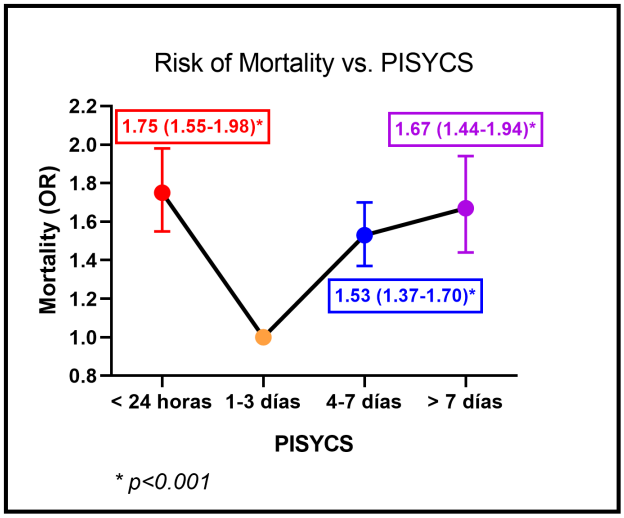
Session: P-20. COVID-19 Pathogenesis

Background. Until now, studies have been focused on patient-centered risk factors, while SARS-CoV-2 aggressiveness has been established as causing 20% of severe and critical patients. However, there are still many unanswered questions concerning the clinical aggressiveness behavior of SARS-CoV-2. This study focuses on progression of symptoms as a marker of such aggressiveness, using the Period between initial symptoms and clinical progression to COVID-19 suspicion (PISYCS) to determine the risk of severe disease and mortality.

Methods. Historic cohort study of Mexican patients. Data from January-April 2020 were provided by the Health Ministry. Setting: Population-based. Patients registered in the Epidemiologic Surveillance System in Mexico. Participants were subjects who sought medical attention for clinical suspicion of COVID-19. All patients were subjected to RT-PCR testing for SARS-CoV-2. We measured the Period between initial symptoms and clinical progression to COVID-19 suspicion (PISYCS) and compared it to the primary outcomes (mortality and pneumonia)

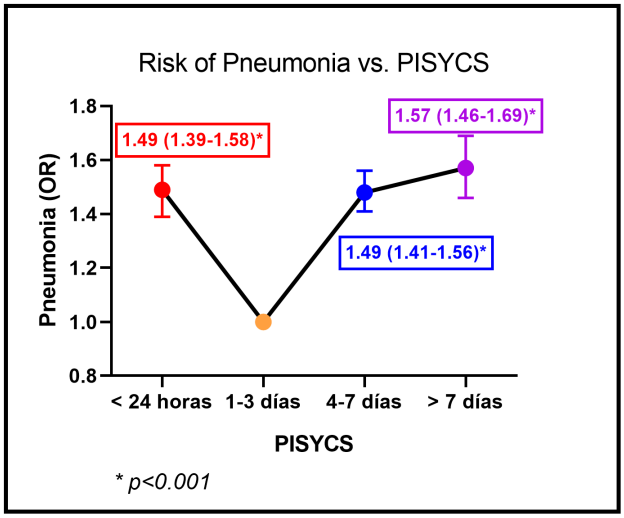
Results. 65,500 patients were included. Reported fatalities and pneumonia were 2176 (3.32%), and 11568 (17.66%), respectively. According to the PISYCS, patients were distributed as follows: 14.89% in < 24 hours, 43.25% between 1–3 days, 31.87% between 4–7 days and 9.97% > 7 days. The distribution for mortality and pneumonia was 5.2% and 22.5% in < 24 hours, 2.5% and 14% between 1–3 days, 3.6% and 19.5% between 4–7 days, 4.1% and 20.6% > 7 days, respectively (p< 0.001). Adjusted-risk of mortality was (OR [95% CI], p-value): < 24 hours = 1.75 [1.55–1.98], p< 0.001; 1–3 days = 1 (reference value); 4–7 days = 1.53 [1.37–1.70], p< 0.001; > 7 days = 1.67 [1.44–1.94], p< 0.001. For pneumonia: < 24 hours = 1.49 [1.39–1.58], p< 0.001; 1–3 days = 1; 4–7 days = 1.48 [1.41–1.56], p< 0.001; > 7 days = 1.57 [1.46–1.69], p< 0.001.

Risk of Mortality vs. PISYCS



Logistic regression anlaysis of mortality based on PISYCS. Note that risk of mortality is significantly higher when PISYCS is > 24 hours and < 7 days

Risk of Pneumonia vs. PISYCS



Logistic regression anlaysis of developing pneumonia based on PISYCS. Note that risk of pneumonia is significantly higher when PISYCS is > 24 hours and < 7 days.

Conclusion. The PISYCS shows a U-shaped SARS-CoV-2 aggressiveness pattern. Further studies are needed to corroborate the time-related pathophysiology behind these findings and possibly justify use of PISYCS as an initial evaluation tool and therapies/monitoring in high-risk patients.

Disclosures. **All Authors**: No reported disclosures

437. Longitudinal Plasma Cytokine Profiles Differentiating COVID-19 Severity Groups

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Session: P-20. COVID-19 Pathogenesis

Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), an infection with widely varying clinical severity. Severe COVID-19 was initially proposed to be secondary to cytokine storm syndrome (CSS). However, studies since showed that patients with severe COVID-19 rarely display CSS cytokine phenotypes, and may have more limited inflammatory responses instead.

Methods. Prospective cohorts, aged 0-90 years of age who tested positive by polymerase chain reaction (PCR) for SARS-CoV-2 were enrolled from inpatient hospitals and outpatient testing centers in Memphis, TN from May 2020-January 2021. Longitudinal blood samples were obtained including acute, sub-acute and convalescent timepoints. Severity scores of asymptomatic, mild, moderate, and severe COVID-19 were assigned at time of convalescent assessment. Plasma was analyzed with a quantitative human magnetic 38-plex cytokine assay.

Results. : 169 participants were enrolled, including 8 asymptomatic, 117 mild, 22 moderate and 17 severe cases, and 5 children with post-COVID-19 multisystem inflammatory syndrome in children (MIS-C). All moderate and severe patients were hospitalized and received treatment (39%). Clear distinctions were seen between asymptomatic-mild cases and moderate-severe cases at acute timepoints and during disease progression for GCSF, IL-8, IL-10, IL-15, IL-1Ra, IP-10, MIP-1a, MIP-1β, and TGFα. There was a significant difference between participants who did and did not require hospitalization for acute timepoint levels of IL-10, IL-15, MIP-1 β and TGFα (p< 0.01). Only 4 participants with active COVID-19 were found to meet criteria for CSS (2%), only 3 of which were severe. MIS-C participants showed nearly universally elevated cytokine levels compared to those with active COVID-19.

Temporal and severity associations of IL-10 and IP-10

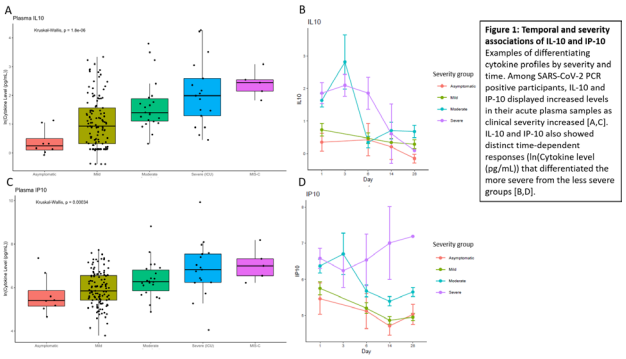

Figure 1. Temporal and severity associations of IL-10 and IP-10 Examples of differentiating cytokine profiles by severity and time. Among SARS-CoV-2 PCR positive participants, IL-10 and IP-10 displayed increased levels in their acute plasma samples as clinical severity increased [A,C]. IL-10 and IP-10 also showed distinct time-dependent responses (ln(Cytokine level (pg/mL)) that differentiated the more severe from the less severe groups [B,D].

Conclusion. Moderate and severe acute COVID-19 has a distinct cytokine profile from asymptomatic and mild cases, as detected from acute, subacute and convalescent plasma.

Disclosures. **Joshua Wolf, MBBS, PhD, FRACP**, **Karius Inc.** (Research Grant or Support) **Joshua Wolf, MBBS, PhD, FRACP**, Nothing to disclose **Paul Thomas, PhD**, **Cytoagents** (Consultant)**Immunoscape** (Consultant)

438. Phenotypic Differences Between Distinct Immune Biomarker Clusters During the 'Hyperinflammatory' Middle-Phase of COVID-19

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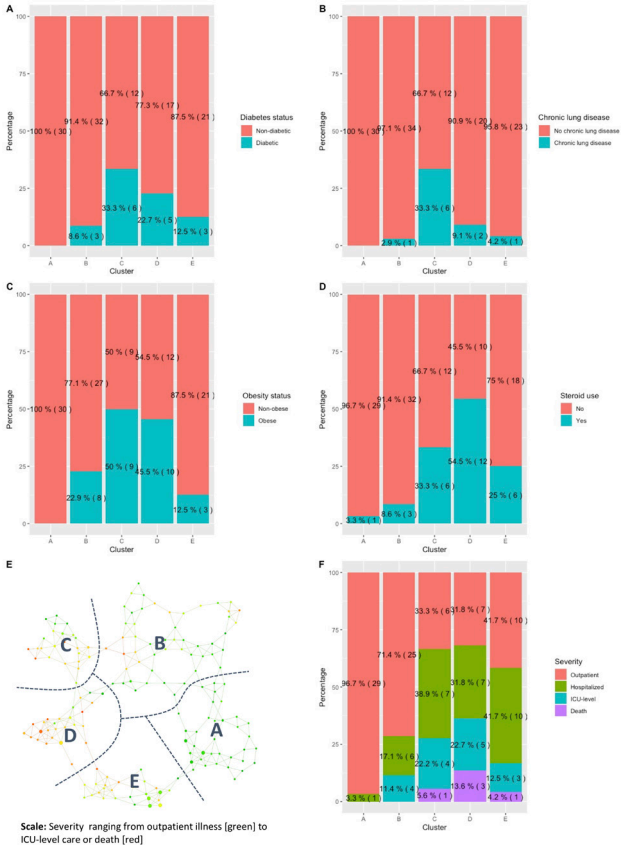
EPICC COVID-19 Cohort Study Group

Session: P-20. COVID-19 Pathogenesis

Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections peak during an inflammatory 'middle' phase and lead to severe illness predominately among those with certain comorbid noncommunicable diseases (NCDs). We used network machine learning to identify inflammation biomarker patterns associated with COVID-19 among those with NCDs.

Methods. SARS-CoV-2 RT-PCR positive subjects who had specimens available within 15-28 days post-symptom onset were selected from the DoD/USU EPICC COVID-19 cohort study. Plasma levels of 15 inflammation protein biomarkers were measured using a broad dynamic range immunoassay on samples collected from individuals with COVID-19 at 8 military hospitals across the United States. A network machine learning algorithm, topological data analysis (TDA), was performed using results from the 'hyperinflammatory' middle phase. Backward selection stepwise logistic regression was used to identify analytes associated with each cluster. NCDs with a significant association (0.05 significance level) across clusters using Fisher's exact test were further evaluated comparing the NCD frequency in each cluster against all other clusters using a Kruskal-Wallis test. A sensitivity analysis excluding mild disease was also performed.

Results. The analysis population (n=129, 33.3% female, median 41.3 years of age) included 77 ambulatory, 31 inpatient, 16 ICU-level, and 5 fatal cases. TDA identified 5 unique clusters (Figure 1). Stepwise regression with a Bonferroni-corrected cutoff adjusted for severity identified representative analytes for each cluster (Table 1). The frequency of diabetes (p=0.01), obesity (p< 0.001), and chronic pulmonary disease (p< 0.001) differed among clusters. When restricting to hospitalized patients, obesity (8 of 11), chronic pulmonary disease (6 of 11), and diabetes (6 of 11) were more prevalent in cluster C than all other clusters.



Cluster differences in comorbid diseases and severity by cluster. 1A: bar plot of diabetes prevalence; 1B: bar plot of chronic lung disease ; 1C: bar plot of obesity prevalence; 1D: prevalence of steroid treatment ; 1E: Topologic data analysis network with clusters labeled; 1F: Bar plot of ordinal levels of severity.

Table 1. Multivariable logistic regression models for clusters and immune biomarkers. Models were fitted comparing each cluster against all other clusters.

Cluster	Covariates in unadjusted model*	OR** (95% CI)	AIC	Covariates in severity-adjusted*** model	OR (95% CI)	AIC
A			82.9			95.2
	VEGFA	0.02 (0.003, 0.2)		CRP	0.2 (0.08, 0.5)	
	RAGE	650.1 (9.6, 44016.7)		Severity	0.03 (0.003, 0.3)	
	IL6	0.02 (0.002, 0.1)				
B			92.3			91.2
	Ferritin	0.02 (0.004, 0.10)		Ferritin	0.03 (0.006, 0.1)	
	ICAM1	519.6 (37.6, 7176.3)		ICAM1	1676.1 (68.9, 40760.0)	
				Severity	0.4 (0.2, 1.2)	
C			74.5			76.4
	IL5	0.08 (0.02, 0.4)		IL5	0.08 (0.02, 0.4)	
	IL1RA	53.7 (8.9, 324.3)		IL1RA	59.2 (8.3, 422.6)	
				Severity	0.9 (0.5, 1.9)	
D			111.0			108.6
	VEGFA	8.8 (2.5, 31.7)		Severity	2.3 (1.4, 3.8)	
E			83.7			82.1
	Ferritin	111.1 (12.5, 986.9)		Ferritin	75.9 (6.9, 837.9)	
	ICAM1	0.0008 (0.00002, 0.03)		ICAM1	0.0006 (0.00001, 0.02)	
	RAGE	203.8 (6.1, 6785.0)		RAGE	242.6 (6.9, 8588.6)	
				Severity	1.4 (0.5, 3.4)	

AIC: Akaike information criterion, CRP: c-reactive protein.

*IL6ra and LCN2 removed due to collinearity with ICAM1

**Estimates are in $\log_{10}$ pg/ml scale.

***Severity on an ordinal scale with outpatient-level= 0, inpatient-level=1, ICU-level care =2, death =3

Conclusion. Machine learning clustering methods are promising analytical tools for identifying inflammation marker patterns associated with baseline risk factors and severe illness due to COVID-19. These approaches may offer new insights for COVID19 prognosis, therapy, and prevention.

Disclosures. **Simon Pollett, MBBS**, **Astra Zeneca** (Other Financial or Material Support, HJF, in support of USU IDCRP, funded under a CRADA to augment the conduct of an unrelated Phase III COVID-19 vaccine trial sponsored by AstraZeneca as part of USG response (unrelated work))

439. Corowa-kun: Impact of a COVID-19 Vaccine Information Chatbot on Vaccine Hesitancy, Japan 2021

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Session: P-21. COVID-19 Research

Background. Japan has one of the highest vaccine hesitancy rates in the world. According to a previous study, less than 30% of people strongly agreed that vaccines were safe, important, or effective. We created a COVID-19 vaccine information chatbot in a popular messenger app in Japan to answer COVID-19 vaccine frequently asked questions (FAQs) via text messages. We assessed the impact of chatbot text messages on COVID-19 vaccine hesitancy by conducting a cross-sectional survey among chatbot users.

Methods. LINE is the most popular messenger app in Japan; about 86 million people in Japan (roughly two-thirds of the population) use this messenger app. Corowa-kun, a free chatbot, was created in LINE on February 6, 2021. Corowa-kun provides instant, automated answers to frequently asked COVID-19 vaccine questions. A cross-sectional survey assessing COVID-19 vaccine hesitancy was conducted via Corowa-kun during April 5 to 12, 2021. We included persons ages 16 years old and older who had not received a COVID-19 vaccine. The survey was written in Japanese and consisted of 21 questions.

Corowa-kun's Consultation Room