Summary of Major Literature Related to COVID-19 (Week of April 20-26)

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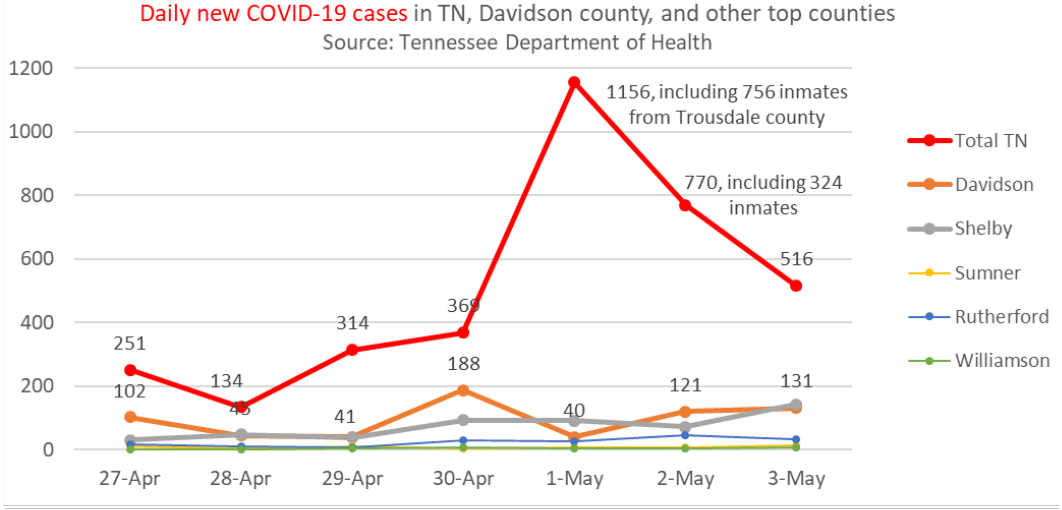
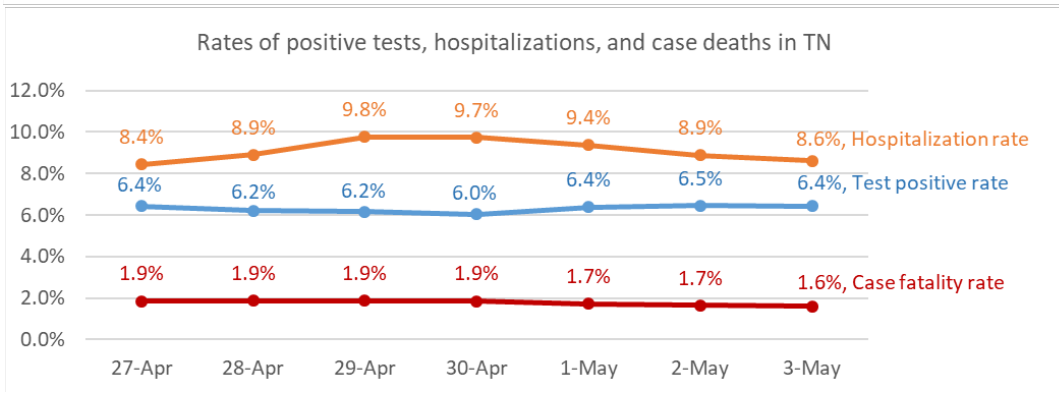
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS - Tennessee and Nashville





- No decreasing trend in daily new cases or test positive rate

- Total cases = 13,177
- Total tests = 204,607
- Top three counties:
  - Davidson = 2,904
  - Shelby = 2,815
  - Sumner = 653
- Demographics:

Groups	Cases	%
By sex		
Female	5,473	41.5%
Male	6,885	52.3%
By race/ethnicity		
White	5,227	39.7%
Black	2,630	20.0%
Hispanic	1,184	9.0%
Asian	295	2.2%
Other	840	6.4%
Pending	3,001	22.8%
By age		
0–10	274	2.1%
11–20	768	5.8%
21–30	2,615	19.8%
31–40	2,540	19.3%
41–50	2,350	17.8%
51–60	2,155	16.4%
61–70	1,302	9.9%
71–80	631	4.8%
80+	393	3.0%

EPIDEMIOLOGY

Impact of COVID-19 pandemic on health care

1. **Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy.** Ovidio De Filippo, et al. NEJM. April 28.

- Retrospective analysis of 547 consecutive patients admitted for acute coronary syndrome (ACS) at 15 cardiovascular centers in northern Italy from Feb 20-Mar 31, 2020
- A significant 26-30% decrease in the hospitalization rate of ACS was observed compared to both a corresponding period during the previous year (Feb 20-Mar 31, 2019) and an earlier period during the same year (Jan 1-Feb 19, 2020)
- Implications: Some patients have died from ACS without seeking medical attention during the Covid-19 pandemic; reported increase in overall mortality during this period is not fully explained by Covid-19

2. **Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy.** Baldi et al. NEJM. April 29.

- Data from the Lombardia Cardiac Arrest Registry showed that during the first 40 days of the Covid-19 outbreak (Feb 21-Mar 31, 2020) 362 cases of out-of-hospital cardiac arrests were identified

    - 58% increase in out-of-hospital cardiac arrest compared to the same period in 2019
- The sex and age of the patients were similar in the 2020 and 2019 periods
- The incidence of out-of-hospital cardiac arrest due to a medical cause was 6.5% higher, cardiac arrest at home was 7.3% higher, and unwitnessed cardiac arrest was 11.3% higher in 2020 than 2019
- The cumulative incidence of out-of-hospital cardiac arrest in 2020 was strongly associated with the cumulative incidence of Covid-19 (Spearman rank correlation coefficient, 0.87)
- Implication: 77% of the observed increase in out-of-hospital cardiac arrest was accounted for by known or suspected COVID-19

3. **Management of Lung Nodules and Lung Cancer Screening During the COVID-19 Pandemic: CHEST Expert Panel Report.** Mazzone et al. CHEST. April 23.

- A panel of 24 experts assessed the risks from potential exposure to COVID-19 and resource reallocation during the pandemic period, and developed a **consensus statement**:
- Delay baseline or repeat annual screening, and delay evaluation of pulmonary nodules detected incidentally or by screening that have a low probability of cancer (pCA) or are likely to be indolent
- For nodules with a pCA <25%, evaluation could be delayed for 3-6 months. When the pCA is 25% to 85%, evaluation with PET or non-surgical biopsy should occur, with subsequent referral for treatment when cancer is confirmed or more strongly suspected
- Patients with a very high pCA (>85%) do not require additional diagnostic testing and can proceed directly to a treatment decision
- Treatment of stage I NSCLC could be delayed in certain circumstances, guided by considerations such as the degree of hypermetabolism or growth rate of the tumor and patient fitness and preferences
- Conclusion: It is appropriate to defer enrollment in lung cancer screening and modify the evaluation of lung nodules due to the added risks from potential exposure and the need for resource reallocation

CLINICAL CHARACTERISTICS

4. **Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young.** Oxley et al. NEJM. April 28.

- A case series of 5 COVID-19 patients who were younger than 50 years of age (youngest age 33) and presented with new-onset symptoms of large-vessel ischaemic stroke
    - two had no fever, respiratory, or GI symptoms
- All 5 patients were seen over a 2-week period from March 23-April 7 at Mount Sinai Health System, NY
    - compared to average of 0.73 patients per 2-week period over the past 12 months
- Only 1 patient had a history of stroke, 2 delayed seeking emergency care because of fear of COVID-19
- Implication: Association between large-vessel stroke and COVID-19 in young patients requires further investigation, alongside evidence of coagulopathy and vascular endothelial dysfunction in COVID-19

5. **Clinical characteristics and outcomes of patients with severe covid-19 with diabetes.** Yan et al. BMJ Open Diab Res Care. 2020:8:e001343.

- Study of 193 severe hospitalized COVID-19 patients in a Wuhan hospital (respiratory rate >30/min, O2 saturation <94%, PaO2/FiO2<=300 mmHg, ventilation or admission to ICU)
    - 48 (25%) had diabetes
    - 110 (57%) received mechanical ventilation and 108 (56%) died
- Compared to patients without diabetes, patients with diabetes:
    - were older (70 vs 60 yrs), had higher frequency of ICU admission (67 vs 41%) and mechanical ventilation (81 vs 49%), and had higher mortality (81 vs 48%)
    - had more severe inflammatory response, characterized by elevated CRP, IL-2R, IL-6, IL-8, TNFα

- had higher white cell count, neutrophil count, D-dimer, lactic dehydrogenase, and NT-proBNP, and lower lymphocyte count
- Implication: After adjustment for age, sex and comorbidities, patients with diabetes had a significantly lower survival rate than non-diabetics

TESTING/TRANSMISSION

6. First Saliva Test for COVID-19 Approved for Emergency Use by FDA. The Scientist.

- The US FDA gave emergency use authorization on April 13 for a saliva-based test, providing an alternative to nasopharyngeal swab testing
  - test builds on the TaqPath SARS-CoV-2 Assay used in existing COVID-19 testing to identify virus RNA from the saliva samples
- FDA reported 100% positive and negative agreement between assay results obtained from testing of saliva and those obtained from nasopharyngeal swabs
- Per FDA instructions, saliva testing should be done under supervision in a healthcare setting
- Advantages of saliva testing: minimally invasive; does not tie up large amounts of PPE; can alleviate testing demands and swab shortages; decrease exposure for health care professionals

See also: **Saliva samples preferable to deep nasal swabs for testing COVID-19.** Wyllie et al. medRxiv preprint. April 22.

- A study conducted at Yale New Haven Hospital of 46 COVID-19 inpatients and 98 health care workers
- Saliva samples provided more sensitive and consistent detection compared with nasopharyngeal swabs

7. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Liu Y et al. Nature. April 27.

- The airborne SARS-CoV-2 and its aerosol deposition at 30 sites and public areas in two designated hospitals were sampled; virus copy counts were quantified using a robust ddPCR method
- Concentration of SARS-CoV-2 RNA in aerosols was very low in isolation wards and ventilated patient rooms but elevated in patient toilet areas
- Levels of airborne SARS-CoV-2 RNA in most public areas were undetectable except in two areas prone to crowding
- Some medical staff areas initially had high concentrations of viral RNA, but these levels were reduced to undetectable levels after implementation of rigorous sanitization procedures
- Unclear if recovered virus is infectious
- Implication: SARS-CoV-2 may have the potential to be transmitted via aerosols. Room ventilation, open space, sanitization of protective apparel, and proper disinfection can effectively limit the concentration of SARS-CoV-2 RNA in aerosols.

TREATMENT/EMERGING DRUG TARGETS

8. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Wang et al. Lancet. April 29.

- 237 patients were enrolled and randomly assigned to a treatment group (158 remdesivir, 79 placebo)
- Eligible patients had RT-PCR confirmed diagnosis, PNA on chest CT, O2 sat <95%, PaO2/FiO2<=300 mmHg, and were within 12 days of symptom onset
- Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio for clinical improvement=1.23 [95% CI 0.87–1.75])
- Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo (18 vs 23 days) if treated within 10 days of symptom onset (hazard ratio for clinical improvement=1.52 [0.95–2.43])

- Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.
    - most common adverse events in the remdesivir group were constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin
- Conclusion: In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.
- **See also Adaptive COVID-19 Treatment Trial (ACTT) (**NCT04280705)
    - revealed faster time to recover in remdesivir-treated patients (11 days) vs. placebo (15 days), p<0.001 and trend towards mortality benefit (8% vs 12%, p=0.059).
    - inclusion criteria differed from above: patients could have been symptomatic for any duration and had SARS-CoV-2+ PCR & infiltrates on imaging or O2 Sat<95% or requires supplemental O2, or requires mechanical ventilation
- May 1: The US FDA issued an Emergency Use Authorization (EUA) for remdesivir for the treatment of hospitalized COVID-19 patients
    - Based on review of the data from the ACTT and from Gilead-sponsored open-label trial that evaluated different durations of remdesivir (NCT04292899)

9. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Gordon et al. Nature. April 30**.**

- The authors cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and identified human proteins physically associated with each using affinity-purification mass spectrometry
    - identified 332 high-confidence SARS-CoV-2-human protein-protein interactions (PPIs)
- From these, they identified 66 druggable human proteins or host factors targeted by 69 compounds (29 FDA-approved drugs, 12 drugs in clinical trials, and 28 preclinical compounds)
- Antiviral tests revealed two broad sets of active drugs and compounds - one group impinging on translation, and another group modulating Sigma1 and Sigma2 receptors.
- Implication: This study reveals a new approach for drug discovery for pan-viral strategies

10. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. Zeng et al. J Infect Dis. April 30**.**

- 6 COVID-19 subjects with respiratory failure received convalescent plasma at a median of 21.5 days after first detection of viral shedding
- Plasma donors were "recovered" for 1-2 weeks, and tested IgM negative, IgG positive
- All tested negative for SARS-CoV-2 RNA by 3 days after infusion, and 5 died eventually.
- Implication: Convalescent plasma treatment can discontinue SARS-CoV-2 shedding but may not reduce mortality in critical end-stage COVID-19 patients
    - earlier initiation of convalescent plasma treatment should be investigated

IMMUNITY

11. Immunity Passports in the context of COVID-19. World Health Organization Scientific Brief. April 24**.**

- Some governments have suggested that detection of antibodies to SARS-CoV-2 could serve as a "risk-free certificate" that would allow individuals to return to daily activities
- There is currently no evidence that people who have recovered from COVID-19 and have antibodies to SARS-CoV-2 are protected from a second infection
- Laboratory tests that detect antibodies to SARS-CoV-2 in humans, including rapid immunodiagnostic tests, need further validation to determine their accuracy and reliability.

- Implication: People who assume that they are immune to a second infection because they have received a positive antibody test result may ignore public health advice, thereby increasing the risks of continued transmission

12. **COVID-19 Antibody Seroprevalence in Santa Clara County, California.** Bendavid et al. medRxiv preprint. April 30**.**

- Measured the seroprevalence of antibodies to SARS-CoV-2 in a community sample from Santa Clara County, California
- Participants were recruited through Facebook ads targeting zip codes and sociodemographic characteristics
    - Recruited 3,285 adults in 24 hours; each adult could bring one child from the same household
- Drive-through testing; antibodies to SARS-CoV-2 were tested using a lateral flow immunoassay
- The crude prevalence of SARS-CoV-2 antibodies was reported to be 1.5% (95% CI 1.1-2.0%).
    - after weighting the sample to approximate Santa Clara County by zip, race, and sex, the prevalence was 2.8% (95% CI 1.3-4.7%)
- Major limitations:
    - Serology assay used has not been FDA approved and test specificity is a concern; study results rely heavily on specificity of the assay and false positive rate may be high
    - Selection bias is a concern
    - No evidence that presence of antibodies confers immunity to subsequent infection

IMMUNOLOGY/PATHOPHYSIOLOGY

13. **Heightened innate immune responses in the respiratory tract of COVID-19 patients.** Zhou et al. Cell Host Microbe. April 28**.**

- Metatranscriptomic sequencing for bronchoalveolar lavage fluid samples from 8 COVID-19 patients, 20 healthy controls and 146 community-acquired pneumonia (CAP) patients.
- Compared to CAPs and healthy controls, COVID-19 patients have markedly elevated expression of proinflammatory genes, especially cytokine and chemokine genes (*IL-1B*, *CXCL17*, *CXCL8*, and *CCL2*) and antiviral IFN-inducible genes (ISGs) such as *IFIT* and *IFITM* genes
- COVID-19 patients also have higher proportion of activated dendritic cells and neutrophils.
- Limitations: Only 8 COVID-19 patients; loose criteria to exclude genes: genes present in < 50% samples in both groups and with reads<5 per million were removed, which may cause false positive results

14. **Hyperinflammation and Derangement of Renin-Angiotensin-Aldosterone System in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis.** Henry et al. Clin Chim Acta. April 30.

- SARS-CoV-2 may impair host antiviral response, causing subsequent hyperinflammation
- SARS-CoV-2 likely deranges the renin angiotensin aldosterone system (RAAS)
- Hyperinflammation and RAAS imbalance may drive acute lung injury and coagulopathy
- RAAS imbalance also impairs fibrinolysis, which can result in relative hypofibrinolysis
    - This can lead widespread immunothrombosis, contributing to multi-organ damage

15. **SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues.** Ziegler et al. Cell. April 24.

- Numerous human, primate and murine single-cell RNA-sequencing (scRNA-seq) datasets were used to identify tissue-resident cell subsets which may be targets of SARS-CoV2 based on expression of ACE2 and TMPRSS2

- ACE2 and TMPRSS2 co-expressing cells include goblet secretory cells in nasal passages, type II pneumocytes in the lungs, and absorptive enterocytes in the intestines
- ACE2 expression correlated with known interferon-stimulated genes and human airway basal cells respond to IFNα by upregulating ACE2. (Murine cells do not have this response)
- Authors provide cautionary note on the interpretation of the scRNA-seq data and focus on differences WITHIN data sets rather than BETWEEN due to differences in tissue dissociation, profiling method, and sequencing depth
- Implications: Interferon as an anti-viral treatment may be more complex with SARS-CoV2 if it upregulates a known host cellular entry factor

16. Type 2 and interferon inflammation strongly regulate SARS-CoV-2 related gene expression in the airway epithelium. Sajuthi et al. bioRxiv preprint. Apr 10.

- Analysis of nasal airway transcriptome data from nearly 700 children (from case-control study of asthma) recognizes the TMPRSS2 gene as highly correlated with gene networks including mucus secretory cell genes and pathways. Expression quantitative trait loci (eQTL) analyses were performed to identify genetic variation in ACE2 and TMPRSS2
- Clustering subjects based on high v. low expression of the Type 2 inflammation gene network demonstrated that TMPRSS2 levels were 1.3-fold higher in T2-high subjects, while ACE2 expression was 1.4-fold lower in T2-high subjects. In vitro assays support scRNA seq data and suggest IL-13 upregulates TMPRSS2 but down regulates ACE2 in secretory cells
- ACE2 expression was highly correlated with expression of two gene networks (1. cytotoxic T cells/Antigen presentation; and 2. IFN & viral response genes). ACE2 expression was 1.7-fold higher in the IFN-high vs. IFN-low group
- 18 of the subjects with viral RNA reads for CoVs were compared to a control group with high rhinovirus reads; the groups had similar increases in the IFN & viral response gene network but CoV^+ samples had significantly higher expression of the cytotoxic immune response gene network
- Limitations: CoV reads are from circulating CoV (not SARS-CoV2); no assessment of whether these factors drive better or worse clinical outcomes for asthmatics; subjects are from limited diversity
- Implications: Determinants of airway ACE2 and TMPRSS2 expression are T2 inflammation and viral-induced IFN, with limited influence from genetic variation