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# COVID-19 Pandemic Changes Epidemiology, Clinical Features and Laboratory Markers of Epstein-Barr Virus Infection in Children: A Three-Period Retrospective Study of 438 Cases

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**[Abstract]**

**Purpose:** This study aimed to explore the shifts in epidemiology, laboratory biomarkers and clinical complications of hospitalized childhood Epstein-Barr virus (EBV) infection across pre-, mid- and post-COVID-19 pandemic periods, and clarify how anti-pandemic containment measures altered EBV infection features in Chinese children.

**Methods:** A retrospective single-center cohort study was performed on 438 pediatric EBV inpatients enrolled between 2019 and 2025, grouped into pre-pandemic (2019, n=35), mid-pandemic (2020–2022, n=96) and post-pandemic (2023–2025, n=307). Demographic, serological, virological and clinical data were collected and analyzed via statistical comparison among three groups.

**Results:** Age distribution shifted toward older children after pandemic; regular seasonal incidence fluctuation of EBV was disrupted in mid-pandemic. Mid-pandemic cases were dominated by primary EBV infection with elevated VCA-IgM, while post-pandemic patients showed higher EBV-DNA and EA-IgM indicating increased viral reactivation. Sepsis peaked in mid-pandemic and severe pneumonia kept rising post-pandemic.

**Conclusion:** COVID-19 pandemic restrictions remarkably changed pediatric EBV epidemiologic and laboratory profiles. The switch from primary infection to latent reactivation post-pandemic guides stratified clinical screening and individualized treatment for childhood EBV infection.

**Keywords:** Epstein-Barr virus; COVID-19 pandemic; child; epidemiology; viral reactivation; complications

**List of Abbreviations**

| Abbreviation | Full name |
|---|---|
| COVID-19 | Coronavirus Disease 2019 |
| EA-IgM | Early antigen-immunoglobulin M |
| EBV | Epstein-Barr virus |
| EBNA | Epstein-Barr nuclear antigen |
| IQR | Interquartile range |
| LOS | Length of hospital stay |
| VCA-IgG | Viral capsid antigen-immunoglobulin G |
| VCA-IgM | Viral capsid antigen-immunoglobulin M |

## 1.Introduction

Epstein-Barr virus (EBV) is a globally prevalent human gammaherpesvirus with significant geographic and demographic variability in childhood seroprevalence, ranging from 10% to 90% worldwide[1] . Primary EBV infection in children is often asymptomatic or manifests as infectious mononucleosis (IM), frequently involving multiple organ systems including the respiratory and digestive tracts. Common clinical phenotypes include non-severe pneumonia, bronchitis, and liver dysfunction, while severe cases may progress to sepsis, severe pneumonia, and multi-organ injury, posing a substantial threat to pediatric health[2].

The COVID-19 pandemic and associated public health measures have profoundly altered the

transmission dynamics, exposure patterns, and immune microenvironment of pediatric respiratory viruses[3] .As EBV is primarily transmitted via close contact, its epidemiology is particularly sensitive to changes in social behavior, school attendance, and population mobility. Pandemic-era interventions—including social distancing, school closures, and mask mandates—delayed natural EBV exposure and reduced immune priming in children, potentially shifting the age of onset, seasonal patterns, clinical manifestations, and severity of EBV-related disease[4].

To date, there remains a paucity of systematic clinical evidence characterizing the long-term, multi-dimensional, and stage-specific impacts of the pandemic on pediatric EBV infection. This study retrospectively analyzed 438 hospitalized children with EBV infection from 2019 to 2025, stratified into pre-pandemic (2019), mid-pandemic (2020–2022), and post-pandemic (2023–2025) periods. This study aimed to explore the long-term impacts of the COVID-19 pandemic on the epidemiology, clinical features, laboratory markers, and complications of pediatric EBV infection across three periods.

## 2. Materials and Methods

### 2.1 Study Population

A retrospective analysis was conducted on clinical data from 438 children hospitalized with EBV infection at Shaoxing Maternity and Child Health Care Hospital between January 1, 2019, and December 31, 2025.

### 2.2 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Age ≤14 years; (2) Meets diagnostic criteria for EBV infection; (3) First diagnosis at our institution with complete clinical data; (4) No prior history of EBV-targeted therapy.

Exclusion criteria: (1) Co-infection with other pathogens; (2) Presence of malignancy, congenital anomalies, or severe pre-existing organ dysfunction; (3) Admission with life-threatening complications

or prior immunomodulatory therapy affecting EBV immunity.

2.3 Diagnostic Criteria

- EBV infection: Defined by either (a) seropositivity for viral capsid antigen (VCA) antibodies with low-avidity VCA-IgG, indicating acute primary or active infection; or (b) detection of EBV nucleic acid in blood, bone marrow, lymph nodes, or other affected tissues via molecular assays [5][6].
- Infectious mononucleosis (IM): Diagnosed in accordance with criteria outlined in *Zhu Futang's Practice of Pediatrics*.(8th ed, People's Medical Publishing House, 2015).

2.4 Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables, including length of stay (LOS), plasma EBV-DNA copy number, and hospitalization costs, are expressed as medians with interquartile ranges (IQR) to describe central tendency and dispersion. Between-group comparisons of categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate. Non-parametric tests (Wilcoxon rank-sum or Kruskal-Wallis H test) were used for non-normally distributed continuous variables and ordinal data. All analyses were conducted using SPSS 29.0 (IBM Corp., Armonk, NY, USA). When overall comparison by Kruskal-Wallis H test yielded $P < 0.05$, post-hoc pairwise comparisons were performed using Mann–Whitney U test with Bonferroni correction ($\alpha$=0.0167). A two-tailed p-value <0.05 was considered statistically significant.

## 3. Results

3.1 Demographic Characteristics

Among the 438 children with EBV infection, 220 (50.22%) were male and 218 (49.78%) were female, with a male-to-female ratio of approximately 1:1. Age distribution was as follows: 0–1 years (4 cases, 0.92%), 1–3 years (222 cases, 50.68%), 4–6 years (152 cases, 34.70%), and 7–14 years (60 cases,

13.70%), with the highest proportion in the 1–3-year age group.

Hospital admissions peaked in 2023 (117 cases, 26.71%) and 2024 (119 cases, 27.17%), followed by 2022 (73 cases, 16.67%), 2025 (71 cases, 16.21%), 2019 (35 cases, 7.99%), 2021 (21 cases, 4.79%), and 2020 (2 cases, 0.46%).

The median LOS was 6 days (IQR 5–7 days), median plasma EBV-DNA copy number was $0.98\times10^2$ copies/mL (IQR 0.17–$12.75\times10^2$ copies/mL), and median hospitalization cost was USD 445.07 (IQR 384.50–521.84 USD). Comorbidities included metabolic disease (1 case, 0.22%) and congenital heart disease (2 cases, 0.46%); no cases of malignancy or autoimmune disease were identified (Table 1).

**Table 1. Demographic and Clinical Characteristics of 438 Children with EBV Infection**

| Characteristic | n (%) or Median (IQR) |
|---|---|
| Total cases | 438 |
| Sex | |
| Male | 220 (50.22) |
| Female | 218 (49.78) |
| Age (years) | |
| 0–1 | 4 (0.92) |
| 1–3 | 222 (50.68) |
| 4–6 | 152 (34.70) |
| 7–14 | 60 (13.70) |
| EBV-DNA (×10² copies/mL) | 0.98 (0.17–12.75) |
| LOS (days) | 6 (5–7) |
| Hospitalization cost (USD) | 445.07 (384.50–521.84) |
| Year of admission | |

| Characteristic | n (%) or Median (IQR) |
|---|---|
| 2019 | 35 (7.99) |
| 2020 | 2 (0.46) |
| 2021 | 21 (4.79) |
| 2022 | 73 (16.67) |
| 2023 | 117 (26.71) |
| 2024 | 119 (27.17) |
| 2025 | 71 (16.21) |
| Comorbidities | |
| Metabolic disease | 1 (0.22) |
| Congenital heart disease | 2 (0.46) |

*Abbreviations: IQR, LOS, EBV etc. see List of Abbreviations*

3.2 Age Distribution Across Time Periods

Age distribution differed significantly across the three periods ($\chi^2$=18.02, p<0.001; Table 2). In 2019, children aged 0–3 years accounted for 68.6% (24/35) of cases, with no cases in the 7–14-year group. During 2020–2022, age distribution became more balanced, with 7–14-year-olds comprising 10.4% (10/96) of cases. In 2023–2025, the proportion of children aged 4–6 years (38.1%, 117/307) and 7–14 years (16.3%, 50/307) increased further, indicating a shift toward older age groups.

**Table 2. Age Distribution of EBV Infection Cases by Time Period**

| Age (years) | 2019 (n=35) | 2020–2022 (n=96) | 2023–2025 (n=307) | $\chi^2$ | P |
|---|---|---|---|---|---|
| 0–3 | 24 | 62 | 140 | 18.02 | <0.001 |
| 4–6 | 11 | 24 | 117 | — | — |
| 7–14 | 0 | 10 | 50 | — | — |

### 3.3 Length of Stay and Hospitalization Costs

Significant differences in LOS and hospitalization costs were observed across periods (H=7.82, $p<0.05$; H=18.18, $p<0.001$, respectively; Table 3). Median LOS was 5 days (IQR 5–7 days) in 2019, increasing to 6 days (IQR 5–7 days) in both 2020–2022 and 2023–2025; the IQR for LOS in 2023–2025 shifted to 6–7 days, indicating longer hospital stays post-pandemic.

Hospitalization costs increased progressively: median costs were USD 405.63 (IQR 359.15–459.15) in 2019, USD 411.72 (IQR 366.11–507.29) in 2020–2022, and USD 462.24 (IQR 401.18–543.84) in 2023–2025, with post-pandemic costs significantly higher than in the pre- and mid-pandemic periods.

**Table 3. Length of Stay and Hospitalization Costs by Time Period**

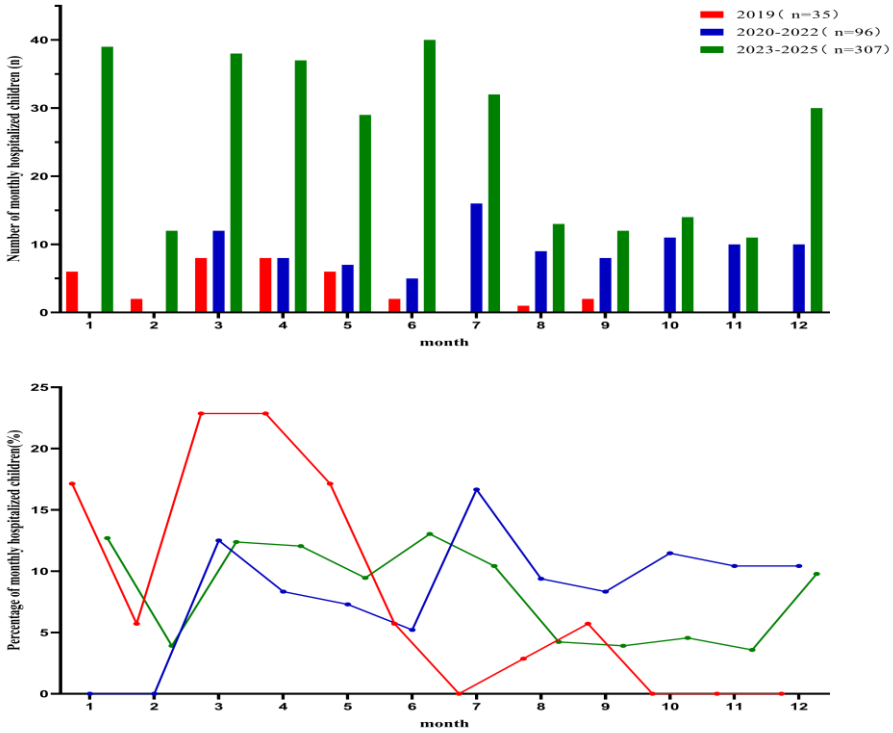
| Variable | 2019 (n=35) | 2020–2022 (n=96) | 2023–2025 (n=307) | H | P |
|---|---|---|---|---|---|
| LOS (days) | 5 (5–7) | 6 (5–7) | 6 (6–7) | 7.82 | <0.05 |
| Hospitalization cost (USD) | 405.63 (359.15–459.15) | 411.72 (366.11–507.29) | 462.24 (401.18–543.84) | 18.18 | <0.001 |

*Abbreviations: IQR, LOS, EBV etc. see List of Abbreviations*

### 3.4 Seasonal Distribution

Overall, EBV-related hospitalizations exhibited a seasonal pattern, with peaks from December to March and troughs from August to October. This pattern was disrupted during 2020–2022: admissions declined sharply in 2020, and seasonal fluctuations were attenuated and irregular in 2021–2022. Typical seasonality was restored in 2019 and 2023–2025 (Figure 1).

**Figure 1. Monthly Distribution of EBV Infection Hospitalizations (2019–2025)**




3.5 Laboratory Markers

Significant between-group differences were observed in EBV-DNA load, VCA-IgM, VCA-IgG, and early antigen (EA)-IgM (H=14.03, 83.06, 29.89, and 44.93, respectively; all p<0.001), while no significant difference was found in EBV nuclear antigen (EBNA) levels (H=2.16, p=0.34; Table 4).

Post-hoc analyses revealed significantly higher VCA-IgM and VCA-IgG levels in the mid-pandemic period, consistent with a surge in primary EBV infections. In contrast, the post-pandemic period was characterized by elevated EBV-DNA loads and EA-IgM levels, indicating increased viral replication and reactivation. Stable EBNA levels across periods suggested no substantial change in the prevalence of prior EBV exposure.

**Table 4. Laboratory Markers of EBV Infection by Time Period**

| Marker | 2019 (n=35) | 2020–2022 (n=96) | 2023–2025 (n=307) | H | p |
|---|---|---|---|---|---|
| EBV-DNA ($\times 10^2$ | 458(47.3-1290) | 2.31(0.13-6.01) | 126.0(18.3-2160) | 14.03 | <0.001 |

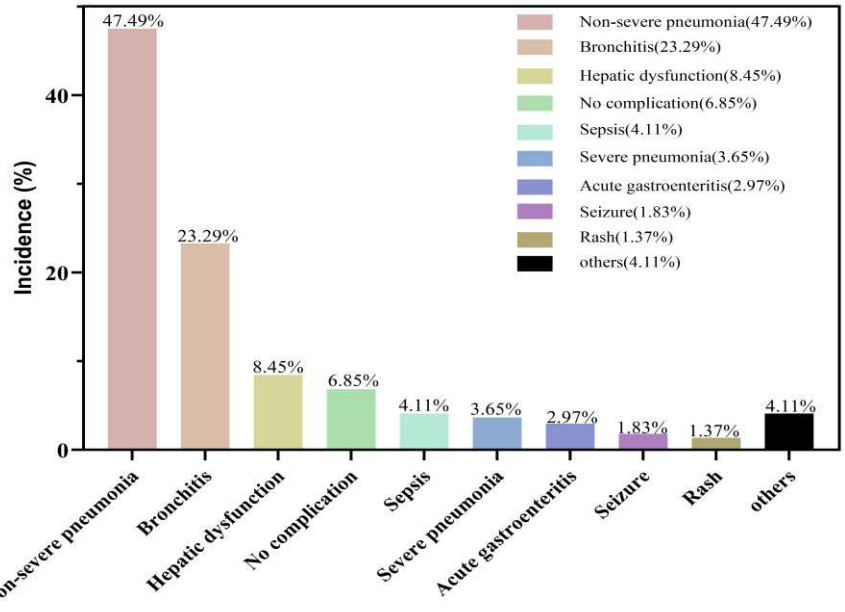
| Marker | 2019 (n=35) | 2020–2022 (n=96) | 2023–2025 (n=307) | H | p |
|---|---|---|---|---|---|
| copies/mL) | | | | | |
| EBNA | 25.50(2.50-423.0) | 15.7(2.93-57.5) | 6.8(3.1-199.0) | 2.16 | 0.34 |
| VCA-IgM | 26.50(6.0-92.80) | 238.0(70.55-550.25) | 41.05(4.70-93.42) | 83.06 | <0.001 |
| VCA-IgG | 136.0(9.0-261.0) | 238.0(70.55-550.25) | 24.80(9.0-243.5) | 29.89 | <0.001 |
| EA-IgM | 0.27(0.12-1.08) | 0.10(0.05-0.27) | 0.35(0.13-1.97) | 44.93 | <0.001 |

*Abbreviations: IQR, LOS, EBV etc. see List of Abbreviations*

3.6 Complications

Complications were present in 408 of 438 children (93.15%), with only 30 (6.85%) experiencing no complications. The most common complications were non-severe pneumonia (47.49%, 208/438), bronchitis (23.29%, 102/438), liver dysfunction (8.45%, 37/438), sepsis (4.11%, 18/438), and severe pneumonia (3.65%, 16/438). Less frequent complications included acute gastroenteritis (2.97%), seizures (1.83%), rash (1.37%), upper airway obstruction, sinusitis, thrombocytopenia, and hemolytic anemia (4.11% combined; Figure 2).

**Figure 2. Proportions of complications in 438 children with EBV infection.**




3.7 Complications by Time Period

Sepsis incidence approached the threshold for statistical significance across periods ($\chi^2$=5.24, p=0.05), with the highest rate observed in the mid-pandemic period (8.33%), compared to 3.26% in the post-pandemic period and 0% in 2019. No significant between-group differences were found in the rates of non-severe pneumonia, bronchitis, liver dysfunction, severe pneumonia, acute gastroenteritis, seizures, or rash (all p>0.05; Table 5).

**Table 5. Complications in Children with EBV Infection by Time Period**

| Complication | 2019 (n=35) n (%) | 2020–2022 (n=96) n (%) | 2023–2025 (n=307) n (%) | $\chi^2$ | P |
|---|---|---|---|---|---|
| Non-severe pneumonia | 11 (31.43) | 46 (47.92) | 151 (49.19) | 3.98 | 0.14 |
| Bronchitis | 8 (22.86) | 16 (16.67) | 78 (25.41) | 3.13 | 0.21 |
| Liver dysfunction | 4 (11.43) | 7 (7.29) | 26 (8.47) | 0.57 | 0.78 |
| Severe pneumonia | 0 (0) | 1 (1.04) | 15 (4.89) | 3.55 | 0.14 |
| Acute gastroenteritis | 0 (0) | 4 (4.17) | 6 (1.95) | 1.90 | 0.38 |

| Complication | 2019 (n=35) n (%) | 2020–2022 (n=96) n (%) | 2023–2025 (n=307) n (%) | $\chi^2$ | P |
|---|---|---|---|---|---|
| Sepsis | 0 (0) | 8 (8.33) | 10 (3.26) | 5.24 | 0.05 |
| Seizures | 0 (0) | 4 (4.17) | 4 (1.30) | 3.13 | 0.16 |
| Rash | 0 (0) | 3 (3.13) | 3 (0.98) | 2.43 | 0.20 |

## 4. Discussion

This study conducted a three-period comparative analysis on 438 pediatric inpatients with Epstein-Barr virus (EBV) infection admitted between 2019 and 2025. It systematically revealed the profound and long-term reshaping effects of the COVID-19 pandemic on the epidemiology, age structure, clinical phenotypes, laboratory parameters, and spectrum of complications of pediatric EBV infections. The observed patterns of change are highly consistent with the latest international research [6], underscoring the significant clinical and public health implications of our findings.

Firstly, our study demonstrated that the COVID-19 pandemic substantially altered the age distribution and seasonal periodicity of pediatric EBV infection. Before the pandemic (2019), cases predominantly occurred in infants aged 0–3 years with no infections observed in older children. During the pandemic (2020–2022), the age distribution became more balanced, whereas the post-pandemic period (2023–2025) saw a sharp rise in proportions of patients aged 4–6 years and 7–14 years, indicating an obvious shift of high-incidence age toward older children. This shift is closely attributed to delayed primary EBV exposure resulting from social distancing restrictions and suspended group activities throughout the pandemic [7]. Multiple international studies have verified that postponed primary EBV infection increases the risk of symptomatic infectious mononucleosis (IM) and severe complications[8, 9], which aligns with our finding of markedly elevated sepsis incidence during the pandemic era. In

addition, distinct seasonal peaks of EBV infection were only identified in pre- and post-pandemic periods, while seasonal fluctuation was severely disrupted amid pandemic restrictions, further verifying that non-pharmaceutical interventions directly interrupted EBV transmission chains [10].

Secondly, distinct immunological patterns of EBV infection were observed across the three pandemic phases, which could be clearly differentiated by laboratory biomarkers. During the pandemic period, serum VCA-IgM and VCA-IgG levels increased significantly, pointing to clustered outbreaks of primary acute EBV infection predominantly concentrated in July and August, likely attributable to intensified close contact among children following school reopening. By contrast, post-pandemic cases were characterized by markedly elevated EBV-DNA loads and EA-IgM positivity, indicating predominance of EBV reactivation and active infection. Several plausible mechanisms have been proposed to explain SARS-CoV-2-triggered EBV reactivation: first, depletion of $CD8^+$ T lymphocytes impairs host immune surveillance against latent EBV [11, 12]; second, synergistic disruption of cellular and mitochondrial signaling pathways compromises antiviral immunity [13]; third, pharmacotherapies for COVID-19 may serve as an additional risk factor for viral reactivation[14]. No intergroup differences in EBNA antibody levels were detected across the three periods, demonstrating stable background seroprevalence of prior EBV infection in the pediatric population. Consistently, our observed post-pandemic rise in EBV-DNA loads and increased frequency of severe pneumonia align well with the aforementioned pathogenetic mechanisms.

Thirdly, the spectrum of complications exhibited prominent phase-specific features, providing evidence for stratified early clinical warning. The incidence of sepsis was significantly higher during the pandemic than in the pre- and post-pandemic cohorts, plausibly resulting from impaired T-cell immune surveillance linked to COVID-19[15]. Recent mechanistic investigations have validated that

SARS-CoV-2 upregulates transforming growth factor-β (TGF-β) to suppress cytotoxic T-cell function, hampering the clearance of EBV-infected B lymphocytes and consequently inducing excessive inflammatory responses [16, 17]. A retrospective study conducted at Wuhan University first documented that patients with concurrent SARS-CoV-2 and EBV coinfection carried approximately threefold higher risks of severe illness relative to those with isolated SARS-CoV-2 infection [12]. Although severe pneumonia showed no significant intergroup difference, an obvious upward trend was observed in the post-pandemic period, as robust EBV replication exacerbates pulmonary injury and prolongs disease course[18]. In contrast, non-severe pneumonia, bronchitis and hepatic injury showed no statistically significant intergroup disparities, indicating that respiratory and hepatic involvement constitutes inherent manifestations of pediatric EBV infection and is barely affected by pandemic-associated indirect factors[19, 20]. Length of hospital stay and hospitalization costs rose progressively from pre-pandemic to post-pandemic periods, reflecting escalating disease complexity and increased medical expenditure driven by aggravated clinical severity and prolonged inpatient management.

This study has several limitations. First, this was a single-center retrospective study, which may lead to potential selection bias. Second, the sample size was relatively limited, and multi-center large-scale data are needed to verify our results. Third, some underlying clinical information was incomplete, which may have affected the analysis. Further prospective studies with long-term follow-up are warranted to confirm our findings.

## 5. Conclusion

The COVID-19 pandemic substantially altered the age distribution, seasonality, immunological patterns, and complication spectrum of pediatric EBV infection. Age- and period-specific strategies are warranted for clinical management.

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## Declarations

**Ethics approval and consent to participate:** This retrospective study was conducted in accordance with the 1964 Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Shaoxing Maternity and Child Health Care Hospital. The requirement for informed consent was waived due to the retrospective and anonymized nature of the study.

**Consent for publication:** Written informed consent for publication was obtained from the parents/legal guardians of the patients.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

**Authors' contributions:** Zheng Zhang and Tao Zhan contributed equally to this work and share first authorship. They conceived the study, drafted the initial manuscript, and critically revised it for important intellectual content. Jiahui Hu collected the clinical data, performed the literature review, and contributed to data interpretation. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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