# **Evaluation of Plasma Proteome and MiRNA Changes Related to COVID-19 Patient Severity Response**

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# Abstract

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The severity outcome of COVID-19 resulting from SARS-CoV-2 infection has been shown to be related to underlying health conditions like diabetes and cancer. There remains an urgent need to gain mechanistic insights at the molecular level to understand factors that influence severity of the infection and discover early biomarkers that enable prediction of severity among COVID-19 patients. These insights could help ease the burden of care and aid in evaluation and development of treatments. In this study, COVID-19-positive patients were categorized into 3 symptom response categories using a 12-point patient response scoring system: mild (score 0-1), moderate (score 2-4), and severe (score 5-12). Blood samples from 93 COVID-19 patients collected at the time of initial diagnoses were processed to plasma and deidentified for proteomic and miRNA analyses. A total of 2,921 proteins and 2,083 miRNAs were analyzed in the plasma samples. Ingenuity Pathway Analysis (IPA) of significant proteins revealed that the top pathways were neutrophil degranulation, cytokine storm, role of osteoblasts in rheumatoid arthritis signaling, interleukin-10 signaling, and wound healing signaling in severe patients. Interleukin-6 (IL6) was involved in nine of the top ten IPA pathways. MicroRNA associations with protein targets were extracted from IPA using experimentally observed and highly predicted criteria. Proteomics and miRNA analyses of plasma from recently diagnosed COVID-19 patients revealed 801 protein and 365 miRNA biomarkers of severity response to COVID which are associated with preexisting health status and acute response to the COVID infection. Additional experiments are needed to validate the biomarkers.

# **Experimental Design**

Blood samples from 93 COVID-19 patients collected from August 2020 until July of 2022 were processed to plasma. The response to COVID was scored using a 12- point patient response scoring system described below and grouped into mild(0-1), moderate(2-4) and severe(5-12) responders depending on their score. Pooled QC samples were made prior to conducting proteomics and miRNA analysis and used to assess data quality. A total of 2,921 proteins were evaluated by OLINK and 2,083 miRNAs were analyzed by Firalis using HTG EdgeSeg technology. Univariate and multivariate analyses were conducted on the proteins and miRNAs. All the proteins were imported into Qiagen's web-based ingenuity pathway analysis (IPA) software. Core analysis of significantly (FC>1.5, p<0.05) altered proteins was performed to evaluate pathways enrichment using Fisher's exact test. Canonical pathways with -log10 p-value >1.3 were considered significantly enriched. IPA also calculates z-scores to predict the activation/inhibition of pathways based on fold changes of altered proteins. Z-score > 2 or z-score < -2 indicate predicted activation or inhibition of pathways, respectively. Information about miRNA and their target proteins was also obtained from IPA using miRNA target filter tool. This information also includes the source and confidence (experimental, highly-predicted or moderately-predicted) in miRNA-protein target relationship. The miRNA target protein relationships were compared with correlation analysis of significant miRNAs and proteins.

### Patient Response Scoring:

- 2 points for hospital admission within 60 days of enrollment;
- 3 points for ICU admission within 60 days of enrollment;
- 1 point for mild symptoms: cough, fever, diarrhea, vomiting, headache, loss of taste or smell, sore throat, myalgias, fatigue, lymphadenopathy, and malaise;
- 2 points for symptoms: shortness of breath (dyspnea), wheezing, SpO2<92% on room air, respiratory rate (RR)>30, and new non-invasive oxygen requirement.
- 2 points for symptoms: invasive or positive-pressure oxygen requirement, acute kidney injury (Cr >1.5x upper limit normal for age or estimated glomerular filtration rate [eGFR] <60), elevated aspartate/alanine transaminase ((AST/ALT); ratio >2x normal), new elevation international normalized ratio (INR) >1.3, and altered mental status;
- 3 points for symptoms: acute respiratory distress syndrome (ARDS), shock requiring pressors, renal failure with dialysis, extracorporeal membrane oxygenation (ECMO) requirement, organ transplant, pulmonary embolism, deep venous thrombosis, and/or stroke.

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	Severity					
	Mild	Moderate	Severe	<sup>1</sup> P-value	<sup>2</sup> P-value	<sup>3</sup> P-value
Ν	33	28	32			
Scoring	0.79 ± 0.42	2.82 ± 0.98	8.50 ± 2.24	4.88E-12	1.89E-19	1.41E-16
Age	39.3 ± 14.3	44.6 ± 14.4	52.2 ± 19.0	1.55E-01	3.20E-03	8.58E-02
Female	15 (45.5%)	16 (57.1%)	16 (50.0%)	3.63E-01	7.14E-01	5.80E-01
Black	4 (12.1%)	10 (35.7%)	22 (68.8%)	3.65E-02	3.27E-06	1.05E-02
White	13 (39.4%)	9 (32.1%)	9 (28.1%)	5.57E-01	3.37E-01	7.35E-01
Other Race	0	2 (7.1%)	1 (3.1%)	2.07E-01	4.92E-01	5.94E-01
Race unknown	16 (48.5%)	7 (25.0%)	0	5.93E-02	2.73E-06	3.10E-03
Diabetic	4/13 (30.8%)	5/15 (33.3%)	11/27 (40.7%)	1.00E+00	7.30E-01	6.36E-01
Hypertension	6/13 (46.2%)	10/16 (62.5%)	20/27 (74.1%)	3.79E-01	8.29E-02	4.24E-01
Cardiovascular						
diseases	3/13 (23.1%)	8/16 (50.0%)	10/27 (37.0%)	2.49E-01	4.84E-01	4.05E-01
Chronic renal						
disease	1/13 (7.7%)	0/14	7/27 (25.9%)	4.82E-01	2.36E-01	7.45E-02
Severe obesity	3/12 (25.0%)	8/16 (50.0%)	11/27 (40.7%)	2.53E-01	4.77E-01	5.55E-01
disease Severe obesity	3/12 (25.0%)	0/14 8/16 (50.0%)	11/27 (25.9%) 11/27 (40.7%)	4.82E-01 2.53E-01	4.77E-01	7.45E-02 5.55E-01



Figure 1. Volcano plots of proteins in severe vs mild (A); severe vs moderate (B); moderate vs mild (C). Volcano Plots of miRNA in severe vs mild (D); severe vs moderate (E); moderate vs mild (F). Significant changes (FC> 1.5 (proteins) FC> 2.0 (miRNAs), p-value <0.05) in red, non-significant changes in green.

### Table 2: Top 10 IPA Canonical Pathways

Ingenuity Canonical Pathways	Severe vs Mild -log (p- value)	Severe vs Mild z-score	Severe vs Moderate -log (p- value)	Severe vs Moderate z-score	Moderate vs Mild -log (p- value)	Modera e vs Mil z-score
Neutrophil degranulation	24.5	7.14	22.1	6.66	0	NA
Pathogen Induced Cytokine Storm Signaling Pathway	15.2	4.72	14.6	3.45	2.41	2.26
Regulation of Insulin-like Growth Factor (IGF) transport	13.3	3.00	14	2.99	2.29	NA
Post-translational protein phosphorylation	12.9	2.71	13.2	2.68	2.47	NA
Interleukin-10 signaling	11.7	3.36	8.85	2.71	0.93	NA
Role of Chondrocytes in Rheumatoid Arthritis Signaling	11.1	3.67	9.09	2.83	1.23	NA
Airway Pathology in Chronic Obstructive Pulmonary Disease	11.1	2.65	9.45	2.24	0.55	NA
Interleukin-4 and Interleukin-13 signaling	10.8	3.58	11.9	2.83	1.42	NA
Role of Osteoblasts in Rheumatoid Arthritis Signaling	10.7	3.29	7.38	1.79	2.31	1
Wound Healing Signaling Pathway	10.4	3.77	13.1	3.16	0.80	NA

**Caption/legend:** All the proteins are significantly (fold change > 1.5; p-value<0.05) altered between severe vs. mild response group. Information about miRNA targeting proteins and proteins' pathway enrichments were obtained pathways with z-score >2.0 B) Top 40 miRNAs with experimental from Qiagen's Ingenuity Pathway Analysis software. observed or highly predicted confidence to mRNA of proteins in **Canonical Pathways Key: A**, Neutrophil degranulation; **B**, Pathogen Induced Cytokine Storm Signaling Pathway; **C**, the top 10 Canonical pathways. Blue to red show the changes of Regulation of Insulin-like Growth Factor (IGF) transport and uptake by IGFBPs; **D**, Post-translational protein phosphorylation; E, Interleukin-10 signaling; F, Airway Pathology in Chronic Obstructive Pulmonary Disease; G the protein or miRNAs in severe vs mild, severe vs moderate and Role of Chondrocytes in Rheumatoid Arthritis Signaling Pathway; H, Interleukin-4 and Interleukin-13 signaling; I moderate vs mild. Role of Osteoblasts in Rheumatoid Arthritis Signaling Pathway; J, Wound Healing Signaling Pathway.

## Conclusion

- severe vs mild.
- moderate.
- highly predicted (not shown) and these miRNA-proteins could be biomarkers of COVID-19 response severity.
- 19 studies, and most of those studies did not have both proteomics and miR profiling. The study findings warrants further investigation in a larger study.







### Table 3: Correlation Between MiRNA and their **Experimentally Observed Target Significant Proteins**

Protein         Minus         Centralion Coefficient         Option of Protein         Per Protein           CRIM1         miR_20a_5p         -0.637         8.38E-12         Per Protein           INPRSF106         miR_30d_5p         -0.637         8.38E-12            INNE2         miR_30d_5p         -0.598         3.10E-11         B           ADAMTS1         miR_144_3p         -0.558         7.45E-09         B; G; J           GSF1         miR_130a_3p         -0.550         1.32E-08         H; B; G; I; J           CD40         miR_145_5p         -0.532         4.90E-08         H; B; G; I; J           CD40         miR_145_5p         -0.520         7.42E-08         H; B; G; I; J           CD47         miR_145_5p         -0.520         1.06E-07         B; G; J           JUN         miR_16_5p         -0.520         3.45E-07         B; G; J           ARID4B         miR_20a_5p         -0.474         1.36E-06         A           VE6FA         miR_145_5p         -0.474         1.31E-06         H; B; G; I; J           JUN         miR_165_5p         -0.474         1.31E-06         H; B; G; I; J           S00A12         miR_145_5p         -0.471         2.15E-06	Protoin		Doarson	Correlation P-Value	Top 10 Canonical Pathways
Coefficient         FF F Volum           CRIM1         miR_20a_5p         -0.637         8.88E-12           INFRSF10B         miR_30d_5p         -0.624         3.10E-11         B           ADAMTS1         miR_125a_5p         -0.598         3.15E-10         A           ADAMTS1         miR_130a_3p         -0.558         7.45E-09         B; G; J           CSF1         miR_135_5p         -0.532         4.87F-08         H; B; G; LJ           CDa0         miR_146a_5p         -0.532         4.87F-08         H; B; G; LJ           CDa0         miR_145a_5p         -0.526         7.42E-08         H; B; G; LJ           CDa0         miR_145a_5p         -0.520         1.06E-07         B; G; J           CDA         miR_145_5p         -0.502         3.45E-07         A           JUN         miR_16_5p         -0.476         1.62E-06         A           CCN2         miR_146a_5p         -0.471         2.15E-06         A           VE6FA         miR_20a_5p         -0.471         2.15E-06         A           SUDA12         miR_146a_5p         -0.471         2.15E-06         A           VE6FA         miR_20a_5p         -0.471         2.15E-06         J	FIOLEIII		Correlation		Por Protoin
CRIM1         miR_20a_5p         0.637         8.88E-12           TNFRSF10B         miR_30d_5p         0.624         3.10E-11         B           LMNB2         miR_30d_5p         0.598         3.15E-10         B           ADAMTS1         miR_125a_5p         0.583         1.04E-09         B; G; J           JUN         miR_144_3p         0.558         7.45E-09         B; G; J           CSF1         miR_185_5p         0.532         4.87E-08         H; B; G; I; J           C040         miR_146a_5p         -0.532         4.87E-08         H; B; G; I; J           C040         miR_145a_5p         -0.526         7.42E-08         H; B; G; I; J           ART19         miR_165_5p         -0.521         1.04E-07         J           JUN         miR_165_5p         -0.522         3.45E-07         B; G; J           CD274         miR_146_5p         -0.478         1.41E-06         CN2           S100A12         miR_146_5p         -0.474         1.86E-06         A           VE6FA         miR_20a_5p         -0.471         2.15E-06         J           S100A12         miR_146_5p         -0.471         2.15E-06         J           S100A12         miR_146_5p			Coefficient		
NUMPLOCUP         OLSA         OLSA           INFRESTION         mill 30d 5p         -0.624         3.10E-11         B           INNB2         mill 30d 5p         -0.598         3.15E-10         ADAMTS1         mill 125a_5p         -0.583         1.04E-09           JUN         mill 125a_5p         -0.550         1.32E-08         E; 0; C           VEGFA         mill 130a_3p         -0.550         1.32E-08         E; 0; C           VEGFA         mill 146a_5p         -0.532         4.87E-08         H; B; G; I; J           C040         mill 146a_5p         -0.526         7.42E-08         ACTA2           ARID4B         mill 215a_5p         -0.520         1.06E-07         B; G; J           JUN         mill 125_5p         -0.520         1.06E-07         B; G; J           CD274         mill 20a_5p         -0.478         1.41E-06         I           CN2         mill 146a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         mill 146a_5p         -0.471         2.15E-06         J           SWAP70         mill 146a_5p         -0.471         2.15E-06         J           JUN         mill 30d 5p         -0.471         2.15E-06         J	CRIM1	miR 20a 5n	-0 637	8 88F-12	
INTRS/105         milk_300_5p         -0.524         5.10E-11         B           ADAMTS1         miR_300_5p         -0.598         3.15E-10           ADAMTS1         miR_125a_5p         -0.583         1.04E-09           JUN         miR_130a_3p         -0.550         1.32E-08         E; D; C           VE6FA         miR_185_5p         -0.532         4.49E-08         E; D; C           VE6FA         miR_146a_5p         -0.524         4.90E-08         E; D; C           CD40         miR_146a_5p         -0.520         1.04E-07         J           JUN         miR_15_5p         -0.520         1.06E-07         B; G; J           QU274         miR_16_5p         -0.520         1.06E-07         B; G; J           QU274         miR_145_5p         -0.670         B; G; J         G           VE6FA         miR_120a_5p         -0.478         1.41E-06         G           S100A12         miR_146a_5p         -0.471         1.86E-06         A           VE6FA         miR_20a_5p         -0.471         2.15E-06         B; G; J           JUN         miR_30d_5p         -0.471         2.16E-06         J           GP837         miR_146a_5p         -0.472		mit_20d_5p	0.037	0.00E 12	D
Dimode         milling_300_pp         0.0356         3.11210           ADAMTS1         miR_125a_5p         -0.583         1.04E-09           JUN         miR_144_3p         -0.555         7.45E-09         B; G; J           CSF1         miR_130a_3p         -0.558         7.45E-09         B; G; J           CSF1         miR_146a_5p         -0.532         4.87E-08         H; B; G; I; J           CD40         miR_145a_5p         -0.532         4.90E-08         A           ARID48         miR_145a_5p         -0.530         5.37E-08         A           ARID48         miR_125_a5p         -0.520         7.42E-08         A           ACTA2         miR_125_p         -0.520         1.06E-07         B; G; J           JUN         miR_145_5p         -0.520         3.45E-07         A           ARID48         miR_20a_5p         -0.478         1.41E-06         A           CCN2         miR_145_5p         -0.471         1.96E-06         A           VEGFA         miR_20a_5p         -0.471         2.15E-06         B; G; J           JUN         miR_30d_5p         -0.471         2.16E-06         J           GPR37         miR_20a_5p         -0.452		mIR_300_5p	-0.624	3.10E-11 2.155 10	В
ADAMTS1         miR_125a_5p         -0.583         1.04E-09           JUN         miR_144_3p         -0.550         7.45E-09         B; G; J           CSF1         miR_130a_3p         -0.550         1.32E-08         E; D; C           VEGFA         miR_135_5p         -0.532         4.87E-08         H; B; G; I; J           CD40         miR_146a_5p         -0.532         4.90E-08		IIIIK_30u_3p	-0.558	5.131-10	
JUN         miR_144_3p         -0.558         7.45E-09         B; G; J           CSF1         miR_130a_3p         -0.550         1.32E-08         E; D; C           VEGFA         miR_135_5p         -0.532         4.87E-08         H; B; G; I; J           CD40         miR_146a_5p         -0.532         4.90E-08	ADAMTS1	miR_125a_5p	-0.583	1.04E-09	
CSF1         miR 120a 3p         -0.550         1.32E-08         E; D; C           VEGFA         miR 185_5p         -0.532         4.87E-08         H; B; G; I; J           CD40         miR 146a_5p         -0.532         4.90E-08         -           ARID4B         miR_486_5p         -0.530         5.37E-08         -           ARID4B         miR_125a_5p         -0.526         7.42E-08         -           ARTA2         miR_115_5p         -0.520         1.04E-07         J           JUN         miR_16_5p         -0.520         1.06E-07         B; G; J           CD274         miR_145_5p         -0.478         1.41E-06         -           CN12         miR_146a_5p         -0.478         1.62E-06         A           S100A12         miR_146a_5p         -0.471         1.86E-06         A           VE6FA         miR_20a_5p         -0.471         2.15E-06         B; G; J           SWAP70         miR_145_5p         -0.471         2.15E-06         B; G; J           JUN         miR_20a_5p         -0.452         6.00E-06         H; B; G; H; J           MMP3         miR_20a_5p         -0.452         6.00E-06         H; G; I           MMP3	JUN	miR_144_3p	-0.558	7.45E-09	B; G; J
VE6FA         miR 185_5p         -0.532         4.87E-08         H; B; G; I; J           CD40         miR_146a_5p         -0.532         4.90E-08         -           ARID4B         miR_146a_5p         -0.530         5.37E-08         -           ARID4B         miR_215a_5p         -0.526         7.42E-08         -           ACTA2         miR_215p         -0.521         1.04E-07         J           JUN         miR_145_5p         -0.520         1.06E-07         B; G; J           CD274         miR_145_5p         -0.521         1.04E-07         J           ARID4B         miR_20a_5p         -0.478         1.41E-06         -           CN2         miR_145_5p         -0.476         1.62E-06         A           VE6FA         miR_20a_5p         -0.471         2.15E-06         H; B; G; I; J           SWAP70         miR_145_5p         -0.471         2.15E-06         B; G; J           JUN         miR_20a_5p         -0.422         6.00E-06         F; E; H; B; G; I; J           MAP2K1         miR_16_5p         -0.432         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J	CSF1	miR_130a_3p	-0.550	1.32E-08	E; D; C
Cb40         miR_146a_5p         -0.532         4.90E-08           ARID4B         miR_486_5p         -0.530         5.37E-08           KRT19         miR_125a_5p         -0.526         7.42E-08           ACTA2         miR_16_5p         -0.520         1.06E-07         B; G; J           JUN         miR_16_5p         -0.520         1.06E-07         B; G; J           CD274         miR_145_5p         -0.502         3.45E-07         Arrows           ARID4B         miR_20a_5p         -0.478         1.41E-06         CN2           CN2         miR_145_5p         -0.476         1.62E-06         A           S100A12         miR_146a_5p         -0.471         1.91E-06         H; B; G; I; J           SWAP70         miR_145_5p         -0.471         2.15E-06         B; G; J           JUN         miR_30d_5p         -0.471         2.16E-06         J           GPR37         miR_20a_5p         -0.452         6.00E-06         H; G; I           MMP3         miR_20a_5p         -0.452         6.00E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.432         1.70E-05         F; E; H; B; D; C; G; I; J           MMP3         miR_20a_5p         -0.432	VEGFA	miR_185_5p	-0.532	4.87E-08	H; B; G; I; J
ARID4B         miR_486_5p         -0.530         5.37E-08           KRT19         miR_125a_5p         -0.526         7.42E-08           ACTA2         miR_21_5p         -0.520         1.04E-07         J           JUN         miR_16_5p         -0.520         3.45E-07         B; G; J           ARID4B         miR_20_5p         -0.672         3.45E-07         B; G; J           ARID4B         miR_20a_5p         -0.478         1.41E-06         CCN2           miR_146a_5p         -0.476         1.62E-06         A           S100A12         miR_146a_5p         -0.471         1.86E-06         A           VEGFA         miR_20a_5p         -0.471         2.15E-06         B; G; J           SWAP70         miR_16_5p         -0.471         2.15E-06         J           MA22K1         miR_16_5p         -0.471         2.15E-06         J           GPR37         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           MMP3         miR_30d_5p         -0.452	CD40	miR_146a_5p	-0.532	4.90E-08	
KRT19         miR_125a_5p         -0.526         7.42E-08           ACTA2         miR_21_5p         0.521         1.04E-07         J           JUN         miR_165p         0.520         1.06E-07         B; G; J           CD274         miR_1455p         0.502         3.45E-07         B; G; J           ARID4B         miR_20a_5p         0.0478         1.41E-06         CCN2           MiR_19b_3p         0.0476         1.62E-06         A           S100A12         miR_146a_5p         0.0471         1.86E-06         A           VEGFA         miR_20a_5p         0.0471         2.15E-06         B; G; J           SWAP70         miR_16_5p         0.0471         2.15E-06         J           JUN         miR_30d_5p         -0.471         2.15E-06         J           GPR37         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP2         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           MMP3         miR_30d_5p         <	ARID4B	miR_486_5p	-0.530	5.37E-08	
ACTA2         miR_21_5p         -0.521         1.04E-07         J           JUN         miR_16_5p         -0.520         1.06E-07         B; G; J           CD274         miR_145_5p         -0.502         3.45E-07         B; G; J           ARID4B         miR_20a_5p         -0.478         1.41E-06            S100A12         miR_146a_5p         -0.474         1.86E-06         A           VEGFA         miR_20a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         miR_145_5p         -0.471         2.15E-06         J           JUN         miR_30d_5p         -0.471         2.15E-06         J           MAP2K1         miR_16_5p         -0.471         2.15E-06         J           GPR37         miR_20a_5p         -0.471         2.15E-06         J           MMP3         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           TNFAIP2         miR_30d_5p         -0.432         1.70E-05            CCN2         miR_30d_5p         -0.432         1.70E-05             CKL8         miR_191_5p         -0.426         2.35E-05         F; E; H; B; C; I; J <tr< th=""><th>KRT19</th><th>miR_125a_5p</th><th>-0.526</th><th>7.42E-08</th><th></th></tr<>	KRT19	miR_125a_5p	-0.526	7.42E-08	
JUN         miR 16 5p         -0.520         1.06E-07         B; G; J           CD274         miR_145 5p         -0.502         3.45E-07	ACTA2	miR_21_5p	-0.521	1.04E-07	J
CD274         miR_145_5p         -0.502         3.45E-07           ARID4B         miR_20a_5p         -0.478         1.41E-06           CCN2         miR_19b_3p         -0.476         1.62E-06           S100A12         miR_146a_5p         -0.474         1.86E-06         A           VEGFA         miR_20a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         miR_30d_5p         -0.471         2.15E-06         B; G; J           JUN         miR_30d_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_16_5p         -0.471         2.15E-06         J           GPR37         miR_20a_5p         -0.471         2.15E-06         J           MMP3         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00F-06         H; G; I           MMP3         miR_20a_5p         -0.432         1.70E-05         CCN2           CN2         miR_30d_5p         -0.432         1.70E-05         F; E; H; B; G; I; J           IL6         miR_146a_5p         -0.432         1.70E-05         F; E; H; B; D; C; G; I; J           CN2         miR_30d_5p	JUN	miR_16_5p	-0.520	1.06E-07	B; G; J
ARID4B         miR_20a_5p         -0.478         1.41E-06           CCN2         miR_19b_3p         -0.476         1.62E-06         A           S100A12         miR_146a_5p         -0.474         1.86E-06         A           VEGFA         miR_20a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         miR_30d_5p         -0.471         2.15E-06         B; G; J           JUN         miR_30d_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_16_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_20a_5p         -0.471         2.16E-06         J           GPR37         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.452         1.02E-05         CCN2           MiR_30d_5p         -0.432         1.70E-05         F; E; H; B; G; I; J           IL6         miR_146a_5p         -0.432         1.70E-05         F; E; H; B; G; I; J           IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; G; I; J           VIM <th>CD274</th> <th>miR_145_5p</th> <th>-0.502</th> <th>3.45E-07</th> <th></th>	CD274	miR_145_5p	-0.502	3.45E-07	
CCN2         miR_19b_3p         -0.476         1.62E-06           S100A12         miR_146a_5p         -0.474         1.86E-06         A           VEGFA         miR_20a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         miR_145_5p         -0.471         2.15E-06         H; B; G; I; J           JUN         miR_30d_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_16_5p         -0.471         2.16E-06         J           GPR37         miR_20a_5p         -0.462         3.60E-06         J           CXL8         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.452         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.432         1.70E-05         H           CCN2         miR_30d_5p         -0.432         1.70E-05         F           CXC18         miR_146a_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           IL6         miR_20a_5p         -0.417         3.60E-05         H; J           VIM	ARID4B	miR_20a_5p	-0.478	1.41E-06	
S100A12         miR_146a_5p         -0.474         1.86E-06         A           VEGFA         miR_20a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         miR_145_5p         -0.471         2.15E-06         H; B; G; I; J           JUN         miR_30d_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_16_5p         -0.471         2.16E-06         J           GPR37         miR_20a_5p         -0.462         3.60E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.00E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.432         1.07E-05         Incertee           CCN2         miR_30d_5p         -0.432         1.70E-05         F; E; H; B; G; I; J           IL6         miR_146a_5p         -0.417         3.52E-05         F; E; H; B; G; I; J           CL6         miR_30d_5p         -0.417         3.60E-05         H; J           UMN81         miR_23a_3p         -0.416         3.77E-05         Incertee           VIM         miR_145_5p         -0.413         4.22E-05	CCN2	miR_19b_3p	-0.476	1.62E-06	
VEGFA         miR_20a_5p         -0.473         1.91E-06         H; B; G; I; J           SWAP70         miR_145_5p         -0.471         2.15E-06	S100A12	miR_146a_5p	-0.474	1.86E-06	A
SWAP70         miR_145_5p         -0.471         2.15E-06           JUN         miR_30d_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_16_5p         -0.471         2.16E-06         J           GPR37         miR_29c_3p         -0.462         3.60E-06         J           CXCL8         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           MMP3         miR_30d_5p         -0.439         1.22E-05         I           CCN2         miR_30d_5p         -0.432         1.70E-05         I           KRT19         let_7e_5p         -0.432         1.70E-05         F; E; H; B; G; I; J           IL6         miR_146a_5p         -0.443         1.85E-05         F; E; H; B; G; I; J           CDCP1         miR_30d_5p         -0.417         3.52E-05         F; E; H; B; D; C; G; I; J           VIM         miR_23a_3p         -0.413         4.21E-05         I           PMS1         miR_16_5p         -0.413         4.21E-05         I           PMIM         miR_122_5p         -0.413         4.22E-05         I           PALM	VEGFA	miR_20a_5p	-0.473	1.91E-06	H; B; G; I; J
JUN         miR_30d_5p         -0.471         2.15E-06         B; G; J           MAP2K1         miR_16_5p         -0.471         2.16E-06         J           GPR37         miR_29c_3p         -0.462         3.60E-06         J           CXCL8         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.439         1.22E-05         -           CCN2         miR_30d_5p         -0.432         1.70E-05         -           KRT19         let_7e_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_146a_5p         -0.430         1.85E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.52E-05         F; E; H; B; D; C; G; I; J           IL6         miR_120_3p         -0.416         3.77E-05         -           VIM         miR_20a_5p         -0.413         4.21E-05         -           PMS1         miR_145_5p         -0.413         4.22E-05         -           PALM         miR_139_5p         0.405         6.12E-05         -	SWAP70	miR_145_5p	-0.471	2.15E-06	
MAP2K1         miR_16_5p         -0.471         2.16E-06         J           GPR37         miR_29c_3p         -0.462         3.60E-06         J           CXCL8         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           MMP3         miR_30d_5p         -0.432         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.439         1.22E-05         CCN2           CCN2         miR_30d_5p         -0.432         1.70E-05         F; E; H; B; G; I; J           KRT19         let_7e_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_146a_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.60E-05         H; J           LMNB1         miR_23a_3p         -0.416         3.77E-05         Figure II (IIII)           PMS1         miR_16_5p         -0.413         4.22E-05         Common II (IIIIII)           AHNAK         miR_122_5p         -0.413         4.22E-05         IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	JUN	miR_30d_5p	-0.471	2.15E-06	B; G; J
GPR37         miR_29c_3p         -0.462         3.60E-06         F           CXCL8         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.439         1.22E-05         -           CCN2         miR_30d_5p         -0.434         1.56E-05         -           KRT19         let_7e_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.50E-05         H; J           UMN81         miR_23a_3p         -0.417         3.60E-05         H; J           LMN81         miR_145_5p         -0.413         4.21E-05         -           PMS1         miR_145_5p         -0.413         4.22E-05         -           AHNAK         miR_139_5p         0.405         6.12E-05         -           PALIM         miR_139_5p         0.405         6.12E-05         -           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           PGL2111<	MAP2K1	miR_16_5p	-0.471	2.16E-06	J
CXCL8         miR_20a_5p         -0.452         6.00E-06         F; E; H; B; G; I; J           MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.439         1.22E-05	GPR37	miR_29c_3p	-0.462	3.60E-06	
MMP3         miR_20a_5p         -0.452         6.07E-06         H; G; I           TNFAIP2         miR_30d_5p         -0.439         1.22E-05	CXCL8	miR_20a_5p	-0.452	6.00E-06	F; E; H; B; G; I; J
TNFAIP2         miR_30d_5p         -0.439         1.22E-05           CCN2         miR_30d_5p         -0.434         1.56E-05           KRT19         let_7e_5p         -0.432         1.70E-05           CXCL8         miR_146a_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.60E-05         H; J           VIM         miR_23a_3p         -0.416         3.77E-05         H; J           PMS1         miR_145_5p         -0.413         4.21E-05         -0.417           AHNAK         miR_145_5p         -0.413         4.21E-05         -0.417           PMS1         miR_145_5p         -0.413         4.21E-05         -0.413           AHNAK         miR_145_5p         -0.413         4.21E-05         -0.413           PALM         miR_139_5p         0.405         6.12E-05         -0.413           PALM         miR_146a_5p         -0.402         7.14E-05         A           PGLYRP1         miR_146a_5p         -0.400         7.94E-05         A	MMP3	miR_20a_5p	-0.452	6.07E-06	H; G; I
CCN2         miR_30d_5p         -0.434         1.56E-05           KRT19         let_7e_5p         -0.432         1.70E-05           CXCL8         miR_146a_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.52E-05         H; J           VIM         miR_20a_5p         -0.417         3.60E-05         H; J           VIM         miR_23a_3p         -0.416         3.77E-05         H; J           PMS1         miR_16_5p         -0.413         4.21E-05         H           PALM         miR_122_5p         -0.412         4.47E-05         H           PALM         miR_139_5p         0.405         6.12E-05         A           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           PGL2L11         miR_92b_3p         -0.400         7.94E-05         A	TNFAIP2	miR_30d_5p	-0.439	1.22E-05	
KRT19         let_7e_5p         -0.432         1.70E-05           CXCL8         miR_146a_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.52E-05         F; E; H; B; D; C; G; I; J           VIM         miR_20a_5p         -0.417         3.60E-05         H; J           LMNB1         miR_23a_3p         -0.416         3.77E-05         H; J           PMS1         miR_16_5p         -0.413         4.21E-05         -           PALM         miR_122_5p         -0.412         4.47E-05         -           PALM         miR_139_5p         0.405         6.12E-05         -           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           PGL2L11         miR_92b_3p         -0.400         7.94E-05         -	CCN2	miR_30d_5p	-0.434	1.56E-05	
CXCL8         miR_146a_5p         -0.430         1.85E-05         F; E; H; B; G; I; J           IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.52E-05         F; E; H; B; D; C; G; I; J           VIM         miR_20a_5p         -0.417         3.60E-05         H; J           LMNB1         miR_23a_3p         -0.416         3.77E-05         H; J           PMS1         miR_16_5p         -0.413         4.21E-05            AHNAK         miR_145_5p         -0.413         4.22E-05            PALM         miR_139_5p         0.405         6.12E-05            PALM         miR_139_5p         0.405         A.47E-05            PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           BCL2L11         miR_92b_3p         -0.400         7.94E-05         A	KRT19	let_7e_5p	-0.432	1.70E-05	
IL6         miR_191_5p         -0.426         2.35E-05         F; E; H; B; D; C; G; I; J           CDCP1         miR_30d_5p         -0.417         3.52E-05         F; E; H; B; D; C; G; I; J           VIM         miR_20a_5p         -0.417         3.60E-05         H; J           LMNB1         miR_23a_3p         -0.416         3.77E-05         H; J           PMS1         miR_16_5p         -0.413         4.21E-05         F           AHNAK         miR_145_5p         -0.413         4.22E-05         F           PALM         miR_122_5p         -0.412         4.47E-05         F           PALM         miR_139_5p         0.405         6.12E-05         A           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A	CXCL8	miR_146a_5p	-0.430	1.85E-05	F; E; H; B; G; I; J
CDCP1         miR_30d_5p         -0.417         3.52E-05           VIM         miR_20a_5p         -0.417         3.60E-05         H; J           LMNB1         miR_23a_3p         -0.416         3.77E-05         H           PMS1         miR_16_5p         -0.413         4.21E-05         H           AHNAK         miR_145_5p         -0.413         4.22E-05         Immediate           PALM         miR_122_5p         -0.412         4.47E-05         Immediate           AMOT         miR_139_5p         0.405         6.12E-05         Immediate           PGLYRP1         miR_146a_5p         -0.400         7.14E-05         A	IL6	miR_191_5p	-0.426	2.35E-05	F; E; H; B; D; C; G; I; J
VIM         miR_20a_5p         -0.417         3.60E-05         H; J           LMNB1         miR_23a_3p         -0.416         3.77E-05         -           PMS1         miR_16_5p         -0.413         4.21E-05         -           AHNAK         miR_145_5p         -0.413         4.22E-05         -           PALM         miR_122_5p         -0.412         4.47E-05         -           AMOT         miR_139_5p         0.405         6.12E-05         -           PGLYRP1         miR_146a_5p         -0.400         7.14E-05         A	CDCP1	miR_30d_5p	-0.417	3.52E-05	
LMNB1       miR_23a_3p       -0.416       3.77E-05         PMS1       miR_16_5p       -0.413       4.21E-05         AHNAK       miR_145_5p       -0.413       4.22E-05         PALM       miR_122_5p       -0.412       4.47E-05         AMOT       miR_139_5p       0.405       6.12E-05         PGLYRP1       miR_146a_5p       -0.402       7.14E-05       A         BCL2L11       miR_92b_3p       -0.400       7.94E-05       A	VIM	miR_20a_5p	-0.417	3.60E-05	H; J
PMS1       miR_16_5p       -0.413       4.21E-05         AHNAK       miR_145_5p       -0.413       4.22E-05         PALM       miR_122_5p       -0.412       4.47E-05         AMOT       miR_139_5p       0.405       6.12E-05         PGLYRP1       miR_146a_5p       -0.402       7.14E-05       A         BCL2L11       miR_92b_3p       0.400       7.94E-05       A	LMNB1	miR_23a_3p	-0.416	3.77E-05	
AHNAK         miR_145_5p         -0.413         4.22E-05           PALM         miR_122_5p         -0.412         4.47E-05           AMOT         miR_139_5p         0.405         6.12E-05           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           BCL2L11         miR_92b_3p         -0.400         7.94E-05         A	PMS1	miR_16_5p	-0.413	4.21E-05	
PALM         miR_122_5p         -0.412         4.47E-05           AMOT         miR_139_5p         0.405         6.12E-05           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           BCL2L11         miR_92b_3p         -0.400         7.94E-05         A	AHNAK	miR_145_5p	-0.413	4.22E-05	
AMOT         miR_139_5p         0.405         6.12E-05           PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           BCL2L11         miR_92b_3p         -0.400         7.94E-05         A	PALM	miR_122_5p	-0.412	4.47E-05	
PGLYRP1         miR_146a_5p         -0.402         7.14E-05         A           BCL2L11         miR_92b_3p         -0.400         7.94E-05         A	AMOT	miR_139_5p	0.405	6.12E-05	
BCL2L11 miR_92b_3p -0.400 7.94E-05	PGLYRP1	miR_146a_5p	-0.402	7.14E-05	A
	BCL2L11	miR_92b_3p	-0.400	7.94E-05	

Black race was significant patient demographic determining severity for all three response groups and age is significant in

Many miRNAs were decreased in severe vs mild and conversely more proteins were increased in severe vs mild. The top two IPA canonical pathways are neutrophil degranulation and cytokine storm in severe vs mild and severe vs

IL6 was involved in 9 of the top 10 IPA canonical pathways and miR 146a 5p was observed in 8 of the top 10 canonical pathways and has been experimentally observed to interact with two proteins in the neutrophil degranulation pathway. Significant correlation of miRNAs with proteins was found in the IPA miRNA confidence with experimental observed or • Many of the protein and miRNA severity response biomarkers reported in the study are consistent with previous COVID-