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# **Early biomarkers in SARS-CoV-2 infection**

Correlation with short/medium/long-term clinical outcomes, and implications on acute patient management and long-term medical and health care (COVID19F06)

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## STUDY DESIGN

Biomarkers at early hospitalization





#### Microbial:

- Viral subgenomic RNAs
- Nasopharyngeal microbiome

#### Cytokines

#### Metabolomics

Clinical outcomes during hospitalization



#### WHO classification:

- Mild / moderate / severe / critical / death
- O<sub>2</sub> supplement, intensive care, complications, .....

Late outcomes (up to 45 months)



#### **Questionnaire-based:**

- Depression
- Anxiety
- Post-traumatic stress disorder
- Cognitive function
- Somatic symptoms
- Fatigue



**99** 

Correlation with infectious viruses in clinical samples ?

Viral Activity Infectivity

<ul> <li>Culture +Ve specimens</li> <li>High viral load (low Ct)</li> <li>Full-set subgenomic PCR +Ve</li> </ul>	0.1	Ct 16 16 16 17 18 21 21	S	Rela sul 3a	ativ bge E	re co enor M	onc mic 6	entr RN 7a	atic A (2 7b	on o 2 <sup>4Ct</sup> 8	f ) N	culture Pos
<ul> <li>Culture -Ve specimens</li> <li>Moderate viral load (Ct)</li> <li>Full-set subgenomic PCR +Ve</li> </ul>	Genomic N Ct	18         21         21         21         22         24         25         26         26         26         27										Neg
<ul> <li>Culture -Ve specimens</li> <li>Low viral load (high Ct)</li> <li>Full-set subgenomic PCR -Ve</li> </ul>		29 29 30 30 30 32 32 36	X		× ×		X	× × ×	× × × × × ×	X X X X	X X	



#### Profile of each subgenomic RNA in associate with Crude viral load, viral variant, age, gender, time from onset, severity





#### Profile of each subgenomic RNA in associate with Crude viral load, viral variant, age, gender, time from onset, severity

Ct value

Viral variant



# **Subgenomic RNAs:**

Correlates with viral activity

Α

- But by itself **NOT** a good predictor of clinical outcome
- Useful in determining infectiousness & triage isolation
- Assess response to antiviral treatment
- Switching of treatment strategy •







- Novel immunosuppressive cytokine / myokine / adipokine
- Secreted by activate macrophages / mucosa / skin / adipose tissue
- Inhibitory potential in metabolic diseases, cardiac vascular diseases, infectious diseases







### METRN-β on admission: Distinguish non-survivors from survivors





7 cytokines / chemokines with levels measured at both the early & late phases **increased** progressively with severity



from onset

from onset

4 cytokines / chemokines with levels measured at both the early & late phases decreased progressively with severity



#### Heat map: Correlation between cytokines measured at the early & late phases with severity



ROC of cytokines measured at the early & late phases to discriminate severe / critical from mild / moderate patients



IL-8, followed by IP-10 and MDC were the best performing early biomarkers to predict disease severity

#### Association of cytokine levels at **ICU admission** with clinical endpoints

# Among critically ill patients, MCP-1 predicted

- Duration of mechanical ventilation
- Dose of norepinephrine
- Length of ICU stay



## METABOLOMIC BIOMARKERS

# <sup>1</sup>H-NMR metabolomics:

- Early plasma samples
- 170 metabolites quantified
- Lipoproteins, lipids, &
- Low-molecular-weight metabolites including amino acids, ketone bodies, glycolysis-related metabolites and glycoprotein acetyls (GlycA), fatty acids





Severe : severe pneumonia (SaO<sub>2</sub><90%), critical and fatal Non-severe : asymptomatic, mild and moderate pneumonia

## Metabolomic Biomarkers

**65** metabolites  $\rightarrow$  strong association with severity

Majority 54 (83.1%) **downregulated** in severe disease (Z score: -3.30—8.61)

### 3 metabolites → highest specificity

- Creatinine (specificity: 0.94)
- Phospholipids in large VLDL (0.94)
- Triglycerides-to-total lipids ratio in large VLDL (0.93)

# 3 metabolites → highest sensitivity for severe disease:

- Triglycerides in medium HDL (sensitivity: 0.94)
- Free cholesterol-to-total lipids ratio in very small VLDL (0.93)
- Cholesteryl esters-to-total lipids ratio in chylomicrons and extremely large VLDL (0.92)

HDL: high-density lipoprotein VLDL: very-low-density lipoprotein

## METABOLOMIC BIOMARKERS

### ROC plots of **sensitivity** and **specificity** on disease severity

#### 1.00 0.75 sensitivity 0.50 0.83 (0.75-0.91) ApoA1: 0.82 (0.74-0.90) Α% 0.25 Glucose: 0.84 (0.76-0.92) Albumin: 0.92 (0.87-0.97) S.HDL.L: 0.89 (0.83-0.95) 0.00 0.75 0.50 0.25 0.00 1.00 specificity

Representative metabolites from 5 subclasses

#### ApoA1: apolipoprotein A1 LA.%: ratio of linoleic acid to total fatty acids S.HDL.L: total lipids in small HDL

#### Five cytokines with highest AUC



## LATE OUTCOMES

Prevalence of a moderate degree of symptoms according to time after onset of COVID-19



# LATE OUTCOMES





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CK Wong



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