Optimizing Outcomes for People with #Cirrhosis in the #COVID Era: What Have We Learned?

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@ebtapper
Disclosures

This presenter has the following declarations of relationship with industry:

• NIH U01, K23 research grant
• Grants to Michigan: Gilead, Valeant, Ambys, Novo Nordisk, Lipocine, Madrigal
Outline

Impact on the liver

Impact on people with cirrhosis

Managing cirrhosis
The only liver disease that SARS-Cov2 causes is the collateral damage it brings to the systems of care on which our patients depend.
The Impact of COVID-19 Unfolds in 3 Waves: 1st Wave of the COVID-19 Pandemic

**1st Wave**
- **Delayed:** LDLT, selected DDLT elective procedures, imaging, routine patient follow-up
- **Prioritized:** high-acuity care

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**2nd Wave**
- **Increased:** Emergent decompensations, transplant waitlist dropout, backlog of deferred visits/tests

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**3rd Wave**
- **Loss to follow-up:** missed diagnoses, incomplete cancer screening, progressive disease

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Tapper and Asrani J Hep April 2020
Declining Cirrhosis Hospitalizations in the Wake of the COVID-19 Pandemic: A National Cohort Study

VA data

Cirrhosis admissions

Mahmud N et al
Gastro May 2020
Adult liver waitlist additions and inactivations

Week of waiting list registration or Most recent period of inactivation

New waiting list addition
Inactivated due to COVID-19 precautions
Inactivated due to another reason
Alcohol Consumption Is Up and So Are Hospitalizations

Figure 3. Alcoholic hepatitis hospitalizations increased during the COVID-19 pandemic (infection point: March 2020).
The Impact of COVID-19 Unfolds in 3 Waves: 2nd Wave of the COVID-19 Pandemic

**First wave**
- **Prioritized:** high-acuity care
- **COVID-19 Pandemic**
- **Delayed:** LDLT, selected DDLT elective procedures, imaging, routine patient follow-up

**Second wave**
- **Increased:** Emergent decompensations, transplant waitlist dropout, backlog of deferred visits/tests

**Third wave**
- **Loss to follow-up:** missed diagnoses, incomplete cancer screening, progressive disease

Tapper and Asrani J Hep April 2020
Cirrhosis Hospitalizations Rebounded Quickly

Figure 1  Weekly number of admissions in 2020 compared with the mean number of admissions in the previous 3 years.


Figure 2  Monthly hospitalization rates for the 3 study cohorts between March 2018 and September 2020.
## Transplants Have Rebounded: UNOS Data

<table>
<thead>
<tr>
<th></th>
<th>To Date</th>
<th>2022</th>
<th>2021</th>
<th>2020</th>
<th>2019</th>
<th>2018</th>
<th>2017</th>
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</thead>
<tbody>
<tr>
<td>All Donor Types</td>
<td>191,894</td>
<td>682</td>
<td>9,236</td>
<td>8,906</td>
<td>8,896</td>
<td>8,250</td>
<td>8,082</td>
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<tr>
<td>Deceased Donor</td>
<td>183,490</td>
<td>648</td>
<td>8,667</td>
<td>8,415</td>
<td>8,372</td>
<td>7,849</td>
<td>7,715</td>
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<tr>
<td>Living Donor</td>
<td>8,404</td>
<td>34</td>
<td>569</td>
<td>491</td>
<td>524</td>
<td>401</td>
<td>367</td>
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</table>

### Transplants

### Waitlists

<table>
<thead>
<tr>
<th>Age Group</th>
<th>To Date</th>
<th>2022</th>
<th>2021</th>
<th>2020</th>
<th>2019</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ages</td>
<td>264,179</td>
<td>964</td>
<td>13,440</td>
<td>12,609</td>
<td>12,941</td>
<td>12,719</td>
<td>12,475</td>
</tr>
<tr>
<td>&lt; 1 Year</td>
<td>6,950</td>
<td>20</td>
<td>202</td>
<td>201</td>
<td>212</td>
<td>242</td>
<td>209</td>
</tr>
<tr>
<td>1-5 Years</td>
<td>5,415</td>
<td>20</td>
<td>193</td>
<td>156</td>
<td>190</td>
<td>203</td>
<td>248</td>
</tr>
<tr>
<td>6-10 Years</td>
<td>2,464</td>
<td>7</td>
<td>76</td>
<td>71</td>
<td>79</td>
<td>103</td>
<td>94</td>
</tr>
<tr>
<td>11-17 Years</td>
<td>4,506</td>
<td>6</td>
<td>177</td>
<td>163</td>
<td>162</td>
<td>156</td>
<td>174</td>
</tr>
<tr>
<td>18-34 Years</td>
<td>15,654</td>
<td>58</td>
<td>955</td>
<td>856</td>
<td>796</td>
<td>763</td>
<td>751</td>
</tr>
<tr>
<td>35-49 Years</td>
<td>62,826</td>
<td>241</td>
<td>2,821</td>
<td>2,496</td>
<td>2,303</td>
<td>2,147</td>
<td>2,040</td>
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<tr>
<td>50-64 Years</td>
<td>137,250</td>
<td>411</td>
<td>6,174</td>
<td>5,884</td>
<td>6,307</td>
<td>6,370</td>
<td>6,463</td>
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<tr>
<td>65+</td>
<td>36,152</td>
<td>201</td>
<td>2,849</td>
<td>2,789</td>
<td>2,901</td>
<td>2,745</td>
<td>2,502</td>
</tr>
</tbody>
</table>

UNOS March 9 2022
The Possible (and Likely) Future

The increased alcohol consumption is a major problem in the long run.
COVID Outcomes for cirrhosis

Table 2. Cumulative Incidences of Mortality, Mechanical Ventilation, and Hospitalization At 30 and 90 Days After Index Date

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noncirrhosis/negative, % (n = 129,864)</th>
<th>Noncirrhosis/positive, % (n = 20,446)</th>
<th>Cirrhosis/negative, % (n = 53,476)</th>
<th>Cirrhosis/positive, % (n = 8,011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization by day 30</td>
<td>27.2 (27.2–27.5)</td>
<td>20.4 (19.9–20.9)</td>
<td>40.0 (48.3–49.2)</td>
<td>47.2 (46.1–48.2)</td>
</tr>
<tr>
<td>Hospitalization by day 90</td>
<td>29.4 (29.2–29.7)</td>
<td>22.9 (22.1–23.1)</td>
<td>51.7 (51.3–52.1)</td>
<td>50.1 (49–51.2)</td>
</tr>
<tr>
<td>Mechanical ventilation by day 30</td>
<td>0.8 (0.7–0.9)</td>
<td>1.8 (1.7–2.0)</td>
<td>4.3 (3.4–6.3)</td>
<td>8.8 (8.2–9.4)</td>
</tr>
<tr>
<td>Mechanical ventilation by day 90</td>
<td>0.9 (0.9–1)</td>
<td>2.0 (1.8–2.1)</td>
<td>6.0 (5.8–6.2)</td>
<td>9.9 (9.3–10.5)</td>
</tr>
<tr>
<td>Mortality by day 30</td>
<td>0.4 (0.4–0.4)</td>
<td>1.7 (1.6–1.9)</td>
<td>3.9 (3.7–4.1)</td>
<td>8.9 (8.3–9.5)</td>
</tr>
<tr>
<td>Mortality by day 90</td>
<td>0.8 (0.7–0.8)</td>
<td>2.3 (2.1–2.4)</td>
<td>7.0 (6.8–7.3)</td>
<td>12.7 (12–13.4)</td>
</tr>
</tbody>
</table>

NOTE. Values are presented as cumulative incidence rate (95% CI).

Gastroenterology 2021;161:1487–1501

Figure 2. Mortality (in-hospital mortality and hospice) comparison between groups.

## Vaccines are terrific

### Table 2. COVID-19 Infection, Hospitalization for COVID-19, and COVID-19-Related Death After Administration of First Dose of the Pfizer BNT162b2 mRNA or the Moderna mRNA-1273 Vaccines

<table>
<thead>
<tr>
<th>Vaccine and control</th>
<th>Day 0-7 Vaccine</th>
<th>Day 0-7 Control</th>
<th>Day 7-14 Vaccine</th>
<th>Day 7-14 Control</th>
<th>Day 14-21 Vaccine</th>
<th>Day 14-21 Control</th>
<th>Day 21-28 Vaccine</th>
<th>Day 21-28 Control</th>
<th>Day 28 onward Vaccine</th>
<th>Day 28 onward Control</th>
<th>Vaccine efficacy day 28 onward, % (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64.8 (10.9-86.1)</td>
<td>.03</td>
</tr>
<tr>
<td>No.</td>
<td>183</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, no.</td>
<td>25</td>
<td>36</td>
<td>21</td>
<td>32</td>
<td>17</td>
<td>12</td>
<td>14</td>
<td>8</td>
<td>6</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative events, no.</td>
<td>25</td>
<td>36</td>
<td>46</td>
<td>68</td>
<td>83</td>
<td>80</td>
<td>77</td>
<td>88</td>
<td>83</td>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>20037</td>
<td>20037</td>
<td>18109</td>
<td>18073</td>
<td>15991</td>
<td>15935</td>
<td>13731</td>
<td>13678</td>
<td>12059</td>
<td>12012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Incidence, %</td>
<td>0.12</td>
<td>0.18</td>
<td>0.23</td>
<td>0.38</td>
<td>0.39</td>
<td>0.50</td>
<td>0.56</td>
<td>0.64</td>
<td>0.69</td>
<td>0.87</td>
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<td></td>
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<tr>
<td>Hospitalization for COVID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0 (99.3-100.0)</td>
<td>.20</td>
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<tr>
<td>No.</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Events, no.</td>
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<td>8</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td></td>
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</tr>
<tr>
<td>Cumulative events, no.</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>15</td>
<td>18</td>
<td>20</td>
<td>28</td>
<td>26</td>
<td>28</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>20037</td>
<td>20037</td>
<td>18109</td>
<td>18073</td>
<td>15991</td>
<td>15935</td>
<td>13731</td>
<td>13678</td>
<td>12059</td>
<td>12012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Incidence, %</td>
<td>0.02</td>
<td>0.04</td>
<td>0.07</td>
<td>0.08</td>
<td>0.11</td>
<td>0.13</td>
<td>0.20</td>
<td>0.19</td>
<td>0.23</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19-related death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0 (99.3-100.0)</td>
<td>.20</td>
</tr>
<tr>
<td>No.</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, no.</td>
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<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative events, no.</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>20037</td>
<td>20037</td>
<td>18109</td>
<td>18073</td>
<td>15991</td>
<td>15935</td>
<td>13731</td>
<td>13678</td>
<td>12059</td>
<td>12012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Incidence, %</td>
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<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.04</td>
<td>0.03</td>
<td>0.05</td>
<td>0.03</td>
<td>0.03</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Vaccine efficacy (VE) = 1 - (IR/IRc) where IR is the incidence rate of the event in vaccinated at risk (i) and controls at risk (c). P values: testing the null hypothesis that incidence rates are the same in both groups using Fisher exact test.
Vaccines are terrific

<table>
<thead>
<tr>
<th>Table 2: Outcomes among patients with postvaccination and unvaccinated COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Event, n (%)</td>
</tr>
<tr>
<td>Death within 60 days of COVID-19</td>
</tr>
<tr>
<td>COVID-19-related death</td>
</tr>
<tr>
<td>Hospitalization</td>
</tr>
<tr>
<td>COVID-19-related hospitalization</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Time to event, median (IQR)</td>
</tr>
<tr>
<td>Death within 60 days of COVID-19</td>
</tr>
<tr>
<td>COVID-19-related death</td>
</tr>
<tr>
<td>Hospitalization</td>
</tr>
<tr>
<td>COVID-19-related hospitalization</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
</tbody>
</table>

Note: Bold indicates significance.
Hard on the Providers

Impact of the Corona Virus Disease 2019 Pandemic on Hepatology Practice and Provider Burnout

Mark W. Russo, Ryan Kwok, Marina Serper, Nneka Ufero, Bilal Hamreel, Jaime Chu, Elizabeth Goucher, John Langerfeld, Norah Terraalt, and K. Rajender Reddy

43% Burnout

Especially APPs
The Impact of COVID-19 Unfolds in 3 Waves:
3rd Wave of the COVID-19 Pandemic

First wave: 
- Delayed: LDLT, selected DDLT elective procedures, imaging, routine patient follow-up
- Prioritized: high-acuity care

Second wave: 
- Increased: Emergent decompensations, transplant waitlist dropout, backlog of deferred visits/tests
- Physical distancing policies

Third wave: 
- Loss to follow-up: missed diagnoses, incomplete cancer screening, progressive disease

Tapper and Asrani J Hep April 2020
New Ways for Old Goals
Seizing Opportunity: Adaptations to Preserve High Quality Care
Major Increase in Televisits During Early COVID-19
COVID visit kinetics

Phreesia data, Mehrotra, Commonwealth Fund

Proportion telemed visits

Number of telemed visits in a given week as a percent of baseline total visits
Telehealth: Some of Our Patients Are Left Behind

National telehealth data

Health Aff (Millwood). 2021 February; 40(2): 349–358
Strategies to Improve Video Visit Use in Persons With Liver Disease
Some Conversations are Tough on the Phone
Our use of ultrasound as a threat to telemed
HCC Screening is Down but Recovering
Improving Access to Telehealth

Figure 1: Barriers to and facilitators of video visit use.
Development of Quality Measures in Cirrhosis

- **Process measures**
  - Published measures (Kanwal, 2010)

- **Clinical outcomes**
  - Clinician solicitation
  - Scoping review (Inception to 2017)

- **Patient reported outcomes**
  - Patient focus groups

**Candidate measures**

**Modified Delphi Panel**

**Patients’ Ratings**
PRACTICE MANAGEMENT: THE ROAD AHEAD

Cirrhosis Quality Collaborative

Michael L. Volk,1 Christina Clarke,2 Sumeet K. Aserani,3 Saira Khader,4 Meena B. Bansal,5 Elliot B. Tapper,6 Chanda Ho,7 Raymond T. Chung,8 John Lake,9 Nicholas Lim,10 Brett E. Fortune,11 Ray Kim12 Deepthi Dronamraju,13 and Fasiha Kanwal1

Figure 1. Number of patients at each site in the Clinic cohort. University of Michigan, 1712; Baylor College of Medicine, 703; Baylor Scott and White, 694; Loma Linda, 424; Massachusetts General, 152; University of Minnesota, 129; Mt. Sinai, 86; Sutter, 23; and Stanford, 9.
PRACTICE MANAGEMENT: THE ROAD AHEAD

Cirrhosis Quality Collaborative

Overall Survey Response Average 74.6%

Figure 3. Proportion of patients with ascites control.
## Screening Questions And Treatment Options For Common Disabling Symptoms In Cirrhosis

<table>
<thead>
<tr>
<th>Sample Question(s)</th>
<th>Therapeutic Options</th>
</tr>
</thead>
</table>
| How often during the last two weeks have you had muscle cramps?                    | • Normalize electrolytes and fluid balance  
• Taurine (3 grams daily)  
• Vitamin E (300 mg three times a day)  
• Baclofen (5–10 mg three times a day as needed) |
| How much of the time have you been troubled by itching during the last two weeks? | • Moisturizing cream for dry skin  
• Cholestyramine (4 grams daily)  
• Naltrexone (50 mg daily)  
• Sertraline (75–100 mg daily)  
• Ursodeoxycholic acid (13–15 mg/kg/day in 2 doses) |
| Have you had difficulty sleeping at night?  
Have you felt sleepy during the day?                                                 | • Optimize treatment for HE  
• Optimize sleep hygiene  
• Referral to sleep specialist to assess for sleep apnea  
• Mindfulness training  
• Melatonin (3–5 mg daily) |
| Have you had any sexual activity in the past few weeks? How satisfied were you with your sexual function during the past few weeks? | • Phosphodiesterase inhibitors (e.g. sildenafil 25–100 mg as needed)  
• Sex therapy referral  
• Referral to Urology |

Thomson et al. (2018)
PRO-Focused Clinical Trials in the COVID Era
Pickle Juice Intervention for Cirrhotic Cramps Reduction: The PICCLES Randomized Controlled Trial

Why we did this trial:
Cramps are common, morbid, and inadequately treated for patients with cirrhosis

What we found: In a trial of 82 patients with cirrhosis and frequent cramps, sips of pickle juice at cramp onset reduce cramp severity, but did not improve global health-related quality of life

Next steps: Trials of agents to prevent cramps
Proactive > Reactive
At-risk population
β Blockers to Prevent Decompensation of Cirrhosis in Patients With Clinically Significant Portal Hypertension

A

Cumulative incidence function for primary endpoint

Placebo group
β-blocker group

HR 0.51 (95% CI 0.26–0.97)
p-value=0.0412

Patients at risk
β blockers Placebo
100 101

Primary outcome (deaths)
β blockers Placebo
1 (1) 2 (2) 3 (1) 5 (2) 1 (1) 0 0 1 (1) 0 1

Censoring events
β blockers Placebo
3 0 6 7 3 8 8 13 14 6 6 7

Villanueva et al. (2019)
It comes down to choice

<table>
<thead>
<tr>
<th>Non selective beta blockers</th>
<th>Endoscopic variceal ligation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
</tr>
<tr>
<td>Dampens portal pressure and prevents decompensation</td>
<td>Can't easily identify responders</td>
</tr>
<tr>
<td>Less bacterial translocation</td>
<td>Side effects such as hypotension, fatigue, impotence, peripheral edema</td>
</tr>
<tr>
<td>No need for repeat endoscopy</td>
<td>Can't be safely used with SBP&lt;90 mmHg</td>
</tr>
</tbody>
</table>

**FIG 3**  Pros and cons of NSBB versus EVL for primary prophylaxis. Diagram was created with Biorender.com.
Which Patients Prefer Beta-blockers First?

Would like to try beta-blocker first

- Prior Endoscopy
- Prior Beta-Blocker
- Prior HE
- Ascites
- Prior Variceal Bleed
- Decompensation

5-point Likert Scale

Che et al (under review)
Acceptance and Use of a Smartphone Application in Cirrhosis

Louissaint et al. (2020)
The Animal Naming Test: An Easy Tool For the Assessment of Hepatic Encephalopathy
Improving Care in Outpatients With Cirrhosis and Ascites: A New Model of Care Coordination by Hepatologists

Skilled Team

Cognitive Testing

Day Hospital

On-Demand Procedures

Relapse Prevention

Morando F, J Hepatol 2013;
Care Management Program Improves 1-Year Survival After Admission For Cirrhosis and Ascites

Morando F, J Hepatol 2013;
The importance of a business plan

And the opportunities posed by covid’s impact
Collaboration
Expansion
Pro-action
The End

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