COVID-19 Natural History of Severe Disease

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Central questions in severe COVID-19

Modern critical care involves supporting failing organs to allow for recovery.

Therapy also targets specific pathogens and the non-specific inflammatory response (steroids).

Can we better understand the natural history of severe COVID-19?
State and Phase

Insult

Hyper-inflammation

ICU

ICU

ICU

Persistent inflammation

Late comorbidities

Recovery

Persistent Immunosuppression

Late Death

MODS Early Death

Hotchkiss et al Nat Rev Dis Primers 2016
Does baseline severity of COVID-19 respiratory failure predict outcomes?

Summary of ventilator data of 260 patients admitted to WCM with respiratory failure treated with mechanical ventilation

Schenck et al Ann Am Thorac Soc 2020
## Day 1 Comparisons

### Ventilator Parameters by Status, Day 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deceased, N = 90</th>
<th>Discharged, N = 170</th>
<th>p-value</th>
<th>q-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO2 Arterial</td>
<td>46 (38, 52)</td>
<td>44 (38, 52)</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>PO2 Arterial</td>
<td>92 (75, 121)</td>
<td>93 (74, 130)</td>
<td>&gt;0.9</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Minute Volume Exhaled</td>
<td>9.80 (8.33, 11.80)</td>
<td>9.30 (8.15, 11.35)</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>PEEP</td>
<td>10.0 (9.0, 12.0)</td>
<td>10.0 (8.5, 12.0)</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>450 (400, 500)</td>
<td>450 (400, 500)</td>
<td>0.8</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Peak Inspiratory Pressure</td>
<td>31.0 (25.0, 35.0)</td>
<td>30.0 (26.0, 34.8)</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Plateau Pressure</td>
<td>26.0 (22.0, 30.0)</td>
<td>24.5 (21.0, 28.0)</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>PF Ratio</td>
<td>105 (84, 137)</td>
<td>117 (86, 160)</td>
<td>0.086</td>
<td>0.5</td>
</tr>
<tr>
<td>Tidal Volume / PBW</td>
<td>6.92 (6.24, 7.70)</td>
<td>7.06 (6.36, 8.31)</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Static Compliance</td>
<td>28 (23, 36)</td>
<td>29 (22, 40)</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Driving Pressure</td>
<td>15.0 (12.0, 18.2)</td>
<td>14.0 (11.0, 16.5)</td>
<td>0.065</td>
<td>0.5</td>
</tr>
<tr>
<td>Ventilatory Ratio</td>
<td>1.93 (1.51, 2.32)</td>
<td>1.80 (1.47, 2.30)</td>
<td>0.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Non-pulmonary severe COVID-19

Intubation → ARDS (26.3%)

Myocardial infarction (4.7%)

Stroke (2.3%)

Thromboembolic events (7%)

Renal failure (7%)

Merkler et al JAMA Neurology 2020
Goyal et al Ann Intern Med 2020
Goyal et al NEJM 2020
Gupta et al JAMA Intern Med 2020
Additive organ dysfunction predicts poor outcomes

Gupta et al JAMA Intern Med 2020
Organ Failure Subphenotyping

SOFA

0-24

Su et al medrxiv 2020
Organ dysfunction trajectory

Status

- SOFA 0–7
- SOFA 8–10
- SOFA 11–12
- SOFA 13–24
- Death

Baseline 8h 24h 48h 72h

Zampieri et al AJRCCM 2019
Two staged evaluation of organ dysfunction trajectory

Data preprocessing

- NYP-WCM: Development
- NYP-LMH: Validation
- SOFA trajectory derivation

Intubated
Time

Two-stage subphenotyping

Stage 1: Baseline grouping
- Mild group
- Intermediate group
- Severe group

Stage 2: SOFA trajectory clustering
- Trajectory similarity calculation
- Patient similarity matrix

Hierarchical clustering

Subphenotypes

Su et al medrxiv 2020
SOFA based grouping by number of failing organs

**Mild**
- N=76

**Intermediate**
- N=116

**Severe**
- N=126

Su et al medrxiv 2020
There are distinct worsening and recovering subphenotypes

A NYP-WCM cohort

Mild group (Baseline SOFA 0-10)

Intermediate group (Baseline SOFA 11-12)

Severe group (Baseline SOFA 13-24)
Trajectory predicts outcomes

A NYP-WCM cohort

Mild group

Intermediate group

Severe group

Proportion of patients

Day post-intubation

Su et al medrxiv 2020
Summary and questions

Pulmonary and non-pulmonary organ dysfunction is important in COVID-19 critical illness.

Additive non-improving organ failure drives outcomes.

Are there specific treatments for pulmonary and non-pulmonary organ dysfunction in COVID-19 to prevent progression?

Can we identify and modulate dynamic COVID-19 inflammatory states in real time?