COVID as a Natural Resilience Experiment: The COVID-19 Virus (and Vaccine) as Stressor

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Disclosures

• Nothing to disclose
Outline

• Magnitude of COVID-19 as health stressor
• COVID-19 patient case report and population data
• How COVID-19 fits in resilience conceptual models
• Papers related to COVID-19 and resilience
• Knowledge Gaps
• Research opportunities
COVID-19

A RAMPAGE THROUGH THE BODY

An invader’s impact
In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body’s response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

1 Lungs
A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.

2 Heart and blood vessels
The virus (teal) enters cells, likely including those lining blood vessels, by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.

3 Brain
Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

4 Eyes
Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

5 Nose
Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose’s nerve endings and damage cells.

6 Liver
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

7 Kidneys
Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

8 Intestines
Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.
Patient Presentation

- 86 yr. old male rehabilitation facility resident
- Past medical history: diabetes mellitus with nephropathy and neuropathy, diabetic foot wound complicated by necrotizing fasciitis requiring left below knee amputation, atrial fibrillation, hypertension, mild cognitive impairment
- Independent basic ADLs, assistance IADLs
- 10 prescription medications; 5 prn
- Developed dry cough and nasal congestion
- Triggered COVID screening, PCR positive for SARS-CoV-2
- Exam: BP 120/64; P 90; R 18; T 97.6; O2 sat 95%; oriented, pleasant, conversant, normal heart and lung exams
- Symptoms resolved in 2 days; no change in functional status; discharged to community residence, living with sister
COVID-19 Cases, Hospital Admissions, Deaths per 100,000 Population Dec 12, 2020

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Cases</th>
<th>Hosp*</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-74</td>
<td>323</td>
<td>7.4</td>
<td>14.5</td>
</tr>
<tr>
<td>75+</td>
<td>366</td>
<td>17.4</td>
<td>58.0</td>
</tr>
</tbody>
</table>

*Hosp = new hospital admission; age 60-69 and 70+

[CDC COVID Data Tracker: Hospital Admissions](https://covid.cdc.gov/covid-data-tracker/#hospitaladmissions)
[CDC COVID Data Tracker: Case & Death Trends by Demographics](https://covid.cdc.gov/covid-data-tracker/#casestrendbydemographics)
Post-Acute COVID-19 Syndrome

### Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years
United States, March 2020–November 2021

<table>
<thead>
<tr>
<th>Age group, yrs</th>
<th>No. of patients (column %)</th>
<th>No. of patients with ≥1 incident condition (column %*)</th>
<th>Absolute risk difference†</th>
<th>No. of COVID-19 survivors with a post-COVID condition§</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–64</td>
<td>Case-patients 254,345 (72.0)</td>
<td>Case-patients 90,111 (35.4)</td>
<td>20.8</td>
<td>1/5</td>
</tr>
<tr>
<td></td>
<td>Control patients 1,051,588 (64.1)</td>
<td>Control patients 154,011 (14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>Case-patients 98,819 (28.0)</td>
<td>Case-patients 44,840 (45.4)</td>
<td>26.9</td>
<td>1/4</td>
</tr>
<tr>
<td></td>
<td>Control patients 589,188 (35.9)</td>
<td>Control patients 108,850 (18.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percentage of COVID-19 case-patients or control patients with ≥1 incident condition divided by the total study COVID-19 cohort or control cohort row’s age group total.
† Percentage point difference between COVID-19 case-patients and control patients (e.g., the value 20.8 is calculated as 35.4 minus 14.6).
§ Number of COVID-19 survivors who experienced a post-COVID condition estimated as the inverse of the absolute risk difference.
Resilience Conceptual Model
Johns Hopkins Pepper Center

Pre-Stressor and Post-Stressor Levels of Function in a Physiological System

Resilience Conceptual Model
Duke Pepper Center

## Examples of Stressors, Resilient Responses and Regulatory Factors*

<table>
<thead>
<tr>
<th>Stressor</th>
<th>Potential Adverse Consequences of Stressor</th>
<th>Resilient Clinical or Functional Response</th>
<th>Example Systems Influencing Level of Resilience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to Infectious Agent</td>
<td>- Septicemia</td>
<td>- Avoidance of infection</td>
<td>- Immune</td>
</tr>
<tr>
<td></td>
<td>- Restricted activity</td>
<td>- Rapid recovery from infection</td>
<td>- Pulmonary</td>
</tr>
<tr>
<td></td>
<td>- Accelerate lean body mass loss</td>
<td></td>
<td>- Genitourinary</td>
</tr>
<tr>
<td></td>
<td>- Mortality</td>
<td></td>
<td>- Dermatologic</td>
</tr>
</tbody>
</table>

Immunologic Resilience and COVID-19 Survival Advantage

Lee GC, Restrepo MI, Harper N. Immunological resilience and COVID-19 survival advantage
J Allergy and Immunology. 2021;148:1176-1191
### Selected Examples of Potential Influences of Biologic Aging-Related Mechanisms on Types of Resilience

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Type of Resilience Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell senescence</td>
<td>Immune responses, cancer chemotherapy tolerance, wound healing</td>
</tr>
<tr>
<td>Impaired stem/progenitor cell function</td>
<td>Resistance to infections, wound healing, cancer chemotherapy tolerance</td>
</tr>
<tr>
<td>Dysregulation of inflammatory factors</td>
<td>Infection resistance and recovery, wound healing, avoiding postsurgical MI, cancer chemotherapy intolerance</td>
</tr>
<tr>
<td>Inadequate DNA repair</td>
<td>Cancer chemotherapy tolerance</td>
</tr>
<tr>
<td>Impaired mitochondrial function</td>
<td>Ability to meet bioenergetic demands posed by stressors (eg, for averting falls, mounting febrile responses)</td>
</tr>
</tbody>
</table>

Geroscience and Immune Resilience: Acute and Long-Term Health

Animal Models in COVID Research

**nature**

**Article**

*Virus-induced senescence is a driver and therapeutic target in COVID-19*

**Science**

**CORONAVIRUS**

*Senolytics reduce coronavirus-related mortality in old mice*

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Knowledge Gaps

• Older patient and population level characteristics associated with a resilient response to acute and post-acute COVID-19
• Molecular and immunological mechanisms underlying reserve and resilience with aging to acute and post-acute COVID-19
• Optimal analytical approaches to address questions regarding resilience and COVID-19
• Factors and mechanisms underlying long-last immunity to COVID-19 vaccination in older adults
• Interventions at points before, during or after COVID-19 to augment reserve and resilience and improve health outcomes
Research Opportunities

• Observational studies (cohorts, database)
  – RECOVER: Researching COVID to Enhance Recovery
    [About the Initiative | RECOVER COVID](RECOVER COVID)
  – Homepage - COVID-19 Research Database (covid19researchdatabase.org)
  – [Open-Access Data and Computational Resources to Address COVID-19 | Data Science at NIH](Data Science at NIH) - NIH Office of Data Science Strategy

• Clinical research
  – Clinical measures (battery) of resilience before, during, and after infection
  – Geroscience based clinical trials
  – Enhancement of duration of vaccine efficacy

• Laboratory based research (cell, animal model, translational)
  – Immunological – mucosal immunity, innate and adaptive immune response with aging for infection and vaccine response
  – Mechanisms of SARS-CoV-2 cell entry and replication in older cells

• Computational and informatics methods (e.g., artificial intelligence) integrating emerging multi-modal data for COVID-19 diagnosis, prevention, and treatment in older adults.

• NOT-AG-21-016: Notice of Special Interest: Neurological and Neurocognitive Sequelae from SARS-CoV-2 Infection and COVID-19 in Aging and Age-Related Neurodegeneration