COVID-19 PATHOLOGIC FINDINGS FROM AUTOPSIES AND BEYOND

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I have no disclosures relevant to this talk

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COVID-19 FACTS

DIFFUSE ALVEOLAR DAMAGE
AND
ACUTE RESPIRATORY DISTRESS SYNDROME
ARDS is associated with increased risk of death in COVID-19.
## COVID-19: February 3, 2020

### United States

<table>
<thead>
<tr>
<th>Total cases</th>
<th>Recovered</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.5M (+114K)</td>
<td>-</td>
<td>447K (+3,406)</td>
</tr>
</tbody>
</table>

### Worldwide

<table>
<thead>
<tr>
<th>Total cases</th>
<th>Recovered</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>103M</td>
<td>57.3M</td>
<td>2.24M</td>
</tr>
</tbody>
</table>
Deaths in 1 year: COVID-19 vs. Cancer (US)

COVID-19: 281,000

Lung cancer: 142,081
Breast cancer: 42,466
Prostate cancer: 33,330
Melanoma: 6,850
Thyroid cancer: 2,180
Pathology of COVID-19

Xu: postmortem biopsy from 1 patient

Tian: lobectomies from 2 patients

COVID-19 GLOBAL DEATHS

>3000

New York Times video

>102,700

320,609

YouTube video: ARDS

Jan 2020 | Feb 2020 | March 2020 | April 2020 | May 2020

ARDS vs. DAD

**Acute Respiratory Distress Syndrome (ARDS)**

... is defined by clinical criteria

**Diffuse Alveolar Damage (DAD)**

... is defined by histologic criteria
ARDS

- Acute = onset within 1 week of a known clinical insult or new or worsening symptoms
- Respiratory failure not explained by heart failure or fluid overload
- Hypoxia (low oxygen levels)
- Bilateral lung opacities on chest imaging
What causes ARDS?

- Sepsis/Infection
- Shock
- Toxic inhalants
- Drug overdose
- Chemotherapy
- Toxic ingestants
- Aspiration
- Irradiation
- Pancreatitis
- Massive blood transfusion
- Major trauma
Courtesy of Mark Sabo, Cleveland Clinic
SARS-CoV-2 detected by IHC in upper airways and lungs but **NOT** in heart, liver, kidney
A. Alveolar space
B. Ciliated cells upper airway
C. Type 2 pneumocyte (virus and surfactant)
D. Membrane bound vacuole
E. Alveolar macrophage
F. Hyaline membrane
DAD, late phase

Normal
ARDS is the result of sudden, **severe injury to the lung** from any cause

When ARDS develops, **oxygen levels drop** and mechanical ventilation may be required to keep patients alive.
COVID-19 AUTOPSIES OK, USA

First published report of complete COVID-19 autopsies in the literature
COVID-19 Autopsies, Oklahoma, USA

Lisa M. Barton, MD, PhD,1 Eric J. Duval, DO,1 Edana Stroberg, DO,1 Subha Ghosh, MD,2 and Sanjay Mukhopadhyay, MD3,*

From the 1Office of the Chief Medical Examiner, Oklahoma City, OK; 2Section of Thoracic Imaging, Imaging Institute, Cleveland Clinic, Cleveland, OH; and 3Department of Pathology, Cleveland Clinic, Cleveland, OH.

Key Words: Coronavirus; COVID-19; SARS-CoV-2; Autopsy; Diffuse alveolar damage; Acute lung injury; Pulmonary pathology.

Am J Clin Pathol 2020;153(6):725-733. PMID 32275742

GLOBAL DEATHS

Jan 2020 | Feb 2020 | March 2020 | April 2020 | May 2020

>102,700 | 320,609

April 10: Barton et al First published report of complete autopsies

Impact

Cited by 458

COVID-19 Autopsies, Oklahoma, USA
Overview of attention for article published in American Journal of Clinical Pathology, April 2020

823

About this Attention Score
in the top 1% of all research outputs scored by Altmetric

One of the highest-scoring outputs from this source (#2 of 2,972)
High Attention Score compared to outputs of the same age (15th percentile)

OUTPUTS FROM AMERICAN JOURNAL OF CLINICAL PATHOLOGY
#10,567 of 16,752,553 outputs
#2 of 2,972 outputs

COVID-19: What the Autopsies Reveal

Study: Autopsies Can Help Determine If Patient Died From Or With COVID-19
Case 1: 77/M

H/o fever, chills x 6 days

H/o hypertension, remote splenectomy

Never tested for COVID-19 pre-mortem

Arrested en route to hospital

Inflammation in COVID-19

Interstitial inflammation: lymphocytes

Case 2: 42/M

H/o abdominal pain f/b respiratory symptoms ("CAP")

H/o myotonic dystrophy

Never tested for COVID-19 pre-mortem

Died after few hours in hospital
Acute bronchopneumonia due to aspiration

OTHER AUTOPSY STUDIES

DIFFUSE ALVEOLAR DAMAGE
ACUTE BRONCHOPNEUMONIA
THROMBOSIS
Menter: 21 cases

Wichmann: 12 cases

Lax: 11 cases

Jan 2020 | Feb 2020 | March 2020 | April 2020 | May 2020

DAD is very common in fatal COVID-19

DAD in 16 (acute) and 8 (org)

DAD in 8/12

DAD in 10/11
Bronchopneumonia in 6 patients, focal to confluent in COVID-19

Focal bronchopneumonia in 4/12

Bronchopneumonia diffuse in 6, focal in 4
Thrombosis is common in fatal COVID-19.
Thrombosis


Prostatic vein

Lung

DVT
Microthrombi in COVID-19

Image courtesy of Dr. Alexandar Tzankov and Dr. Sambit Mohanty

Immunostain for fibrin.

Image courtesy of Dr. Alexandar Tzankov

Menter T, et al.  
*Histopathology* 2020.  
PMID 32364264.
Microthrombi in glomerular capillaries
Thrombi in small pulmonary arteries are common in DAD

“Fibrin thrombi in various stages of organization are often present in small pulmonary arteries and they may be numerous. They are thought to occur secondary to endothelial damage”

Thromboemboli, were the most consistently observed vascular feature, present in 21 of 22 patients.

"Microthrombi, also present in 19 patients..."

Déjà vu

“Although microscopic thrombi within the pulmonary arterial system have been described in association with influenza and DAD, the number, size and peripheral location of the thrombi observed in our study may be unique to novel H1N1 influenza virus infection.”

What is your diagnosis?
Thrombi in H1N1 (2009)
(this is not COVID-19)
68 autopsies; Sept 2020

DAD = 87%

Acute inflammation = 43%

Large thrombi = 32%

Microthrombi = 65%
OBSERVATIONS

BEYOND AUTOPSIES

OBSERVATIONS
Endotracheal Tube Obstruction Among Patients Mechanically Ventilated for ARDS Due to COVID-19: A Case Series

Samuel Wiles, MD, Eduardo Mireles-Cabodevila, MD, Scott Neuhofer, RRT, MBA, Sanjay Mukhopadhyay, MD, Jordan P. Reynolds, MD, and Umur Hatioglu, MD, MBA

**Table 1**

Timeline of Major Events in Three Patients With Severe COVID-19

<table>
<thead>
<tr>
<th>Event</th>
<th>Case 1 (46 y/M)</th>
<th>Case 2 (57 y/F)</th>
<th>Case 3 (57 y/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for COVID-19 positive</td>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
</tr>
<tr>
<td>ECMO</td>
<td>Day 21</td>
<td>Day 12</td>
<td>Day 54</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Day 14</td>
<td>Day 5</td>
<td>Day 15</td>
</tr>
<tr>
<td>Pathology</td>
<td>Lung debridement on day 38, 5 weeks after positive test; autopsy on day 57</td>
<td>Open lung biopsy on day 74, 10 weeks after positive test</td>
<td>Bilateral lung transplantation on day 126, 4 months after positive test</td>
</tr>
<tr>
<td>Last follow-up or death</td>
<td>Died on day 57, 8 weeks after positive test</td>
<td>Died on day 74, 10 weeks after positive test</td>
<td>Alive, 7 months after positive test</td>
</tr>
</tbody>
</table>

*Day 1 in this table is the day of the first positive severe acute respiratory syndrome coronavirus 2 test.
Diffuse interstitial fibrosis

Day 126: bilateral lung transplant

Massive unilateral infarction + DAD

Day 38: debridement

Day 57: autopsy

Diffuse interstitial fibrosis

Day 74: surgical bx

Diffuse interstitial fibrosis

Day 126: bilateral lung transplant

Detection of SARS-CoV-2 in formalin-fixed paraffin-embedded tissue sections using commercially available reagents

Alejandro Best Rocha¹ · Edana Stroberg² · Lisa M. Barton² · Eric J. Duval² · Sanjay Mukhopadhyay³ · Nicole Yarid⁴ · Tiffany Caza¹ · Jon D. Wilson¹ · Daniel J. Kenan⁵ · Michael Kuperman¹ · Shree G. Sharma¹ · Christopher P. Larsen⁷
Sex differences in COVID-19 outcomes are independent of TMPRSS2

Sex, androgens and regulation of pulmonary AR, TMPRSS2 and ACE2

Mehdi Baratchian, Jeffrey M McManus, Mike Berk, Fumihiro Nakamura, Sanjay Mukhopadhyay, Weiling Xu, Serpil Erzurum, Judy Drazba, John Peterson, Eric A Klein, Ben Gaston, Nima Sharifi

PMID: 33083800  PMCID: PMC7574256  DOI: 10.1101/2020.04.21.051201

Abstract

The sex discordance in COVID-19 outcomes has been widely recognized, with males generally faring worse than females and a potential link to sex steroids. A plausible mechanism is androgen-induced expression of TMPRSS2 and/or ACE2 in pulmonary tissues that may increase susceptibility or severity in males. This hypothesis is the subject of several clinical trials of anti-androgen therapies around the world. Here, we investigated the sex-associated TMPRSS2 and ACE2 expression in human and mouse lungs and interrogated the possibility of pharmacologic modification of their expression with anti-androgens. We found no evidence for increased TMPRSS2 expression in the lungs of males compared to females in humans or mice. Furthermore, in male mice, treatment with the androgen receptor antagonist enzalutamide did not decrease pulmonary TMPRSS2. On the other hand, ACE2 and AR expression was sexually dimorphic and higher in males than females. ACE2 was moderately suppressible with enzalutamide therapy. Our work suggests that sex differences in COVID-19 outcomes attributable to viral entry are independent of TMPRSS2. Modest changes in ACE2 could account for some of the sex discordance.
FACT OR FICTION?

CONTROVERSIES
Myocarditis in COVID-19?

78% had abnormal cardiovascular MR findings (only 3 with pathology)

4/26 (15%) competitive athletes had CMR findings suggestive of myocarditis

Lymphocytic myocarditis in 14%
Interstitial macrophage infiltration in 86%
Non-occlusive fibrin microthrombi in microvasculature most (12/15)*

**Virus in endothelial cells?**

Endothelial cell infection and endothelitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.\(^1\)\(^2\) SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells.\(^1\)\(^2\) Further vascular derangements in COVID-19 are due to endothelial cell involvement by the virus as is currently unclear.

**Figure:** Pathology of endothelial cell dysfunction in COVID-19

(A, B) Electron microscopy of kidney tissue shows viral inclusions bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear in dense circular surface and lumen center. The asterisk in panel B marks peritubular space consistent with capillary containing viral particles. The inset in panel B shows the glomerular basement membrane with endothelial cell and a viral particle (arrow; about 150 nm in diameter). (C) Small bowel resection specimen of patient 3 stained with haematoxylin and eosin. Arrows point to dominant monomorphic cell infiltrates within the intima along the lumen of many vessels. The inset of panel C shows an immunohistochemical staining of capase 3 in small bowel specimens from serial sections of tissue described in panel D. Staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections, indicating that apoptosis is induced in a substantial proportion of these cells. (D) Post-mortem lung specimen stained with haematoxylin and eosin showed thickened lung septa, including a large arterial vessel with mononuclear and neutrophil infiltration (arrow in upper inset). The lower inset shows an immunohistochemical staining of capase 3 on the same lung specimen; these staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections. COVID-19-coronavirus disease 2019.


Misinterpretation of clathrin-coated vesicles as viral particles

Ultrasound Evidence for Direct Renal Infection with SARS-CoV-2

Evan A. Farkash, Allecia M. Wilson, and Jeffrey M. Jentzen
1Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan
2Washtenaw County Medical Examiner’s Office, Ann Arbor, Michigan


“4 times as large as SARS-CoV-2, not located within cell membranes, lack viral nucleocapsids, not within vesicles”
Cytokine storm?

Is a “Cytokine Storm” Relevant to COVID-19?

Pratik Sinha, MB, ChB, PhD; Michael A. Matthyay, MD; Carolyn S. Calfee, MD, MAS

Table. Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS

<table>
<thead>
<tr>
<th>COVID-19</th>
<th>Total population</th>
<th>IL-6 levels, pg/mL</th>
<th>Severe disease</th>
<th>IL-6 levels, pg/mL</th>
<th>Measurement platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al$^4$</td>
<td>191</td>
<td>7 (5-11)</td>
<td>54$^b$</td>
<td>11 (8-14)</td>
<td>CL</td>
</tr>
<tr>
<td>Wu et al$^1$</td>
<td>123</td>
<td>7 (6-9)</td>
<td>84$^c$</td>
<td>7 (6-11)</td>
<td>CL</td>
</tr>
<tr>
<td>Mo et al$^5$</td>
<td>155</td>
<td>45 (17-96)</td>
<td>85$^d$</td>
<td>64 (31-165)</td>
<td>CL</td>
</tr>
<tr>
<td>Qin et al$^2$</td>
<td>452</td>
<td>21 (6-47)</td>
<td>286$^e$</td>
<td>25 (10-55)</td>
<td>CL</td>
</tr>
<tr>
<td>Cummings et al$^6$</td>
<td>NR</td>
<td>NR</td>
<td>237$^f$</td>
<td>26 (11-69)</td>
<td>CL</td>
</tr>
</tbody>
</table>

| ARDS | Total population | Hypoinflammatory | 
|-------|------------------|-----------------|-----------------|
| ALVEOLI$^7$ | 521 | 238 (94-741)$^f$ | 386 | 154 (67-344) | 135 | 1525 (584-3802) | ELISA |
| FACTT$^8$ | 884 | 130 (46-411)$^f$ | 638 | 86 (34-216) | 246 | 578 (181-2621) | ELISA |
| SAILS$^9$ | 720 | 443 (173-1513)$^f$ | 451 | 282 (115-600) | 269 | 1618 (517-3205) | ELISA |

COVID-19 facts:
Lung involvement
Diffuse alveolar damage (DAD)
Bronchopneumonia
Thrombi

COVID-19 controversies:
Degree of extrapulmonary involvement
“Viral particles” in endothelium
“Cytokine storm”
Thank you for your attention