC) between survival gene lists. Links indicate absolute IC (sum of common gene scores) between studies.



**Figure 7: Sub-group functional enrichment.** (a) Significantly enriched Reactome, WikiPathways, and KEGG terms ( $P < 0.01$ ) for prioritised genes in the susceptibility sub-group. Terms are coloured by pathway and size is proportional to recall. (b) A protein-protein interaction network of prioritised genes in the susceptibility 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.

**Supplementary Table 1. Gene list information content and contribution.**

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

<b>Study</b>	<b>Method</b>	<b>Category</b>	<b>N genes</b>	<b>rIC (%)</b>	<b>rICtb (%)</b>
Zhang <sup>36</sup>	Transcriptomics	RNA-seq	5	< 0.1	< 0.1
Shortt <sup>37</sup>	GWAS	WES	3	< 0.1	< 0.1
Bowler <sup>38</sup>	Proteomics	Mass Spec	18	< 0.1	< 0.1
Morrell <sup>39</sup>	Transcriptomics	Microarray	1	< 0.1	< 0.1

Abbreviations: GWAS - Genome-wide association study; Mass Spec - Mass spectrometry; rIC - Relative information content; rICtb - Relative information contribution; WES - Whole-exome sequencing.

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

Abbreviations: GWAS - Genome-wide association study; Mass Spec - Mass spectrometry; rIC - Relative information content; rICtb - Relative information contribution; WES - Whole-exome sequencing.

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

<b>Study</b>	<b>Method</b>	<b>Category</b>	<b>N genes</b>	<b>rIC (%)</b>	<b>rICtb (%)</b>
Bhargava <sup>7</sup>	Proteomics	Mass Spec	144	30.4	30.3
Morrell <sup>8</sup>	Transcriptomics	Microarray	155	29.7	29.7
Liao <sup>10</sup>	GWAS	Genotyping	67	12.9	13
Batra <sup>12</sup>	Proteomics	Other	39	9.4	9.4
Liao <sup>10</sup>	Transcriptomics	RNA-seq	43	8.5	8.5
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Chen <sup>22</sup>	Proteomics	Mass Spec	16	3.4	3.4
Lu <sup>29</sup>	Transcriptomics	Microarray	12	2.2	2.2

Abbreviations: GWAS - Genome-wide association study; Mass Spec - Mass spectrometry; rIC - Relative information content; rICtb - Relative information contribution; WES - Whole-exome sequencing.

## **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](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](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](https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_3.csv)

**Supplementary Data File 4. MAIC output - susceptibility sub-group.**

[https://github.com/JonathanEMillar/ards\\_maic\\_manuscript/Supplementary\\_Data\\_File\\_4.csv](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](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](https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_6.csv)

**Supplementary Data File 7. Functional enrichment results - susceptibility sub-group.**

[https://github.com/JonathanEMillar/ards\\_maic\\_manuscript/Supplementary\\_Data\\_File\\_7.csv](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](https://github.com/JonathanEMillar/ards_maic_manuscript/Supplementary_Data_File_8.csv)

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