SARS-CoV-2 Infection in Children Less Than Forty Days Hospitalized in Belgium Between 2020 and 2022

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Abstract: Our study aimed to assess the severity of severe acute respiratory syndrome coronavirus 2 infection in hospitalized infants under 40 days old, across 21 Belgian hospitals between 2020 and 2022. Of the 365 infants studied, 14.2% needed respiratory support. The median hospital stay was 3 days (interquartile range, 2–4), and there were no deaths. Infection severity was similar during the Omicron and Alpha/Delta periods.

Key Words: SARS-CoV-2 infection, COVID-19, severe disease

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is now over, but COVID-19 remains an issue.

The outcomes of young infants with COVID-19 are concerning due to limited published data with varying results: an English study found severe infections in 42% (60 cases)[1] and an Italian cohort (216 infants under 90 days old) showed that 5% required respiratory support and 2.3% admitted to intensive care unit (ICU).[2]

Variants of concern (VOCs) have emerged throughout the pandemic: the Alpha variant (lineage B.1.1.7) from March 2020 to April 2021, the Delta variant (lineage B.1.617.2) from May to November 2021 and the Omicron variant (lineage B.1.1.529/BA.1) since then.[3] During the Omicron wave in December 2021, there was an increase in pediatric cases of COVID-19, resulting in higher hospitalization rates among children under 5 years of age.[4]

Our objective was to evaluate the severity of SARS-CoV-2 infection in hospitalized infants less than 40 days old. We sought to identify differences in clinical outcomes linked to specific VOCs. Additionally, we aimed to assess the incidence of invasive bacterial infections (IBIs) among those infants admitted with fever.

METHODS

This multicenter retrospective observational study focuses on infants hospitalized in Belgium with a positive real-time reverse transcriptase polymerase chain reaction (PCR) test for SARS-CoV-2, between March 1, 2020, and December 31, 2022, and under 40 days old at admission. Infants with confirmed SARS-CoV-2 infection who presented to the emergency department but were not subsequently hospitalized were excluded from the study. Infants with a positive PCR test who were asymptomatic and/or hospitalized for reasons unrelated to a SARS-CoV-2 infection were not included in the cohort for the primary objective analysis. For the secondary analysis, we included all patients with fever, regardless of whether the fever was finally related to COVID-19 or another condition.

Recorded data included demographic characteristics, comorbidities, symptoms, laboratory results, treatments, hospital management, ICU admission and final diagnosis.

The infection's severity was assessed based on the need for respiratory support [low-flow or high-flow oxygen via nasal cannula, noninvasive/invasive ventilation], ICU admission and duration of hospitalization.

The coronavirus strains were determined from medical records or estimated based on the predominant VOC during hospitalization.

We also noted family contact and maternal infection, including maternal symptoms during delivery.

Statistical analysis is described in Text, Supplemental Digital Content 1, http://links.lww.com/INF/F558.

RESULTS

Between March 1, 2020, and December 31, 2022, 391 infants under 40 days old were hospitalized in 21 Belgian hospitals with a positive SARS-CoV-2 PCR test. Twenty-six patients were excluded from primary analysis due to incidental SARS-CoV-2 PCR detection during screening (Text, Supplemental Digital Content 2, http://links.lww.com/INF/F559).

The median age was 26 days (interquartile range, 17–33 days) (Table, Supplemental Digital Content 3, http://links.lww.com/INF/F560), 58.1% were boys and 10.1% had comorbidities. The main symptoms were fever (87.4%), respiratory (72.3%) and digestive (21.6%) complaints. Diagnoses included SARS-CoV-2 upper respiratory tract infection (64.9%), isolated fever (18.9%), low respiratory tract infection (13.2%) and other SARS-CoV-2 forms (3%; enteritis, brief resolved unexplained event, delayed resorption of pulmonary fluid with possible virus-induced worsening).

Regarding severity, 52 infants (14.2%) required respiratory support: 25 (6.8%) low-flow oxygen, 16 (4.4%) high-flow oxygen via nasal cannula, 9 (2.5%) noninvasive ventilation, 2 (0.5%) invasive ventilation. Furthermore, 17 (4.7%) were admitted to the ICU: 11 to the pediatric ICU for respiratory monitoring and 6 to the neonatal ICU within the first hours of life (4 were tested at birth due to respiratory distress, and 2 premature were tested at 20 days and 30 days of life after developing respiratory symptoms).

Three received corticosteroids, and none received antiviral treatment or hemodynamic support. There were no reported fatalities. The median length of stay was 3 days (interquartile range, 2–4 days) and 5 days (interquartile range, 3–8) for those with respiratory support.

Multivariate analyses conducted to assess risk factors to require respiratory assistance (Table, Supplemental Digital Content 4, http://links.lww.com/INF/F561) showed age under 28 days and coinfection with another respiratory virus as the 2 factors associated with severity.

We observed 47.7% of cases during the Omicron period, 29.9% during the Alpha period and 22.5% during the Delta period. Hospitalizations displayed 3 peaks, aligned with the 3 periods, with a notable peak in January 2022 during the Omicron phase (Fig. 1). Among the patients hospitalized during the Alpha, Delta and Omicron periods, 16/109 (14.7%), 9/82 (11%) and 27/174 (15.5%), respectively, required respiratory support.

The virus was identified by PCR in 42.5% of the child's close contacts and suspected in 34.8% (12.8% missing data and 10% no reported contact history).

Mothers tested positive during 13 deliveries; 3 newborns were tested positive at birth (none were tested a second time after 24 hours of life). We lacked information on maternal vaccination status and sufficient data for vertical transmission estimation.

Among all infants admitted at the hospital with fever, even if the cause was unrelated to SARS-CoV-2 infection (n = 329) (Table, Supplemental Digital Content 5, http://links.lww.com/INF/F562), bacteremia was diagnosed in 0.9% (3/329, 2 cases of *Escherichia coli* and one of *Enterococcus faecalis)*, urinary tract infections in 3.3% (11/329) and no cases of bacterial meningitis but 4 cases of viral meningitis (3 with enterovirus and 1 with parechovirus). Viral respiratory coinfection was detected in 4.3% (14/329) cases (10 respiratory syncytial virus, 2 influenza A, 1 rhinovirus and 1 metapneumovirus).

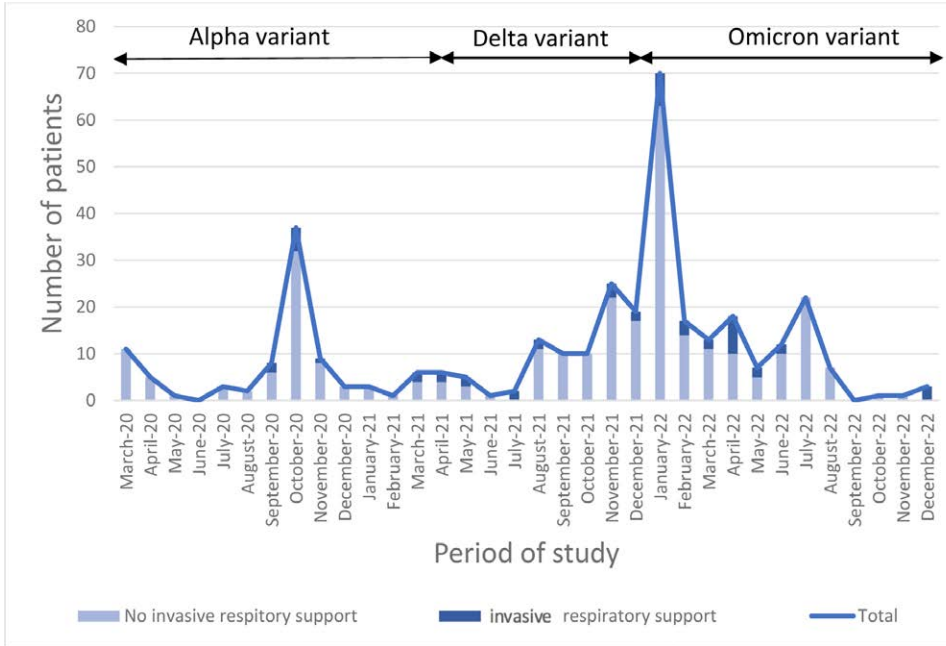

FIGURE 1. Trend in monthly hospitalizations of children with SARS-CoV-2 infection, N = 365, with or without respiratory support.

DISCUSSION

To our knowledge, this is the largest cohort of infants under 40 days old hospitalized with SARS-CoV-2 infection. It confirms that COVID-19 in young children typically manifests as a mild disease. No deaths were reported across all sites.

This information is particularly valuable considering the initial concerns regarding severe outcomes associated with SARS-CoV-2 infection in very young children. Including infants from nontertiary hospitals provides a more comprehensive representation and reduces potential bias from focusing only on severe cases in tertiary hospitals.

Severity rating scales vary among authors[2]: Gale et al[1] reported a high percentage of severity forms (42%) considering clinical, radiological and laboratory parameters to define severity. But Devin et al[5] described only 7.7% of severe forms using similar criteria. ICU admission contributes sometimes to severity definitions, which makes it challenging to compare studies, as ICU admission protocols vary widely. The present work may have overestimated severe cases because high-flow oxygen via nasal cannula support is readily available in most pediatric departments of primary and secondary hospitals, leading to its more frequent use. A more appropriate point of comparison would be the requirement for supplemental oxygen, which affected 14.2% (52/365) of infants in our cohort, including 9 on noninvasive ventilation and 2 on invasive ventilation. In contrast, Dona et al[2] reported a lower rate of respiratory assistance at 4.6% in their cohort, which included a smaller number of premature infants and an older population than ours, with only a quarter of infants aged less than 28 days.

De Luca et al[6] identified 97 children under 30 days of age, with 30.1% of them requiring respiratory assistance and a median hospital stay of 8 days. However, one-third of the cohort was born prematurely, and they did not specify the type of respiratory support used.

The Omicron variant has been associated with increased hospitalizations in children. Wang et al[7] conducted a US study comparing Omicron and Delta VOCs severity in children under 5 years of age. Omicron is linked to lower severe outcomes. Our study showed higher rates of hospitalizations during Omicron versus Alpha/Delta periods, without increased severity. Omicron's higher contagiousness leads to a wider circulation of the virus and increases hospitalizations across the general population.

Previous studies suggest a lower IBI risk with a respiratory virus infection.[8] Jacob et al[9] conducted a study in Israel on febrile infants up to 90 days of age with SARS-CoV-2 infection, finding 6% (26/417) of bacterial infections, primarily urinary tract infections, without bacteremia or meningitis. In our febrile infant cohort, we found 3.3% urinary tract infections, 0.9% bacteremia and no bacterial meningitis. Consequently, while SARS-CoV-2 infection does not eliminate IBI evaluation need, the systematic performance of lumbar punctures in SARS-CoV-2-infected newborns could be questionable due to low meningitis rates.

Our study has limitations, including data loss due to retrospective collection. Focusing on hospitalized infants restricted our ability to assess overall infection rates and asymptomatic cases. The severity rate in the general newborn population could be lower.

We selected the 40-day limit to broaden our cohort, aligning with the cautious approach commonly observed in clinical practice, where infants 30–40 days old are often managed similarly to those 28 days of age.

Hospitalization data according to VOC could be criticized due to unavailable viral sequencing data, leading to a deduction based on the time of hospitalization.

CONCLUSIONS

Infants under 40 days old typically experience mild SARS-CoV-2 infections, with no deaths reported in this cohort. Although hospital stays are short, 14.2% required respiratory assistance. Hospitalizations increased during the Omicron period, but overall disease severity remained consistent.

Febrile hospitalized infants with positive SARS-CoV-2 PCR had lower IBI rates compared with SARS-CoV-2-uninfected newborns. Further investigations should clarify clinical practices for managing these infants, ensuring optimal care while minimizing unnecessary procedures.

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