SUPPLEMENTARY MATERIALS

SUPPLEMENTARY FIGURES

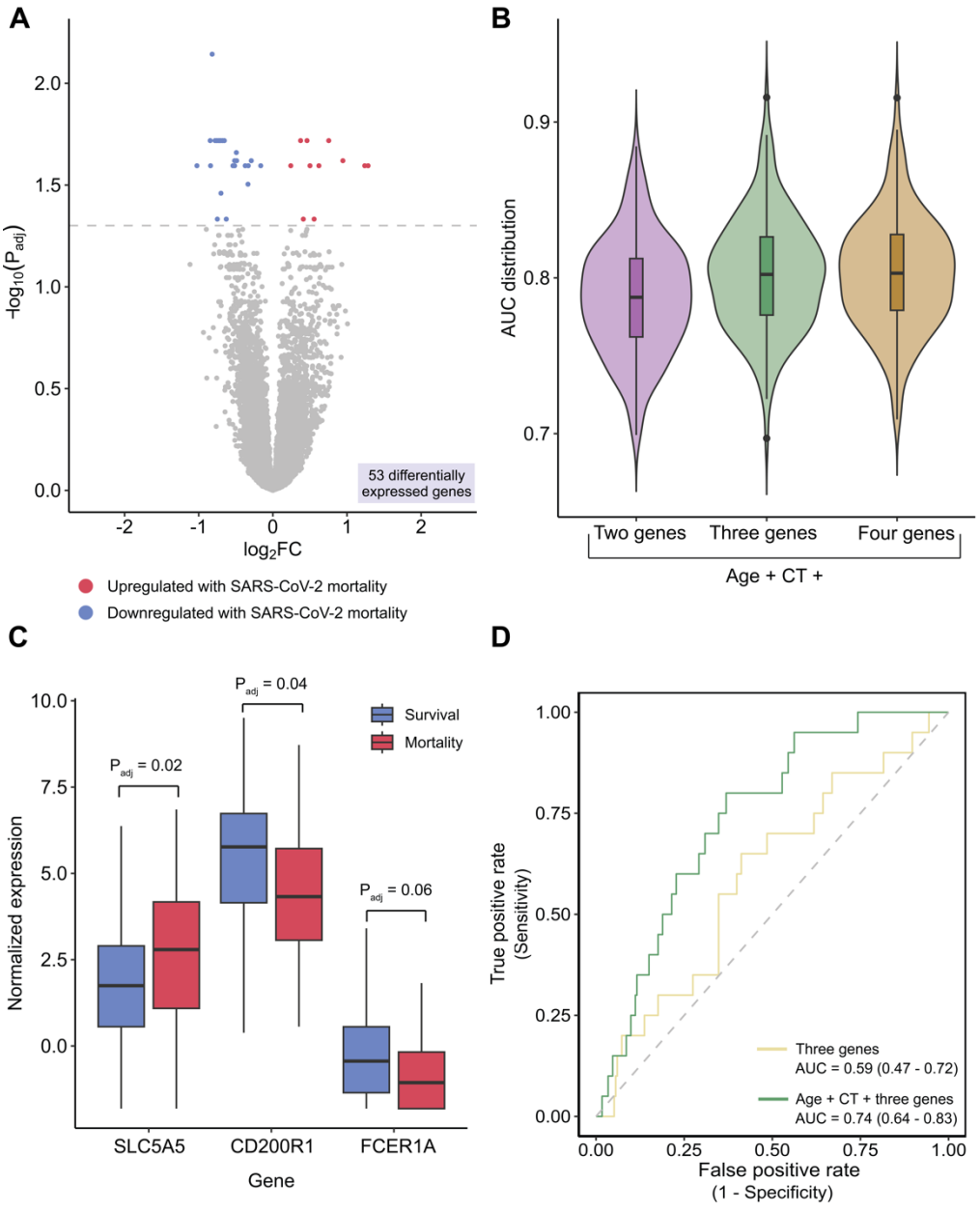

Figure S1. Upper respiratory tract differential expression and host-viral classifier development and evaluation. **A.** Volcano plot demonstrating the 53 differentially expressed genes between mortality and survival in the upper respiratory tract in the IMPACC cohort (red = upregulated with mortality, blue = downregulated with mortality), using a Benjamini-Hochberg adjusted p-value of 0.05. **B.** Violin plots showing the area under the curve (AUC) distribution for each of the upper respiratory tract classifiers, evaluated in the training cohort. **C.** Boxplots comparing the $\log_2$ counts per million normalized gene expression of the three-gene classifier genes *(SLC5A5, CD200R1*, *FCER1A*) between survival (blue) and mortality (red) in the IMPACC upper respiratory tract data set. **D**. Performance of three-gene classifier with (green) and without (yellow) the addition of age and CT value in the validation cohort. Area under the curve (AUC) listed as value with 95% confidence interval**.**

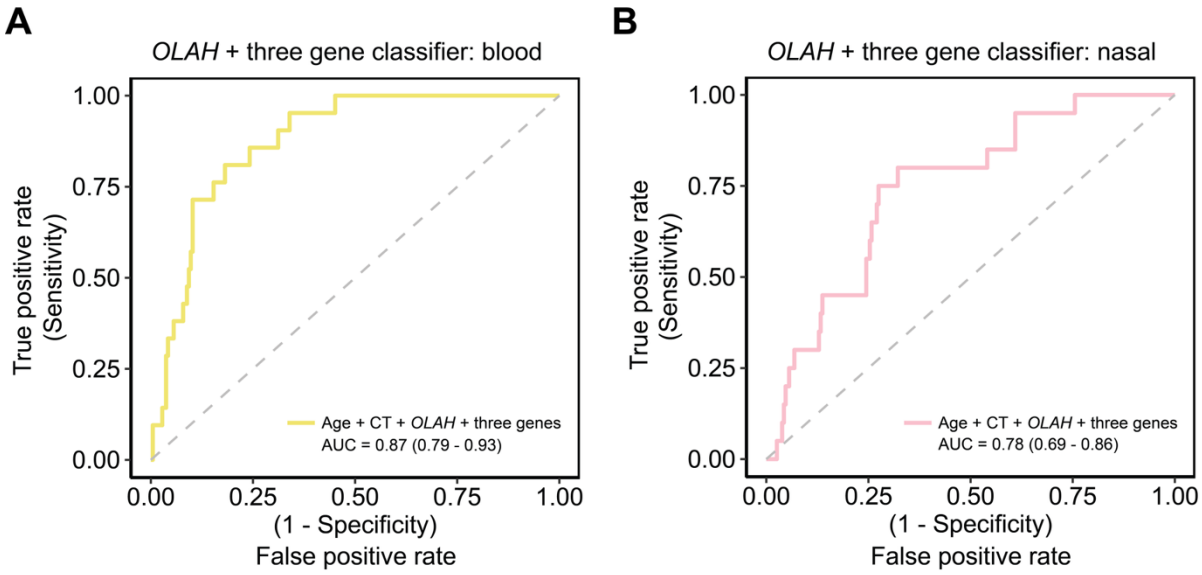

Figure S2. Performance of combined prognostic classifiers in the IMPACC cohort. A. Receiver operating characteristic (ROC) curve displaying the performance of a combined classifier consisting of *OLAH,* the three genes from the blood prognostic classifier, age, and SARS-CoV-2 cycle threshold (CT) in the IMPACC peripheral blood data. Area under the curve (AUC) listed as a value with 95% confidence interval. **B.** ROC curve displaying performance of a classifier consisting of *OLAH,* the three genes from the nasal prognostic classifier, age, and CT.

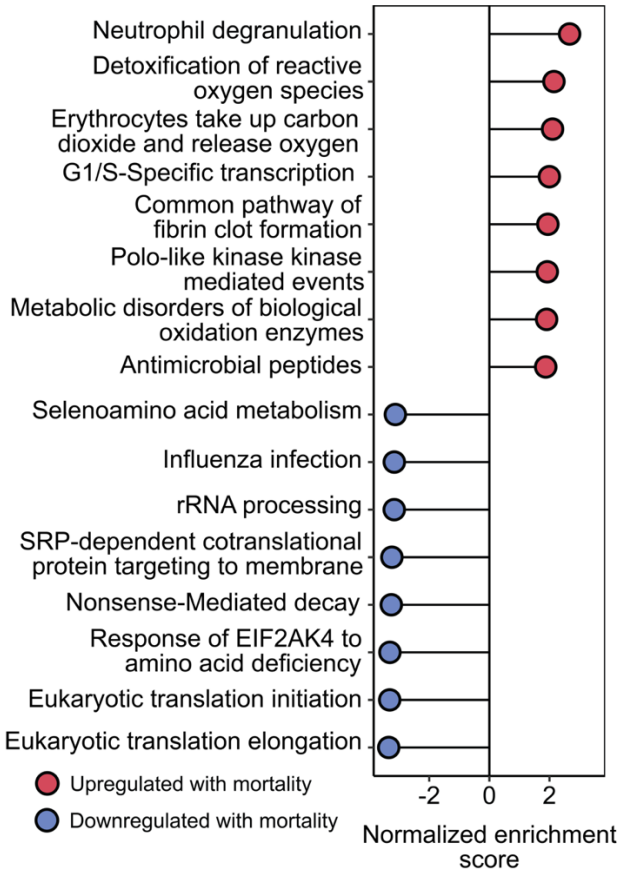

Figure S3. Pathways associated with mortality in the validation cohort. Gene set enrichment analysis (GSEA) demonstrating statistically significant pathways based on Benjamini-Hochberg adjusted p-value in the validation cohort (red = upregulated pathways, blue = downregulated pathways).

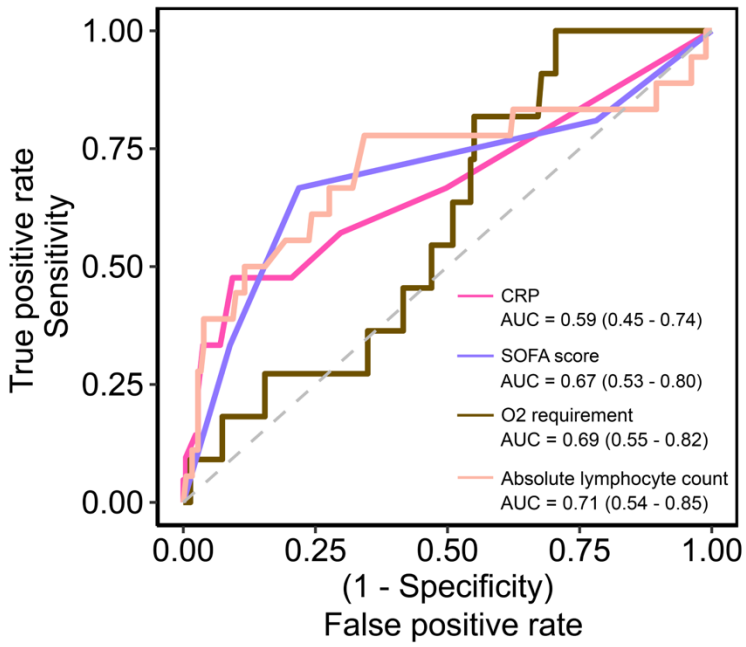

Figure S4. Performance of classifiers consisting of clinical variables in the IMPACC cohort. Receiver operating characteristic (ROC) curve displaying the performance of classifiers consisting of C-reactive protein (CRP), sepsis-related organ failure assessment score (SOFA) score, baseline respiratory ordinal score (O2 requirement), and absolute lymphocyte count. Area under the curve (AUC) listed as a value with 95% confidence intervals. Analysis was performed on individuals with PBMC RNA-seq data available.

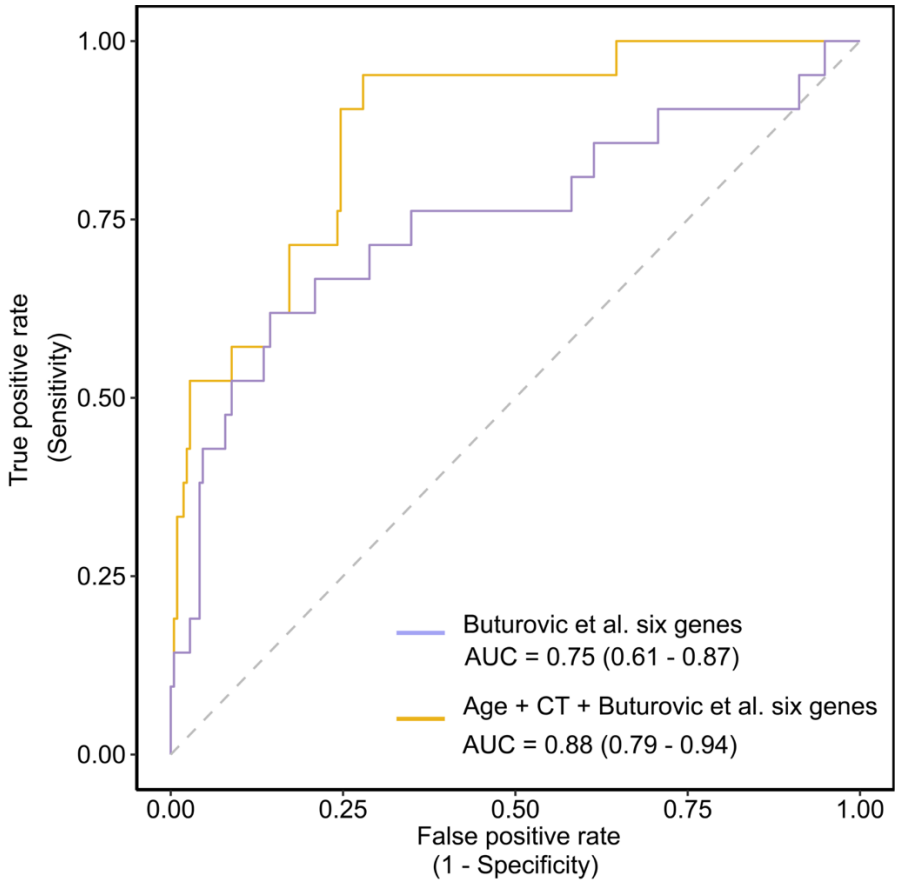

Figure S5. Performance of a previously published mortality classifier in the IMPACC cohort. Performance of the Buturovic et al. six gene classifier with (yellow) and without (purple) the added features of age and SARS-CoV-2 cycle threshold in IMPACC. Area under the curve (AUC) listed as value with 95% confidence interval.

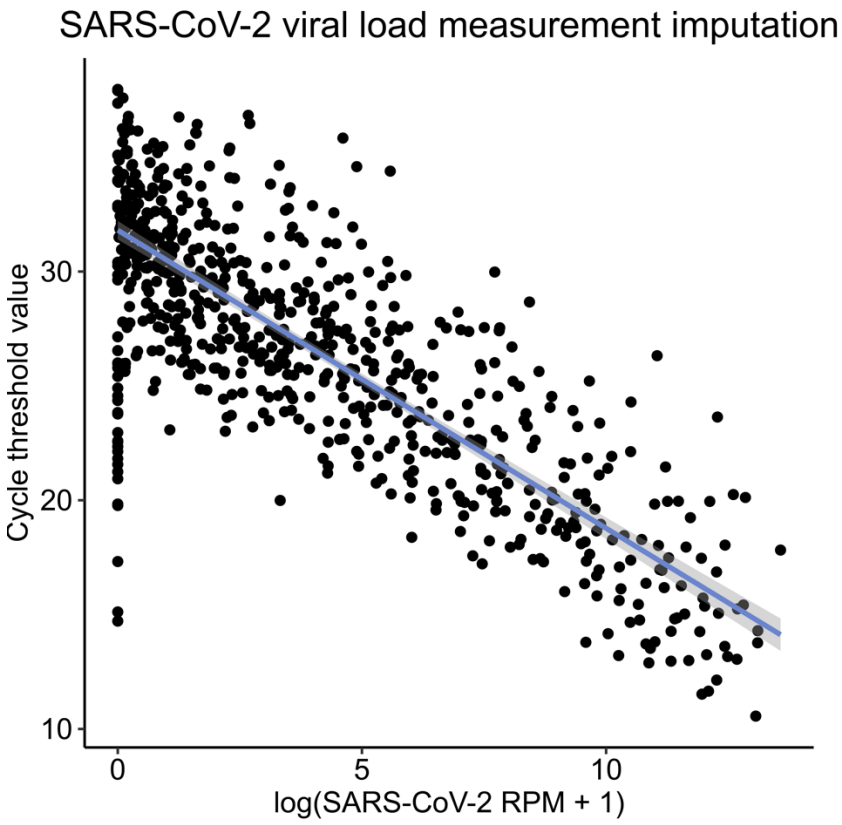

Figure S6. Robust regression for integrating SARS-CoV-2 reads-per-million (RPM) and cycle threshold values. Scatter plot showing the relationship between log(SARS-CoV2 RPM + 1) and SARS-CoV-2 cycle threshold (CT), for all subjects with both data available (n = 708). The line of best fit is based on a robust regression model (adjusted R-squared = 0.693, residual standard error = 2.978). Both the intercept and rpM value were significantly associated with CT value (P < 2e-16) based on linear regression.

SUPPLEMENTARY TABLES

	Survival (n=80)	Mortality (n=42)	P-value
Age, median (IQR)	65.5 (54.0-74.5)	69.5 (58.0-79.0)	0.234
Male, n (%)	48 (60.0%)	28 (66.7%)	0.557
Female, n (%)	32 (40.0%)	14 (33.3%)	0.557
Race, n (%)			0.722
White	34 (42.5%)	13 (31.0%)	
Black/African American	11 (13.8%)	7 (16.7%)	
Asian	22 (27.5%)	14 (33.3%)	
American Indian/Alaska Native	1 (1.3%)	0 (0.0%)	
Unknown	12 (15.0%)	8 (19.0%)	
Hispanic ethnicity, n (%)	9 (11.3%)	6 (14.3%)	0.762
Comorbidities, n (%)			
Diabetes	25 (31.3%)	15 (35.7%)	0.686
Hypertension	31 (38.8%)	14 (33.3%)	0.693
Chronic pulmonary disease	20 (25.0%)	8 (19.0%)	0.505
Cancer	13 (16.3%)	10 (23.8%)	0.337
Immunocompromised	6 (6.5%)	7 (16.7%)	0.133
Autoimmune disease	3 (3.8%)	0 (0.0%)	0.551
Mechanical ventilation, n (%)	65 (81.3%)	35 (83.3%)	0.999
Vasopressor use, n (%)	62 (77.5%)	37 (88.1%)	0.223

Table S1: Sepsis cohort (EARLI) demographics. Demographics are stratified by survival status. Race was noted "unknown" if patient declined, was unable to answer, if they selected "other" as an option, or if data were missing. Mann-Whitney test was used for all continuous variables, and Fisher's exact test was used for all categorical values. IQR, interquartile range; EARLI, Early Assessment of Renal and Lung Injury.

Size	Genes	AUC Mean	AUC Std. Dev.
2	***ATP1B2***, ***DAAM2***	0.79	0.04
3	***ATP1B2***, ***DAAM2***, ***CD83***	0.80	0.04
4	***ATP1B2***, ***DAAM2***, *TSPAN7, KCNH8*	0.81	0.04
5	***ATP1B2***, ***DAAM2***, *TSPAN7, KCNH8,* ***CD83***	0.82	0.04
6	***ATP1B2***, ***DAAM2***, *TSPAN7, KCNH8,* ***CD83***, *FCER1A*	0.82	0.04
8	***ATP1B2***, ***DAAM2***, *TSPAN7, KCNH8,* ***CD83***, *FCER1A, NR4A3, CPA3*	0.82	0.05
10	***ATP1B2***, ***DAAM2***, *TSPAN7, KCNH8,* ***CD83***, *FCER1A, NR4A3, CPA3, TMEM45A, MLNR*	0.82	0.04

Table S2. Peripheral blood candidate mortality classifiers generated by LASSO. The best performing gene sets for feature lengths n = 2-6, 8, and 10 based on the 3-fold random partitioning evaluation of performance characteristics. Bolded genes are the genes included in the final three gene classifier. LASSO, least absolute shrinkage and selection operator; AUC, area under the receiver operating characteristic curve.

Length	Genes	AUC mean	AUC Std. Dev
2	***SLC5A5, CD200R1***	0.79	0.04
3	***SLC5A5, CD200R1***, ***FCER1A***	0.80	0.04
4	***SLC5A5, CD200R1***, ***FCER1A***, *MARCO*	0.80	0.04

Table S3. Nasal swab candidate mortality classifiers generated by LASSO. The best performing gene sets for feature lengths n = 2-4 based on the 3-fold random partitioning evaluation of performance characteristics. Bolded genes are the genes included in the final three gene classifier. LASSO, least absolute shrinkage and selection operator; AUC, area under the receiver operating characteristic curve.

	Survival (n=116)	Mortality (n=21)	P-value
Age, median (IQR)	56.0 (44.3-70.2)	67.5 (49.9-78.2)	0.052
Male, n (%)	78 (67.2%)	13 (61.9%)	0.625
Female, n (%)	38 (32.8%)	8 (38.1%)	0.625
Race, n (%)			0.391
White	38 (32.8%)	6 (28.6%)	
Black/African American	10 (8.6%)	5 (23.8%)	
Asian	18 (15.5%)	4 (19.0%)	
Native Hawaiian/Pacific Islander	2 (1.7%)	0 (0.0%)	
American Indian/Alaska Native	1 (0.9%)	0 (0.0%)	
Unknown	47 (40.5%)	6 (28.6%)	
Hispanic ethnicity, n (%)	48 (41.4%)	8 (38.1%)	0.815
Comorbidities, n (%)			
BMI > 30	51 (44.0%)	10 (47.6%)	0.814
HIV	3 (2.6%)	1 (4.8%)	0.490
Rheumatologic disorder	15 (12.9%)	2 (9.5%)	0.999
Solid organ transplant	17 (14.7%)	2 (9.5%)	0.737
Mechanical ventilation, n (%)	34 (29.3%)	16 (76.2%)	<0.001
Steroid use, n (%)	59 (50.9%)	17 (81.0%)	0.016
Vaccinated for COVID-19, n (%)	45 (38.8%)	10 (47.6%)	0.476

Table S4: COVID-19 external validation cohort (COMET) demographics. Demographics are stratified by survival status. Race was noted “unknown” if patient declined, was unable to answer, if they selected “other” as an option, or if data were missing. Mann-Whitney test was used for all continuous variables, and Fisher’s exact test was used for all categorical values. IQR, interquartile range; BMI, body mass index; COMET, COVID-19 Multi-immunophenotyping projects for Effective Therapies.

SOFA classifier	AUC (95% CI)	Comparison classifier	AUC (95% CI)	DeLong P-value
SOFA	0.67 (0.51 - 0.80)	Three genes + Age + CT (PBMC)	0.88 (0.82 - 0.94)	0.003
SOFA	0.67 (0.51 - 0.80)	OLAH + Age + CT (PBMC)	0.86 (0.79 - 0.93)	0.010
SOFA	0.73 (0.61 - 0.83)	Three genes + Age + CT (NS)	0.74(0.64 - 0.83)	0.400
SOFA	0.73 (0.61 - 0.83)	OLAH + Age + CT (NS)	0.78 (0.69 - 0.86)	0.064

Table S5: Comparison between performance of a prognostic model based on Sepsis-related Organ Failure Assessment (SOFA) score and parsimonious classifiers. Performance is based on analysis in the respective cohort (PBMC or NS). Significance between the area under the curve (AUC) values was determined based on the paired DeLong test. PBMC, peripheral blood mononuclear cell; NS, nasal swab.

Model	Feature	Coefficients
PBMC 3 gene + age + CT	*CD83*	-0.52
	ATP1B2	0.54
	DAAM2	0.45
	Age	0.66
	CT	-0.28
PBMC *OLAH* + age + CT	*OLAH*	0.42
	Age	0.68
	CT	-0.30
NS 3 gene + age + CT	*SLC5A5*	0.57
	CD200R1	-0.51
	FCER1A	0.47
	Age	0.75
	CT	-0.25
NS *OLAH* + age + CT	*OLAH*	0.44
	Age	0.82
	CT	-0.36

Table S6. Model coefficients for features for the four main models discussed in the main manuscript. Each model consisted of a combination of genes, age, and SARS-CoV-2 cycle threshold value. Coefficients are generalized linear model coefficients with a logistic regression binary task. PBMC, peripheral blood mononuclear cell; CT, cycle threshold.

SUPPLEMENTARY DATA FILES

Supplementary Data File 1. **A.** Genes differentially expressed with mortality in IMPACC blood samples (n=785), adjusted for age and sex. **B.** Gene set enrichment analysis (GSEA) of differentially expressed genes. Legend: logFC = log(2) fold change; padj = Benjamini-Hochberg adjusted P value; NES = normalized enrichment score; size = size of Reactome pathway; LeadingEdge = leading edge genes.

Supplementary Data File 2. **A.** Genes differentially expressed with mortality in IMPACC upper respiratory tract samples (n=842), adjusted for age and sex . **B.** Gene set enrichment analysis (GSEA) of differentially expressed genes. Legend: logFC = log(2) fold change; padj = Benjamini-Hochberg adjusted P value; NES = normalized enrichment score; size = size of Reactome pathway; LeadingEdge = leading edge genes.

Supplementary Data File 3. **A.** Genes differentially expressed with mortality in EARLI blood samples (n=122), adjusted for age and sex. **B.** Gene set enrichment analysis (GSEA) of differentially expressed genes. Legend: logFC = log(2) fold change; padj = Benjamini-Hochberg adjusted P value; NES = normalized enrichment score; size = size of Reactome pathway.

Supplementary Data File 4. **A.** Genes differentially expressed with mortality in COMET blood samples (n=137), adjusted for age and sex. **B.** Gene set enrichment analysis (GSEA) of differentially expressed genes. Legend: logFC = log(2) fold change; padj = Benjamini-Hochberg adjusted P value; NES = normalized enrichment score; size = size of Reactome pathway; LeadingEdge = leading edge genes.

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A. IMPACC Network Consortium

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C. EARLI Consortium

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Conflict of interest: The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays, NDV-based SARS-CoV-2 vaccines influenza virus vaccines, and influenza virus therapeutics which list FK as coinventor and he has received royalty payments from some of these patents, US Patents 20250228929A1, 20250186578A1, and 20250041402A1. Mount Sinai has spun out a company, Kantaro, to market serological tests for SARS-CoV-2 and another company, Castlevax, to develop SARS-CoV-2 vaccines, and FK is cofounder and scientific advisory board member. FK has consulted for Merck, GSK, Sanofi, Curevac, Seqirus, and Pfizer and is currently consulting for 3rd Rock Ventures, Gritstone and Avimex, as well as collaborating with Dynavax on influenza vaccine development and with VIR on influenza virus therapeutics. OL is a named inventor on US patents 12268739 and 11730810 held by Boston Children's Hospital relating to vaccine adjuvants and human in vitro platforms that model vaccine action. His laboratory has received research support from GlaxoSmithKline (GSK), where he is a consultant. He is also a cofounder of and advisor to ARMR Sciences. CBC serves as a consultant to bioMerieux and is funded for a grant from Bill & Melinda Gates Foundation. JAO is a consultant at Knocean Inc. JLS serves as a scientific advisor of Precion Inc. SRH, GM, and KW are employees of Metabolon Inc. VSM is a current employee of MyOwnMed. NR reports grants or contracts with Merck, Sanofi, Pfizer, Vaccine Company, Quidel, Lilly, and Immorna and has participated on data safety monitoring boards for Moderna, Sanofi, Seqirus, Pfizer, EMMES, ICON, BARDA, Imunon, CyanVac, and Micron. NR has also received support for meetings/travel from Sanofi and Moderna and honoraria from Virology Education.