**COVID-19 and liver dysfunction: A systematic review and meta-analysis of retrospective studies**

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**Abstract**

Recently, Coronavirus Disease 2019 (COVID-19) pandemic is the most significant global health crisis. In this study, we conducted a meta-analysis to find the association between liver injuries and the severity of COVID-19 disease. Online databases, including PubMed, Web of Science, Scopus, and Science direct, were searched to detect relevant publications up to 16 April 2020. Depending on the heterogeneity between studies, a fixed- or random-effects model was applied to pool data. Publication bias Egger’s test was also performed. Meta-analysis of 20 retrospective studies (3428 patients), identified that patients with a severe manifestation of COVID-19 exhibited significantly higher levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin values with prolonged prothrombin time. Furthermore, lower albumin level was associated with a severe presentation of COVID-19. Liver dysfunction was associated with a severe outcome of COVID-19 disease. Close monitoring of the occurrence of liver dysfunction is beneficial in early warning of unfavorable outcomes.

**KEYWORDS**

COVID-19, liver function, meta-analysis, outcome, SARS-CoV-2

**1 | INTRODUCTION**

In December 2019, a novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a causative pathogen for a cluster of pneumonia initially detected in Wuhan City, China.1 As of 3 May 2020, the World Health Organization has reported Worldwide 3 267 184 confirmed cases and 229 971 deaths. The United States has reported 1067 127 confirmed cases and 57 406 deaths.2

Coronavirus Disease 2019 (COVID-19) is typically characterized by the symptoms of viral pneumonia, such as fever, fatigue, dry cough, anosmia, and headache, which may evolve to respiratory failure.3,4 The pathogen, however, displays a wide range of severity causing difficulty in determining infection outcome. COVID-19 may cause hepatic, intestinal, and respiratory diseases, and lead to respiratory distress syndrome, organ failure, and even death in severe cases.5,6

Currently, studies about the relationship between underlying mechanisms of COVID-19 and liver dysfunction are limited. COVID-19 uses the angiotensin-converting enzyme 2 (ACE2) as the binding site to enter the host cell in the lungs, kidneys, and heart.7 Chai et al8 found that both liver cells and bile duct cells express ACE2. However,
the ACE2 expression of bile duct cells is much higher than that of liver cells. These findings suggest that liver injury in patients with COVID-19 may be the result of damage to bile duct cells. Various studies have reported the laboratory findings and the clinical characteristics associated with different degrees of liver dysfunction in patients with COVID-19 disease.

However, to date, there is still limited research regarding the concomitant association between the COVID-19 and the hepato-biliary system. Therefore, by meta-analyzing data in the observational studies available so far, our study aimed to assess liver dysfunction among patients infected with SARS-CoV-2 to investigate the potential relationship between acute liver injury and COVID-19.

2 | METHODS

2.1 | Literature search strategy

A comprehensive literature review of all qualifying studies was conducted to identify the association of COVID-19 with acute liver injury based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors (RE, MY) independently screened the following medical electronic database: PubMed, Web of Science, Scopus, and Science direct for relevant data published up to 16 April 2020, using a combination of the following keywords and medical subjects headings (MeSHs): ("COVID-19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus SARS-CoV-2" OR "2019-nCoV" OR "Wuhan coronavirus" OR "Wuhan pneumonia") AND ("Liver" OR "Acute Liver injury" OR "Liver enzymes" Chronic Liver) AND ("outcome" OR "survival" OR "mortality" OR "complications" Or "infection"). The reference list of previous studies and systematic reviews were also searched for identifying eligible studies. The identified records were screened for the inclusion criteria specified for the present systematic review and meta-analysis.

2.2 | Eligibility criteria

We applied the following criteria to all extracted studies: (a) Types of studies: observational, retrospective cohort, prospective case-control, or clinical trials reporting laboratory features of COVID-19 patients, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin, and prothrombin time (PT); (b) Subjects: diagnosed patients with COVID-19; and (c) Severity: mild cases of COVID-19 disease with patients that do not require extraordinary measures to manage the diseases and severe cases of COVID-19 infection who developed COVID-related complications such as acute respiratory distress syndrome (ARDS) and respiratory failure, or expired. Exclusion criteria were as follows: (a) duplicate data (b) case reports, series, abstract-only articles, conference article and comment, editorials and expert opinions (c) studies with insufficient outcome data, and (d) preprints (articles in the peer-review stage).

2.3 | Data extraction

Data extraction was conducted by four authors (MY, GZ, AA, and AF). The process included using a two-step approach: first, we screened titles and abstracts for eligibility according to the study objective, and second, we screened the full-text article of relevant abstracts.

2.4 | Quality assessment

The Newcastle-Ottawa Scale was used for assessing the quality of eligible manuscripts. Publication bias was assessed with the Newcastle-Ottawa Quality Assessment Scale cohort studies.

2.5 | Pairwise comparison and heterogeneity assessment

The pooled estimates were extracted using RevMan version 5.3. Descriptive summary statistics in the form of mean, standard deviation, and range for continuous parametric measures were tabulated. Pairwise comparison between mild and severe COVID-19 patients was performed. Overall pooled odds ratio (OR) or standardized mean difference (SMD) with 95% confidence intervals (CI) were estimated for categorical and quantitative variables, respectively. A Fixed-effects model was employed unless significant heterogeneity was detected. In this case, the Random-effects model has been applied. Heterogeneity was considered significant if the I² value exceeds 50%, or its P value was less than .1.

Subgroup analyses by the location of the patients, publication date, sample size, and quality score were performed. Sensitivity analysis was carried out by removing one study each time, to reflect its effect size on the overall OR.

Publication bias was assessed via Begg’s funnel plot and Egger’s linear regression approach using Comprehensive Meta-analysis software. An asymmetric funnel-shape or a P value less than .1 indicated significant bias.

2.6 | Meta-regression analysis

Meta-regression analysis was employed using OpenMeta Analyst software, taking into consideration the following study characteristics: sample size, mean age of patients, percentage of males, city of the hospital, publication date, and quality score.

2.7 | Trial sequential analysis

To evaluate the reliability of statistical appraisal of this meta-analysis study, we used trial sequential analysis (TSA) software (version 0.9.5.10 beta) by merging several available sample sizes of applicable studies with the threshold of statistical influence to reduce the
unintentional miscalculations and improve the strength of anticipa-
tions. We used two-side trials and type I error with a calculated power of 5% and 80%. If the cumulative Z-curve crosses the mon-
itoring boundaries, no additional trials would be required. On the contrary, if the Z-curve did not accomplish the boundary levels, the necessary threshold requires additional records to achieve a promi-
nent significance.

3 | RESULTS

3.1 | Characteristics of the included studies

Following the removal of duplicates (n = 1870), our database search identified 2582 unique citations, of which 186 full-text articles were assessed. A total of 20 eligible retrospective cohort studies, including 3428 positively confirmed COVID-19 patients, were enrolled in the current meta-analysis. The workflow of the process of study selection is demonstrated in Figure 1. All articles were published during the period between 30 January and 16 April 2020. Most of them were from Wuhan city (13), three from Zhejiang, one from Guangdong, one from Hubei, one from Guangdong, and one from Anhui. As depicted in Table 1, the sample size of studies ranged from 21 to 651 cohorts. The mean age of patients was 53.8 years, and 57.8% were men. In the included studies, the severe disease was detected in 36.2% of pa-
tients and the average survival rate was 72.18%. All studies except for three scored more than 5 on the scale. Two studies scored a three, and one study scored a two.

3.2 | Pooled analysis of laboratory findings

Table 2 summarizes pairwise comparison, heterogeneity analysis, and publication bias of the meta-analysis. Patients who had severe

![Figure 1](image-url)  The workflow of the selection process
### TABLE 1  Characteristics of the included studies

| Author | Date of publication | Year | Ref | Journal name         | Study | Country | City | Sample Size | Mean age | Male/female | Severe cases (%) | Survival rate (%) | Quality score |
|--------|---------------------|------|-----|----------------------|-------|---------|------|-------------|----------|-------------|------------------|------------------|---------------|
| Huang  | 30 Jan 2020         | 2020 | [4] | The Lancet           | Retro | China   | Wuhun| 41          | 49       | 30/11        | 31.7             | 85.37            | 7             |
| Wang   | 7 Feb 2020          | 2020 | [21]| JAMA                 | Retro | China   | Wuhun| 138         | 58.5     | 75/63        | 26.1             | NA              | 5             |
| Yang   | 21 Feb 2020         | 2020 | [22]| The Lancet           | Retro | China   | Wuhun| 52          | 58.25    | 35/17        | 61.5             | 38.46            | 6             |
| Liu    | 28 Feb 2020         | 2020 | [23]| Chin Med J (Engl)    | Retro | China   | Wuhun| 78          | 51.5     | 39/39        | 14.1             | NA              | 5             |
| Ruan   | 3 Mar 2020          | 2020 | [24]| Intensive Care Med   | Retro | China   | Wuhun| 150         | 58.5     | 102/48       | 45.3             | 54.67            | 5             |
| Zhou   | 11 Mar 2020         | 2020 | [25]| The Lancet           | Retro | China   | Wuhun| 191         | 60.5     | 119/72       | 28.3             | 71.73            | 8             |
| Gao    | 13 Mar 2020         | 2020 | [11]| J Med Virol          | Retro | China   | Anhui| 43          | 44       | 26/17        | 34.9             | NA              | 5             |
| Wu     | 13 Mar 2020         | 2020 | [14]| JAMA Intern Med      | Retro | China   | Wuhun| 201         | 53.25    | 128/73       | 41.8             | 78.11            | 5             |
| Zhang  | 15 Mar 2020         | 2020 | [15]| Int J Infect Dis     | Retro | China   | Zhejiang| 645        | 40.77    | 328/317      | 88.8             | NA              | 7             |
| Mo     | 16 Mar 2020         | 2020 | [10]| Clin Infect Dis      | Retro | China   | Wuhun| 155         | 53.5     | 86/69        | 54.8             | NA              | 5             |
| Wang   | 16 Mar 2020         | 2020 | [26]| Clin Infect Dis      | Retro | China   | Wuhun| 69          | 53.75    | 32/37        | 20.3             | 92.75            | 8             |
| Chen   | 17 Mar 2020         | 2020 | [12]| BMJ                  | Retro | China   | Wuhun| 274         | 59.5     | 171/103      | 41.2             | 58.76            | 8             |
| Qian   | 17 Mar 2020         | 2020 | [27]| QJM                  | Retro | China   | Zhejiang| 91         | 57.5     | 37/54        | 9.9              | NA              | 3             |
| Qi     | 17 Mar 2020         | 2020 | [28]| J Med Virol          | Retro | China   | Guangdong| 30        | 54.72    | NA           | 10.0             | NA              | 2             |
| Deng   | 20 Mar 2020         | 2020 | [29]| Chin Med J (Engl)    | Retro | China   | Wuhun| 225         | 54.5     | 124/101      | 48.4             | 51.56            | 7             |
| Wan    | 21 Mar 2020         | 2020 | [30]| J Med Virol          | Retro | China   | Chongqing| 135       | 50       | 72/63        | 29.6             | 99.26            | 8             |
| Jin    | 24 Mar 2020         | 2020 | [31]| Gut                  | Retro | China   | Zhejiang| 651        | 45.61    | 331/320      | 11.4             | NA              | 8             |
| Chen   | 27 Mar 2020         | 2020 | [13]| J Clin Invest        | Retro | China   | Wuhun| 21          | 56.5     | 17/4         | 52.4             | 80.95            | 6             |
| Pan    | 14 Apr 2020         | 2020 | [32]| Am J Gastroenterol   | Retro | China   | Hubei| 204         | 52.9     | 107/97       | 50.5             | 82.35            | 7             |
| Zhou   | 16 Apr 2020         | 2020 | [33]| J Infect             | Retro | China   | Wuhun| 34          | 65       | 17/17        | 23.5             | NA              | 3             |

Abbreviations: Ref, reference number; Retro, retrospective.
| Characteristics          | Number studies | Sample size       | Test of association | Effect size | Heterogeneity | Publication bias |
|-------------------------|----------------|-------------------|---------------------|-------------|---------------|-----------------|
|                         |                | Total  | Mild  | Severe  | Method  | Model  | Estimate | 95% CI     | P value | I²     | P value | P (Egger's) |
| Laboratory tests        |                |        |       |         |         |        |          |            |          |        |         |           |
| ALT                     | 19             | 3376   | 1953  | 1423    | SMD, IV| Fixed  | 0.35     | 0.27, 0.43 | .073     | 34.13% | <.001  | 0.279     |
| AST                     | 19             | 3376   | 1953  | 1423    | SMD, IV| Random | 0.44     | 0.17, 0.70 | <.001    | 88.80% | .001   | 0.940     |
| Bilirubin               | 11             | 2512   | 1365  | 1147    | SMD, IV| Random | 0.41     | 0.20, 0.62 | <.001    | 75.02% | <.001  | 0.773     |
| Albumin                 | 11             | 2605   | 1434  | 1171    | SMD, IV| Random | −0.84    | −1.20, −0.48 | <.001    | 91.4%  | <.001  | 0.204     |
| PT                      | 10             | 1300   | 799   | 501     | SMD, IV| Random | 0.62     | 0.32, 0.91 | <.001    | 81.34% | <.001  | 0.512     |
| Comorbidities           |                |        |       |         |         |        |          |            |          |        |         |           |
| Hypertension            | 13             | 2141   | 1024  | 1117    | OR, M-H| Fixed  | 2.36     | 1.86, 3.01 | .30       | 14.01% | <.001  | 0.976     |
| Chronic kidney dis      | 7              | 1675   | 690   | 985     | OR, M-H| Fixed  | 7.28     | 3.25, 16.26 | .54       | 0.00%  | <.001  | 0.279     |
| Diabetes                | 14             | 2193   | 1044  | 1149    | OR, M-H| Fixed  | 2.72     | 2.05, 3.60 | .05       | 41.58% | <.001  | 0.453     |
| Cardiovascular dis      | 12             | 2327   | 1086  | 1241    | OR, M-H| Random | 5.11     | 2.03, 12.83 | <.001    | 77.27% | <.001  | 0.061     |
| Chronic liver dis       | 9              | 1659   | 685   | 974     | OR, M-H| Fixed  | 1.17     | 0.66, 2.06 | .87       | 0.00%  | 0.58   | 0.824     |
| Malignancy              | 12             | 2132   | 990   | 1142    | OR, M-H| Fixed  | 2.20     | 1.28, 3.77 | .90       | 0.00%  | .004   | 0.890     |
| Cerebrovascular dis     | 5              | 769    | 435   | 334     | OR, M-H| Fixed  | 5.73     | 2.52, 13.04 | .20       | 32.59% | <.001  | 0.041     |
| Treatment               |                |        |       |         |         |        |          |            |          |        |         |           |
| Antiviral               | 10             | 1685   | 1002  | 683     | OR, M-H| Random | 0.70     | 0.42, 1.16 | .16       | 62.06% | <.001  | 0.52      |
| Antibiotics             | 7              | 1991   | 1387  | 604     | OR, M-H| Random | 2.13     | 0.86, 5.29 | .10       | 81.93% | <.001  | 0.64      |
| Glucocorticoids         | 13             | 2981   | 1651  | 1330    | OR, M-H| Random | 3.17     | 2.03, 4.97 | <.001    | 73.41% | <.001  | 0.49      |
| Immunoglobulins         | 6              | 1101   | 605   | 496     | OR, M-H| Random | 2.75     | 1.09, 6.94 | .032      | 89.10% | <.001  | 0.32      |
| Outcomes                |                |        |       |         |         |        |          |            |          |        |         |           |
| ARDS                    | 9              | 2204   | 1230  | 974     | OR, M-H| Random | 18.84    | 5.39, 65.87 | <.001    | 89.58% | <.001  | 0.106     |
| AKI                     | 6              | 1300   | 516   | 784     | OR, M-H| Random | 7.20     | 1.38, 37.74 | .003      | 71.59% | <.001  | 0.511     |
| Sepsis                  | 5              | 1259   | 488   | 771     | OR, M-H| Random | 21.19    | 4.21, 106.73 | .085     | 50.99% | <.001  | 0.680     |
| Acute liver injury      | 2              | 1296   | 649   | 647     | OR, M-H| Fixed  | 1.93     | 1.11, 3.34 | .60       | 0.00%  | .001   | NA        |
| Myocardial injury       | 3              | 464    | 334   | 130     | OR, M-H| Random | 11.19    | 0.44, 285.9 | <.001    | 90.44% | <.001  | 0.408     |
| Mortality               | 11             | 1563   | 922   | 641     | OR, M-H| Random | 55.22    | 12.62, 241.66 | <.001    | 90.82% | <.001  | 0.028     |

Abbreviations: AKI, acute kidney injury; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, confidence interval; I², the ratio of true heterogeneity to total observed variation; IV, inverse variance; M-H, Mantel-Haenszel; OR, odds ratio; PT, prothrombin time; SMD, standardized mean difference.
presentations of COVID disease had higher levels of AST (SMD = 0.36; 95% CI = 0.27; 0.44; P < .001), ALT (SMD = 0.44; 95% CI = 0.35, 0.52; P < .001), bilirubin (SMD = 0.40; 95% CI = 0.31, 0.50; P < .001), and PT (SMD = 0.69; 95% CI = 0.57, 0.81; P < .001). In contrast, lower albumin level was associated with severe presentation (SMD = −0.68; 95% CI = −0.7, −0.58; P < .001) (Figure S1). Apart from ALT data, significant heterogeneity was detected in laboratory results. Subgroup analysis by the origin of the hospital, publication date, sample size, and quality score of the studies failed to resolve the obvious heterogeneity.

3.3 | Pooled analysis of comorbidities

The analysis showed that patients with hypertension (OR = 2.37; 95% CI = 1.86-3.01; P < .001), chronic kidney disease (OR = 7.28; 95% CI = 3.26-16.26; P < .001), and diabetes (OR = 2.72; 95% CI = 2.06-3.61; P < .001) were nearly twofold more likely to develop severe presentation of COVID-19. Patients with underlying cardiovascular disease or cerebrovascular disease were five-times more liable to develop severe phenotype (OR = 5.11; 95% CI = 2.04-12.83; P < .0001 and OR = 5.73; 95% CI = 2.52-13.04; P < .0001, respectively). Cancer patients also exhibited severe manifestations of the disease (OR = 2.20; 95% CI = 1.28-3.78; P = .004) (Figure S2). Apart of cardiovascular disease, homogeneity between studies was detected.

3.4 | Pooled analysis of treatment

A total of 17 studies reported treatment to be administered to COVID-19 patients. On comparison between the two groups, severe patients were nearly three times more likely to receive steroids (OR = 3.17; 95% CI = 3.02-4.97; P < .001) and immunoglobulins (OR = 2.75; 95% CI = 1.09-6.94; P = .032). Sensitivity analysis revealed that the studies of Wang21 and Zhang15 contributed in the significant heterogeneity observed in treatment results (Table 2).

3.5 | Pooled analysis of COVID-19 outcomes

Our analysis confirmed that patients with severe COVID-19 disease had higher odds of developing ARDS (OR = 18.84; 95% CI = 5.39-65.87; P < .0001) and sepsis (OR = 21.19; 95% CI = 4.21-106.7; P < .001). Similarly, acute liver injury (OR = 1.93; 95% CI = 1.12-3.34; P = .001) and acute kidney injury (OR = 7.2; 95% CI = 1.38-37.74; P < .001) were more prevalent among patient with severe disease. Moreover, our analysis revealed that mortality was more likely to occur among patients with severe COVID-19 patients (OR = 55.22; 95% CI = 12.62-241.66; P < .001) (Figure S3). Considerable heterogeneity was observed for the outcomes. Meta-regression analysis for study characteristics showed higher odds of mortality in articles involving Wuhun hospitals (coefficient = 4.30; 95% CI = 3.07-5.54; P < .001) (Table S1).

3.6 | Publication bias

The funnel plot of laboratory and clinical parameters is shown in Figure S4. Egger’s test showed no publication bias for all variables (P > .1) except for two; cardiovascular and cerebrovascular diseases (P = .061 and .041) (Table 2).

3.7 | Trial sequential analysis

We applied TSA on mortality rate available among all eligible articles of COVID-19 patients with a mild and severe exhibition and indicated that the cumulative Z-curve transverses the monitoring boundaries before reaching the required sample size and achieving considerable significant and so no further studies are necessary (Figure 2).

4 | DISCUSSION

Our meta-analysis including 3428 subjects from 20 retrospective studies explored the potential relationship between liver injury and the severity of COVID-19 disease. We found that liver dysfunction seemed to be higher in patients with severe outcomes from COVID-19 infection.

Our results were in agreement with a previous study review.36 Previously, liver injury has been reported as an important risk factor for severe outcome and death in SARS and Middle East Respiratory Syndrome.35,37,39

Patients in our study who had severe presentations of COVID-19 disease had higher levels of AST, ALT, bilirubin, and lower albumin levels. Our results are consistent with recent studies on COVID-19 disease that showed that the incidence of liver injury ranged from 58% to 78%, mainly indicated by elevated AST, ALT, and total bilirubin levels accompanied by slightly decreased albumin levels.40,41 In a recent study, Guan et al39 documented that higher serum levels of AST were observed in nearly 18% of patients with nonsevere COVID-19 disease and approximately 56% of patients with severe COVID-19 infection. Moreover, in that study, higher serum levels of ALT were also observed in nearly 20% of patients with nonsevere COVID-19 presentation, and approximately 28% of patients with severe COVID manifestion.42 Similar findings in Huang et al42 were also observed, where patients with severe COVID-19 features had an increased incidence of liver injury.

Postmortem liver biopsies specimens were observed in deceased COVID-19 patients. The findings showed mild lobular and portal activity along with microvascular stenosis, indicating the injury could have been caused by either COVID-19 disease or drug-induced liver injury.3 Similar to the treatment of SARS, steroids, antivirals, and antibiotics are widely used for the treatment of COVID-19.34,43,44 These drugs are all potential causes of liver injury during COVID-19 treatment but have not yet been evident.45 A recent study reported that the liver injury observed in COVID-19 patients might be caused...
by lopinavir, which is used as an antiviral for the treatment of SARS-CoV-2 infection. It is worth noting that the specific underlying causes of liver injury and elevated levels of liver enzymes in COVID-19 patients are still limited. However, collectively the proposed mechanisms might include "hyperactivated immune responses and cytokine storm-related systemic inflammation, psychological stress, drug toxicity, and progression of pre-existing liver diseases" as detailed by Li and Fan.

Further studies are needed to investigate the mechanisms of liver dysfunction in COVID-19 disease as a direct outcome of infection and the possible effects that treatment has on the liver.

Limitations of our study include the following: First, all the studies included in this meta-analysis used a case-control or cohort design, which are susceptible to recall and selection biases. Second, we could not distinguish if the liver dysfunction in COVID-19 patients was an acute liver injury or exacerbated chronic liver disease. Last, the enrolled studies focused on Chinese patients, which restricted a more precise estimation of liver dysfunction in the context of other races.

5 | CONCLUSIONS

In this meta-analysis, we comprehensively analyzed liver dysfunction in accordance with the severity of clinical outcomes in COVID-19 patients. Liver dysfunction was associated with severe COVID-19 infection. Patients presented with abnormal liver function tests are at higher risk of severe clinical outcomes. Close monitoring of the presence of liver dysfunction may be beneficial as an early indicator of worse outcomes. This may serve to better prepare the treatment of patients.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

MY, ASA, RE: study design; MY, ASA, MO, GZ, AE, AS: study identification and data extraction; MH, RE, EAT: statistical analysis; MH, RE, EAT, MSF: data interpretation; MY, ASA, RE, MO, GZ, AF, EAT, MSF: original draft preparation. All authors revised and approved the final version of the manuscript.

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FIGURE 2  Trial sequential analysis for mortality
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**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.

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