Table 2. GRADE evidence profile, PICO 2

**Question:** Hydroxychloroquine and azithromycin compared to no hydroxychloroquine/azithromycin for hospitalized patients with COVID-19

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
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</table>

**Mortality (RCTs) (follow up: range 22 days to 49 days)**

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>not serious</th>
<th>not serious</th>
<th>very serious</th>
<th>none</th>
<th>5/172 (2.9%)</th>
<th>6/173 (3.5%)</th>
<th>HR 0.64 (0.18 to 2.21)</th>
<th>12 fewer per 1,000 (from 28 fewer to 40 more)</th>
<th>![GRADE Icon] ⨁◯◯ LOW CRITICAL</th>
</tr>
</thead>
</table>

**Mortality (NRS)**

| 3 | observational studies | very serious | not serious | not serious | serious | none | Three non-randomized studies failed to identify an association between persons treated with HCQ + AZ and mortality: Ip reported an adjusted HR of 0.98 (95% CI: 0.75, 1.28); Magagnoli reported an adjusted HR in a subset after propensity score adjustment of 0.89 (95% CI: 0.45, 1.77); Rosenberg 2020 reported an adjusted hazard ratio (HR) of 1.35 (95% CI: 0.79, 2.40)(Ip, Magagnoli 2020, Rosenberg 2020). | ![GRADE Icon] ⨁◯◯◯ VERY LOW CRITICAL |
|---|----------------------|--------------|-------------|-------------|---------|------|--------------------------------------------------|-----------------------------------------------|------------------------------------------|

**Clinical status (assessed with: 7-point scale, higher values represent worse clinical outcomes)**

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>serious</th>
<th>not serious</th>
<th>not serious</th>
<th>serious</th>
<th>none</th>
<th>172</th>
<th>173</th>
<th>MD 0.99 higher (0.57 higher to 1.73 higher)</th>
<th>![GRADE Icon] ⨁◯◯ LOW CRITICAL</th>
</tr>
</thead>
</table>

**Virologic Failure (follow up: range 5 days to 6 days; assessed with: PCR Test)**
## QT prolongation (RCTs)

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>very serious</th>
<th>not serious</th>
<th>serious</th>
<th>none</th>
<th>29/71 (40.8%)</th>
<th>12/12 (100.0%)</th>
<th>not estimable</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

## QT prolongation (NRS)

<table>
<thead>
<tr>
<th>2</th>
<th>observational studies</th>
<th>very serious</th>
<th>not serious</th>
<th>serious</th>
<th>none</th>
<th>10/95 (10.5%)</th>
<th>-</th>
<th>-</th>
<th>VERY LOW</th>
</tr>
</thead>
</table>

## Serious adverse events

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>serious</th>
<th>not serious</th>
<th>not serious</th>
<th>serious</th>
<th>none</th>
<th>5/239 (2.1%)</th>
<th>0/50 (0.0%)</th>
<th>RR 2.34 (0.13 to 41.61)</th>
<th>0 fewer per 1,000 (from 0 fewer to 0 fewer)</th>
<th>LOW</th>
<th>CRITICAL</th>
</tr>
</thead>
</table>

### GRADE Working Group grades of evidence

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

### Risk of bias

- **Study limitations**
- **Inconsistency:** Unexplained heterogeneity across study findings
- **Indirectness:** Applicability or generalizability to the research question
- **Imprecision:** The confidence in the estimate of an effect to support a particular decision
- **Publication bias:** Selective publication of studies
Explanations

a. Co-interventions were provided to patients but balanced across arms. Cavalcanti 2020 was open label; however, likely did not influence the outcome of mortality.
b. Cavalcanti 2020 excludes persons receiving supplemental oxygen at a rate of more than 4 liters per minute.
c. A very small number of events. Optimal information size not met.
d. The 95% CI includes the potential for both benefit and harm.
e. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
f. Cavalcanti was an open-label trial.
g. Optimal information size not met.
h. No contemporaneous control groups; no adjustment for baseline severity, resulting in high risk for residual confounding
i. 2 case series from France showed divergent results
j. Surrogate marker for mortality or resolution of COVID-19.
k. Gautret reported 21/61 patients as positive at day 6 (estimate from supplied graph); Molina reported 8/10 patients positive at day 5 or 6. Pooled rates of virologic failure using fixed effects inverse variance method resulted in a 43% failure rate (95% CI, 32% to 54%)
l. Gautret reported on a historical viral clearance rate in symptomatic patients from a separate hospital. Criteria for selection of patients remains unclear, as presumably a sizable number of untreated patients could have been available with data on viral clearance.
m. Indirect measure of arrhythmia-specific mortality.

References