

Clinical features of infants with SARS-CoV-2 infection: a systematic review and meta-analysis

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to coronavirus disease 2019 (COVID-19) and is a public health problem. This meta-analysis reviewed the clinical features of SARS-CoV-2 infection among infants.

Methods: PubMed, Scopus, Web of Science, and the Cochrane Library were searched for studies on clinical features of infants with SARS-CoV-2 published before May 1, 2022. Two authors screened and extracted data on the number of infants with SARS-CoV-2 infection, clinical features, and number of clinical features. The proportion of asymptomatic infection, mild symptoms, moderate symptoms, severe symptoms, and the clinical features were analyzed.

Results: Forty-four studies with 6,304 infants with SARS-CoV-2 infections were included in this study. The proportion of asymptomatic infection was 20% (95% CI: 11–28%, I²=97%, P<0.01) in infants with SARS-CoV-2 infections. The proportion of infants with mild, moderate, and severe symptoms was 48% (95% CI: 30–65%, I²=96%, P<0.01), 27% (95% CI: 10–44%, I²=93%, P<0.01), and 8% (95% CI: 0–16%, I²=90%, P<0.01), respectively. Notably, the most common clinical features of infants with SARS-CoV-2 infection were fever (64%), cough (34%), and nasal symptoms (31%).

Conclusions: This meta-analysis found that 20% of infants with SARS-CoV-2 infections were asymptomatic, while most infants with COVID-19 presented with mild symptoms.

Keywords: Clinical features; infants; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); meta

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to coronavirus disease 2019 (COVID-19) (1), which has become a pandemic since it was discovered in December 2019. Multiple variants of SARS-CoV-2 have subsequently emerged, with some variants of concern (such as Alpha, Beta, Delta, and Omicron)

varying in their transmissibility and virulence (2-4). The Alpha variant is more transmissible than the wild-type of SARS-CoV-2 among children (5). A recent study found that children may play an important role in transmission of the Delta variant compared with previously circulating SARS-CoV-2 variants (6). A large cohort study found that individuals aged 10–19 years infected with the Omicron

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variant were less likely to be hospitalized than those infected with the Delta variant (7). Globally, by August 2022, almost 600 million cases of SARS-CoV-2 infection and almost 6.5 million deaths had been reported to the World Health Organization (https://covid19.who.int/).

The clinical severity of SARS-CoV-2 infection varies according to age and the infecting variant, and ranges from asymptomatic infection to critical illness and death (8-10). The most common features of SARS-CoV-2 infection are fever, cough, fatigue, and loss of taste and smell (11-14). Although children with COVID-19 generally have milder symptoms than adults, infants are susceptible to infection (15-18). Raschetti et al. (19) performed a meta-analysis that included 176 neonates with SARS-CoV-2 infection and found that 55% of infected neonates developed clinical features of COVID-19. In addition, Bhuiyan et al. (20) conducted a meta-analysis of clinical features of COVID-19 disease in children aged younger than 5 years and found that 50% of the cases were in infants; however, Bhuiyan et al. (20) did not report the clinical features of COVID-19 in infants. Therefore, the aim of this systematic review and meta-analysis was to summarize the clinical features of SARS-CoV-2 infection in infants. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/ view/10.21037/apm-22-933/rc).

Methods

This systematic review and meta-analysis were registered in the International Prospective Register of Systematic Reviews (CRD42022332861). This study was performed by reviewing previous publications; therefore, ethical approval was not required.

Literature search

Relevant publications were searched in four significant databases (PubMed, Web of Science, Scopus, and Cochrane Library), without language restriction, for articles published before May 1, 2022. The following terms were used for the literature search: ("severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "COVID-19" OR "2019 Novel Coronavirus" OR "2019-nCoV Diseases") AND ("neonate" OR "newborn" OR "infant"). In addition, the reference lists of the articles identified were searched manually for further relevant publications. Studies that were reported in more than one publication were included only once in the analysis.

Inclusion and exclusion criteria

Two researchers (F Xiao and M Tang) independently reviewed and assessed studies for eligibility. Studies were required to meet following inclusion criteria: (I) infants aged from birth to 1 year; (II) confirmed SARS-CoV-2 infection; and (III) the clinical features of SARS-CoV-2 infection in infants were reported. The exclusion criteria were as follows: (I) case reports, reviews, preprint studies, and conference abstracts; (II) studies with less than ten infants with SARS-CoV-2 infections; and (III) studies for which the full text was not available.

Data collection and quality assessment

Two authors (F Xiao and M Tang) extracted data independently, and the third author (K Yan) resolved disagreements. The following data were extracted: the name of the first author, year of publication, number of infants with SARS-CoV-2 infection, age of the infected infants, the definition of the severity of COVID-19 (table available at: https://cdn.amegroups.cn/static/public/apm-22-933-01.pdf); clinical features (such as fever and cough), and the number of clinical features. The tool for evaluating the methodological quality of case reports and case series was used for the quality assessment in case series studies (21). This tool included four domains: selection, ascertainment, causality, and reporting. The Newcastle-Ottawa scale was used for quality assessment in cohort studies (22).

Statistical analysis

The pooled results were reported as proportions with 95% confidence intervals (CIs). Heterogeneity was evaluated using the I² statistic (23). Values of I²<25%, 25–50%, and >50% indicated low, moderate, and high heterogeneity, respectively. When I²<50%, a fixed effects model was used; however, when I²>50%, a random effects model was selected. Sensitivity analysis was conducted to explore the source of heterogeneity and evaluate the stability of the pooled results. The funnel plots and Egger's test evaluated potential publication bias when the number of included studies was not less than ten in the analysis (24). All statistical analyses were conducted by the 'meta' (version 5.2-0) and 'metafor' (version 3.4-0) packages in the RStudio software (version 1.2.5033, RStudio PBC, Boston, MA, USA).

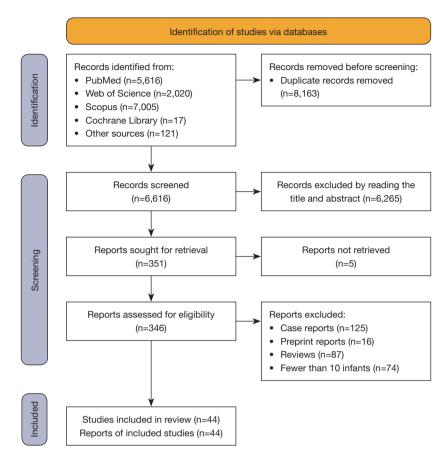


Figure 1 The flowchart of study selection.

Results

Study selection and characteristics of included studies

A total of 14,779 potentially relevant studies were obtained in the databases. Finally, based on our inclusion and exclusion criteria, 44 studies with 6,304 infants with SARS-CoV-2 infections were included in this study. Of these studies, 13 studies (25-37), 23 studies (38-60), and 8 studies (61-68) published in 2020, 2021, and 2022, respectively. The detailed process of study selection is shown in *Figure 1*. The detailed clinical characteristics included are presented in *Table 1*. Results of quality assessments are demonstrated in Table S1 and Table S2.

Meta-analysis

Proportion of asymptomatic infection

Totally, 22 studies (25-30,36,38-43,54,55,60-65,68) with 23 trials of 3,301 infants with SARS-CoV-2 infections were included for asymptomatic infection analysis. The

proportion of asymptomatic infection was 20% (95% CI: 11-28%, I²=97%, P<0.01) in infants with SARS-CoV-2 infection (*Table 2* and *Figure 2A*).

Proportion of disease severity

Overall, ten studies (25,29-32,36,37,41,43,58) reported mild symptoms, eight studies reported moderate symptoms (30,31,36,37,41,43,44,58), and nine studies (25-27,29,30,36-38,58) reported severe symptoms. The proportion of mild symptoms was 48% (95% CI: 30–65%, I²=96%, P<0.01, *Figure 2B*), moderate symptoms was 27% (95% CI: 10–44%, I²=93%, P<0.01, *Figure 3A*), and severe symptoms was 8% (95% CI: 0–16%, I²=90%, P<0.01, *Figure 3B*, *Table 2*).

Proportion of clinical symptoms

As shown in *Table 2*, respiratory symptoms were evaluated in 22 studies (26,28,33,34,38,39,45-52,54,55,57,58,62,64,65,67), and the proportion of these was 23% (95% CI: 18–29%, I^2 =81%, P<0.01, Figure S1A). Nasal symptoms were evaluated in 17 studies (27,28,33,38,39,45,47,48,52-55,58,62,63,65,67),

Diaz-Convilient et.i. S1 Mixed 16/37 <th>Total Total Age Author number of Age patients group*</th> <th>Total number of patients</th> <th></th> <th>Number of asymptotic infections</th> <th>Mild symptoms</th> <th>Moderate symptoms</th> <th>Severe symptoms</th> <th>Respiration symptoms</th> <th>Nasal symptoms</th> <th>Fever</th> <th>Cough</th> <th>Diarrhea</th> <th>Vomit</th> <th>Rash</th> <th>Feeding difficulty</th>	Total Total Age Author number of Age patients group*	Total number of patients		Number of asymptotic infections	Mild symptoms	Moderate symptoms	Severe symptoms	Respiration symptoms	Nasal symptoms	Fever	Cough	Diarrhea	Vomit	Rash	Feeding difficulty
0 22 vector 222 vector 15/22 vector 5/23 36 Mked 1/36 - - - - - - 5/13 5/13 36 Mked 1/36 - - - - - - 5/13 14 Mked 5/32 6/61 7/39 1/39 -<	Díaz-Corvillón <i>et al.</i> [2020] (25)	37	Mixed	16/37	18/21	1	3/21	1	1	1	1	I	1	I	1
36 Mked 1/36 - - - - - - - 1/36 1/36 16 Mked 1/38 - - - - - - - - - 1/36	Schwartz <i>et al.</i> [2022] (26)		Neonate	2/22	I	I	I	15/22	I	5/22	3/22	1/22	I	I	1/22
18 Mixed 1/18 - - - - 1/18 5/18 1/14 528 Mixed 43/528 104/528 -	Sun <i>et al.</i> [2020] (27)	36	Mixed	1/36	I	I	I	I	6/36	17/36	28/36	9/36	4/36	I	I
528 Mixed 33/528 104/528 - 21/528 -	Mithal <i>et al.</i> [2020] (28)	18	Mixed	1/18	I	I	I	1/18	5/18	14/18	8/18			1/18	5/18
61 Mixed 5/39 26/61 7/39 1/39 - - - 0 23 Mixed 5/23 6/23 11/23 1/23 -	Bellino <i>et al.</i> [2020] (29)	528	Mixed	43/528	104/528	I	21/528	I	I	I	I	I	I	I	I
0) 23 Mixed 5/23 6/23 11/23 1/23 $ -$	Parri <i>et al.</i> [2020] (36)	61	Mixed	5/39	26/61	7/39	1/39	I	I	I	I	I	I	I	I
66 Neomate 7/66 - - 28/66 24/66 26/66 35/66 82 Mixed 17/82 - - - 13/82 29/82 42/82 41 Mixed 3/41 -	Maltezou <i>et al.</i> [2020] (30)	23	Mixed	5/23	6/23	11/23	1/23	I	I	I	I	I	I	I	I
82 Mixed 17/82 - - - 13/82 29/82 42/82 41 Mixed 3/41 - <td< td=""><td>Gale <i>et al.</i> [2021] (38)</td><td></td><td>Neonate</td><td>7/66</td><td>I</td><td>I</td><td>28/66</td><td>24/66</td><td>26/66</td><td>35/66</td><td>11/66</td><td>4/66</td><td>I</td><td>2/66</td><td>33/66</td></td<>	Gale <i>et al.</i> [2021] (38)		Neonate	7/66	I	I	28/66	24/66	26/66	35/66	11/66	4/66	I	2/66	33/66
41Mixed $3/41$ $ -$ <td>Biko <i>et al.</i> [2021] (39)</td> <td>82</td> <td>Mixed</td> <td>17/82</td> <td>I</td> <td>I</td> <td>I</td> <td>13/82</td> <td>29/82</td> <td>42/82</td> <td>37/82</td> <td>10/82</td> <td>12/82</td> <td>I</td> <td>8/82</td>	Biko <i>et al.</i> [2021] (39)	82	Mixed	17/82	I	I	I	13/82	29/82	42/82	37/82	10/82	12/82	I	8/82
27 Mixed $3/27$ $8/27$ $1/27$ $ -$ <	Peng <i>et al.</i> [2021] (40)	41	Mixed	3/41	I	I	I	I	I	I	I	I	I	I	I
3 12 $Mixed$ $4/12$ $ 5/12$ $3/12$ $7/12$ 36 $Mixed$ $2/36$ $ 18/36$ 143 $Mixed$ $2/36$ $ 18/36$ 143 $Mixed$ $102/132$ $ 18/36$ 39 $Mixed$ $102/132$ $ 36$ $Mixed$ $102/132$ $ 22$ $Mixed$ $102/132$ $ 22$ $Mixed$ $1/22$ $ 86$ $Mixed$ $1/22$ $ 176$ $Nixed$ $1/13$ $ 176$ $Nixed$ $1/13$ $ 176$ $Nixed$ $1/13$ $ 176$ $Nixed$ $1/13$ $ 116$ $Mixed$ $1/16$ $-$	Soysal <i>et al.</i> [2021] (41)	27	Mixed	3/27	8/27	1/27	I	I	I	I	I	I	I	I	I
36 Mixed 2/36 - - - - - 18/36 143 Mixed 102/132 - - - - - 18/36 39 Mixed 102/132 -	Kulkarni <i>et al.</i> [2021] (55)	12	Mixed	4/12	I	I	I	5/12	3/12	7/12	I	I	1/12	I	2/12
143 Mixed 102/132 - <	Zhang <i>et al.</i> [2021] (42)	36	Mixed	2/36	I	I	I	I	I	18/36	13/36	5/36	I	I	I
39 Mixed 14/27 -	More <i>et al.</i> [2021] (60)	143	Mixed	102/132	I	I	I	I	I	I	I	I	I	I	I
22 Mixed 1/22 - - - 1/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/22 2/23 2/24	More <i>et al.</i> [2021] (60)	39	Mixed	14/27	I	I	I	I	I	I	I	2/39	I	I	I
36 Mixed 2/36 5/36 - - - 2/34 86 Mixed 30/86 - - - - 2/34 176 Neonate 19/176 - - - - - - 2/34 176 Neonate 19/176 -	Paret <i>et al.</i> [2021] (54)	22	Mixed	1/22	I	I	I	1/22	2/22	20/22	3/22	I	1/22	2/22	2/22
86 Mixed 30/86 - 13/176 113/176 13/1	Shaiba <i>et al.</i> [2021] (65)	36	Mixed	2/36	25/36	5/36	I	I	I	25/34	I	I	I	I	I
176 Neonate 19/176 - - - 33/176 14/176 113/176 13 Mixed 1/13 - - - 9/13 8/13 829 Mixed 1/13 - - - 9/13 8/13 829 Mixed 14/829 - - - 9/13 8/13 115 Mixed 74/115 - - - - - - - 898 Mixed 140/898 - - - 218/898 603/898 603/898 31 - - 6/31 25/31 0/31 -	Ochoa <i>et al.</i> [2022] (61)	86	Mixed	30/86	I	I	I	I	I	I	I	I	I	I	I
13 Mixed 1/13 - - - 9/13 8/13 8/13 829 Mixed 14/829 -	Akin <i>et al.</i> [2022] (62)		Neonate	19/176	I	I	I	33/176	14/176	113/176	38/176	14/176	I	3/176	45/176
829 Mixed 14/829 - - - - - - - - - - - - - 1/115 1 - 7/1/115 - 2/1/115 - 2/1/115	lijima <i>et al.</i> [2022] (63)	13	Mixed	1/13	I	I	I		9/13	8/13	7/13	I	2/13	I	7/13
115 Mixed 74/115 - - 13/115 - 71/115 898 Mixed 140/898 - - 2 2 2 2 31 - - 6/31 25/31 0/31 - - - -	Funk <i>et al.</i> [2022] (68)	829	Mixed	14/829	I	I	I		I	I	I	I	I	I	I
898 Mixed 140/898 218/898 219/898 603/898 31 6/31 25/31 0/31	Albuali <i>et al.</i> [2022] (64)	115	Mixed	74/115	I	I	I	13/115	I	71/115	30/115	15/115	I	I	I
31 – – 6/31 25/31 0/31 – – –	Shaiba <i>et al.</i> [2022] (65)	868	Mixed	140/898	I	I	ļ	218/898	219/898	603/898	216/898	217/898	103/898	63/898	158/898
	Lu X <i>et al.</i> [2020] (37)	31	I	I	6/31	25/31	0/31	I	I	I	I	I	I	I	I
Kainth <i>et al.</i> [2020] (31) 19 – – 14/19 5/19 0/19 – – – – – –	Kainth <i>et al.</i> [2020] (31)	19	I	I	14/19	5/19	0/19	I	I	I	I	I	I	I	I

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Table 1 (continued)														
Author	Total number of patients	Age group*	Number of asymptotic infections	Mild symptoms	Moderate symptoms	Severe symptoms	Respiration symptoms	Nasal symptoms	Fever	Cough	Diarrhea	Vomit	Rash	Feeding difficulty
Panetta <i>et al.</i> [2020] (32)	27	ı	I	24/27	I	I	I	I	22/27	ı	ı	ı	ı	1
Drouin <i>et al.</i> [2021] (58)	97	Mixed	I	25/97	17/97	10/97	14/97	22/97	44/97	17/97	12/97	15/97	6/97	21/97
Bayesheva <i>et al.</i> [2021] (44)	156	I	I	I	20/156	0/156	I	I	I	I	I	I	I	I
Zachariah <i>et al.</i> [2020] (34)	14	Mixed	I	I	I	I	1/14	I	I	I	I	I	I	I
Kanburoglu <i>et al.</i> [2020] (33)	37	Neonate	I	I	I	I	9/37	2/37	18/37	10/37	2/37	I	1/37	6/37
Leung [2021] (50)	749	Neonate	I	I	I	I	187/749	I	402/749	394/749	I	I	I	I
Ouldali <i>et al.</i> [2021] (47)	193	Mixed	I	I	I	I	53/189	117/188	162/186	71/188	44/190	24/189	I	7/176
Nanavati <i>et al.</i> [2021] (46)	21	Neonate	I	I	I	I	5/21	I	I	I	I	1/21	I	I
Shah <i>et al.</i> [2021] (57)	18	Neonate	I	I	I	I	5/18	I	3/18	I	I	I	I	I
Spoulou <i>et al.</i> [2021] (48)	14	Mixed	I	I	I	I	2/14	9/14	11/14	3/14	4/14	I	I	3/14
Yaman e <i>t al.</i> [2022] (49)	12	Neonate	I	I	I	I	5/12	I	5/12	6/12	I	I	I	7/12
Yarden Bilavski <i>et al.</i> [2021] (52)	75	Mixed	I	I	I	I	1/75	18/75	I	12/75	6/75	I	3/75	6/75
Munian <i>et al.</i> [2021] (51)	19	Neonate	I	I	I	I	7/19	I	I	I	2/19	2/19	I	3/19
Ji <i>et al.</i> [2021] (45)	40	Mixed	I	I	I	I	2/40	5/40	30/40	28/40	8/40	4/40	I	I
Marks <i>et al.</i> [2022] (67)	1,137	Mixed	I	I	I	I	85/252	135/252	I	119/252	I	40/252	I	75/252
Hassan <i>et al.</i> [2021] (53)	41	Neonate	I	I	I	I	I	16/41	36/41	12/41	6/41	3/41	I	9/41
McLaren <i>et al.</i> [2020] (35)	20	Mixed	I	I	I	I	I	I	7/20	I	I	I	I	I
Leibowitz <i>et al.</i> [2021] (56)	20	Mixed	I	I	I	I	I	I	20/20	I	I	I	I	I
Andina-Martinez <i>et al.</i> [2022] (66)	12	Mixed	I	I	I	I	I	I	9/12	I	I	I	I	1/12
Wanga <i>et al.</i> [2021] (59)	206	Mixed	I	I	I	I	I	I	I	I	I	I	I	7/176
*, the mixed studies were infants (≤1 year).	e infants (≤	s1 year).												

Table 2 Results of meta-analysis	alysis										
Group	Total and subgroup analyses	Subcategories	No. of trials	No. of patients	Model	Proportion	95% CI	-	τ2	٩	Publication bias
Asymptomatic infection	Total analysis		23	3,301	Random	0.20	0.11-0.28	97%	0.0412	<0.01	Yes
	Subgroup by year	2020	7	703	Random	0.13	0.04-0.22	77%	0.0121	<0.01	NC
		2021	10	481	Random	0.22	0.07-0.38	97%	0.058	<0.01	None
		2022	9	2,117	Random	0.22	0.04-0.41	%66	0.0529	<0.01	NC
	Subgroup by number	<100	17	623	Random	0.11	0.09-0.13	80%	0.0144	<0.01	Yes
		≥100	9	2,678	Random	0.29	0.04-0.55	%66	0.1039	<0.01	NC
	Subgroup by age	Neonate	9	460	Random	0.26	0.12-0.55	96%	0.8092	<0.01	NC
		Infants (mixed age)	17	2,841	Random	0.15	0.07-0.23	96%	0.0233	<0.01	Yes
Disease severity	Mild symptoms	I	10	870	Random	0.48	0.30-0.65	96%	0.0752	<0.01	Yes
	Moderate symptoms	I	8	428	Random	0.27	0.10-0.44	93%	0.0579	<0.01	NC
	Severe symptoms	I	6	980	Random	0.08	0-0.16	%06	0.0136	<0.01	NC
Clinical features	Respiration symptoms	I	22	2,948	Random	0.23	0.18-0.29	81%	0.2304	<0.01	Yes
	Subgroup by year	2020	4	91	Random	0.26	0-0.53	91%	0.0749	<0.01	NC
		2021	14	1,416	Random	0.23	0.18-0.30	%99	0.1363	<0.01	None
		2022	4	1,441	Random	0.21	0.14-0.32	88%	0.1596	<0.01	NC
	Subgroup by number	<100	16	569	Random	0.21	0.12-0.29	88%	0.0248	<0.01	Yes
		≥100	9	2,379	Random	0.24	0.18-0.30	80%	0.0761	<0.01	NC
	Subgroup by age	Neonate	6	1,120	Random	0.32	0.23-0.41	73%	0.0136	<0.01	NC
		Infants (mixed age)	13	1,828	Random	0.15	0.09-0.21	95%	0.0107	<0.01	None
	Nasal symptoms		17	2,067	Random	0.31	0.21-0.40	95%	0.0342	<0.01	Yes
	Subgroup by year	2020	С	91	Random	0.16	0.07-0.35	55%	0.2555	0.11	NC
		2021	10	637	Random	0.33	0.21-0.44	92%	0.0291	<0.01	Yes
		2022	4	1,339	Random	0.30	0.12-0.75	98%	0.8751	<0.01	NC
	Subgroup by number	<100	13	553	Random	0.28	0.19–0.37	84%	0.0244	<0.01	Yes
		≥100	4	1,514	Random	0.29	0.12-0.71	88%	0.8236	<0.01	NC
	Subgroup by age	Neonate	4	320	Random	0.22	0.04-0.40	93%	0.0325	<0.01	NC
		Infants (mixed age)	13	1,747	Random	0.33	0.23-0.44	94%	0.0345	<0.01	None

Table 2 (continued)

Table 2 (continued)											
Group	Total and subgroup analyses	Subcategories	No. of trials	No. of patients	Model	Proportion	95% CI	-2	42	٩	Publication bias
	Fever		26	2,803	Random	0.64	0.57-0.71	92%	0.061	<0.01	None
	Subgroup by year	2020	9	160	Random	0.52	0.34-0.71	81%	0.0434	<0.01	NC
		2021	15	1,429	Random	0.66	0.56-0.77	95%	0.071	<0.01	None
		2022	S	1,214	Fixed	0.67	0.64-0.69	%0	0	0.7	NC
	Subgroup by number	<100	21	679	Random	0.62	0.54-0.72	88%	0.0813	<0.01	None
		≥100	5	2,124	Random	0.67	0.55-0.78	96%	0.0191	<0.01	NC
	Subgroup by age	Neonate	œ	1,121	Random	0.50	0.34-0.66	86%	0.046	<0.01	NC
		Infants (mixed age)	18	1,682	Random	0.68	0.60-0.77	91%	0.0507	<0.01	None
	Cough		21	2,989	Random	0.34	0.26-0.42	93%	0.0308	<0.01	None
	Subgroup by year	2020	4	113	Random	0.41	0.13-0.69	93%	0.0739	<0.01	NC
		2021	12	1,422	Random	0.33	0.23-0.44	94%	0.0279	<0.01	None
		2022	S	1,454	Random	0.32	0.21-0.44	93%	0.0166	<0.01	NC
	Subgroup by number	<100	15	611	Random	0.35	0.24-0.45	89%	0.0385	<0.01	None
		≥100	9	2,378	Random	0.35	0.24-0.45	97%	0.0181	<0.01	NC
	Subgroup by age	Neonate	7	1,103	Random	0.29	0.18-0.41	95%	0.0199	<0.01	NC
		Infants (mixed age)	14	1,886	Random	0.37	0.27-0.48	91%	0.0362	<0.01	None
	Diarrhea		17	1,983	Random	0.13	0.09-0.16	84%	0.0037	<0.01	Yes
	Subgroup by year	2020	ო	95	Random	0.11	0.01-0.25	71%	0.0184	0.03	NC
		2021	1	669	Random	0.13	0.09-0.17	63%	0.0025	<0.01	None
		2022	ო	1,189	Random	0.15	0.06-0.25	96%	0.0068	<0.01	NC
	Subgroup by number	<100	13	604	Fixed	0.1	0.07-0.12	34%	0.0005	0.11	Yes
		≥100	4	1,379	Random	0.17	0.10-0.25	91%	0.0106	<0.01	NC
	Subgroup by age	Neonate	7	400	Fixed	0.07	0.05-0.10	%0	0	0.78	NC
		Infants (mixed age)	10	1,583	Random	0.17	0.13-0.22	73%	0.0051	<0.01	Yes
	Vomit		13	1,722	Fixed	0.13	0.11-0.15	%0	0.006	0.76	None
	Subgroup by year	2021	6	523	Fixed	0.11	0.09-0.14	%0	0	0.84	NC
		2022	ო	1,163	Fixed	0.13	0.10-0.18	45%	0.032	0.16	NC

Table 2 (continued)

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Table 2	

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Group	Total and subgroup analyses	Subcategories	No. of trials	No. of patients	Model	Proportion	95% CI	-2	ß	٩	Publication bias
	Subgroup by number	<100	10	383	Fixed	0.13	0.10-0.17	%0	0	0.85	Yes
		≥100	ო	1,339	Fixed	0.13	0.10-0.15	34%	0.0002	0.22	NC
	Subgroup by age	Neonate	ი	81	Fixed	0.07	0.02-0.14	%0	0	0.81	NC
		Infants (mixed age)	10	1,641	Fixed	0.13	0.11-0.14	%0	0.0073	0.71	None
	Rash		œ	1,389	Random	0.04	0.02-0.06	63%	0.0004	<0.01	NC
	Subgroup by year	2021	4	260	Fixed	0.05	0.02-0.08	%0	0	0.64	NC
	Subgroup by number	<100	9	315	Fixed	0.04	0.02-0.07	%0	0	0.84	NC
	Subgroup by age	Neonate	ი	279	Fixed	0.02	0-0.04	%0	0	0.68	NC
		Infants (mixed age)	5	1,110	Fixed	0.06	0.04-0.07	%0	0	0.87	NC
	Feeding difficulty		19	2,044	Random	0.20	0.14-0.26	89%	0.0145	<0.01	Yes
	Subgroup by year	2020	с	77	Fixed	0.19	0.11-0.31	40%	0.064	0.19	NC
		2021	10	440	Random	0.22	012-0.31	83%	0.0187	<0.01	None
		2022	9	1,527	Random	0.21	0.09-0.32	95%	0.0167	<0.01	NC
	Subgroup by number	<100	15	542	Random	0.21	0.13-0.28	80%	0.0175	<0.01	Yes
		≥100	4	1,502	Random	0.16	0.07-0.37	93%	0.6826	<0.01	NC
	Subgroup by age	Neonate	7	373	Random	0.26	0.13-0.39	87%	0.0264	<0.01	NC

Cl, confidence interval; NC, not conducted.

None

<0.01

0.0081

89%

0.10-0.23

0.16

Random

1,671

42

Infants (mixed age)

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A	Study	Events	Total		Proportion	95% CI	Weight (common)	
	Diaz-Corvillon et al.(2020)	16	37	: :	0.43	[0.27; 0.61]	0.2%	4.0%
	Schwartz et al.(2022)	2	22			[0.01; 0.29]		4.3%
	Sun et al.(2020)	1	36 -	• <u>+</u>		[0.00; 0.15]		4.6%
	Mithal et al.(2020)	1	18 -			[0.00; 0.27]		4.4%
	Bellino et al.(2020)	43	528	·		[0.06; 0.11]		4.7%
	Parri et al.(2020)	5	39			[0.04; 0.27]		4.4%
	Maltezou et al.(2020)	5	23	·	0.22	[0.07; 0.44]	0.2%	4.0%
	Gale et al.(2021)	7	66			[0.04; 0.21]		4.5%
	Biko et al.(2021)	17	82		0.21	[0.13; 0.31]	0.7%	4.5%
	Peng et al.(2021)	3	41		0.07	[0.02; 0.20]	0.8%	4.5%
	Soysal et al.(2021)	3	27		0.11	[0.02; 0.29]	0.4%	4.3%
	Kulkarni et al.(2021)	4	12			0.10: 0.65		3.2%
	Zhang et al.(2021)	2	36		0.06	[0.01; 0.19]	0.9%	4.5%
	More et al.(2021)-1	102	132		0.77	[0.69; 0.84]	1.0%	4.5%
	More et al.(2021)-2	14	27		0.52	[0.32; 0.71]	0.1%	3.8%
	Paret et al. (2021)	1	22 -	+	0.05	[0.00; 0.23]	0.7%	4.5%
	Shaiba et al.(2021)	2	36		0.06	[0.01; 0.19]	0.9%	4.5%
	Ochoa et al.(2022)	30	86		0.35	[0.25; 0.46]	0.5%	4.4%
	Akin et al.(2022)	19	176		0.11	[0.07; 0.16]	2.5%	4.6%
	lijima et al.(2022)	1	13 -		0.08	[0.00; 0.36]	0.2%	4.1%
	Funk et al.(2022)	14	829		0.02	[0.01; 0.03]	67.3%	4.7%
	Albuali et al.(2022)	74	115		0.64	[0.55; 0.73]	0.7%	4.5%
	Shaiba et al.(2022)	140	898	*	0.16	[0.13; 0.18]	9.2%	4.7%
	Common effect model		3301	ò		[0.05; 0.07]		
	Random effects model				0.20	[0.11; 0.28]		100.0%
	Heterogeneity: $I^2 = 97\%$, $\tau^2 =$	0.0412, <i>p</i>	0 < 0.01	0.2 0.4 0.6 0.8				
В							Weight	Weight
-	Study	Events	Total		Proportion	95% CI	(common)	
	Lu X et al.(2020)	6	31 -		0,19	[0.07; 0.37]	3.8%	10.0%
	Diaz-Corvillon et al.(2020)	18	21	· · · · ·		[0.64: 0.97]		9.9%
	Kainth et al.(2020)	14	19			[0.49; 0.91]		9.4%
	Bellino et al.(2020)	104	528	-		[0.16; 0.23]	63.5%	10.6%
	Parri et al.(2020)	26	61			[0.30; 0.56]		10.2%
	Maltezou et al.(2020)	6	23			[0.10: 0.48]		9.6%
	Panetta et al.(2020)	24	27			[0.71; 0.98]		10.2%
	Soysal et al.(2021)	8	27			[0.14: 0.50]		9.7%
	Shaiba et al.(2021)	25	36			[0.52; 0.84]		9.9%
	Drouin et al.(2021)	25	97			[0.17; 0.36]		10.4%
	Common effect model		870	\$	0.30	[0.27; 0.33]	100.0%	
	Random effects model				0.48	[0.30; 0.65]		100.0%
	Heterogeneity: $I^2 = 96\%$, $\tau^2 =$	0.0752, p	0.01			- · ·		
	C , , , , , , , , , ,			0.2 0.4 0.6 0.8				

Figure 2 Forest plot of two analyses. (A) Asymptomatic infection analysis; (B) mild symptoms analysis. CI, confidence interval.

and the proportion of these was 31% (95% CI: 21–40%, $I^2=95\%$, P<0.01, Figure S1B). Fever was evaluated in 26 studies. Of these studies, six studies (26-28,32,33,35) published in 2020, 15 studies (38,39,42,43,45,47-50,53-58) published in 2021, and five studies (62-66) published in 2022. The proportion of this symptom was 64% (95% CI: 57–71%, $I^2=92\%$, P<0.01, Figure S1C). Cough was evaluated in 21 studies (26-28,33,38,39,42,45,47-50,52-54,58,62-65,67), and the proportion of this symptom was 34% (95% CI: 26–42%, $I^2=93\%$, P<0.01, Figure S1D). Diarrhea were evaluated in 17 studies (26,27,33,38,39,42,45,47,48,51-53,58,60,62,64,65), and the proportion of this symptom was 13% (95% CI: 9–16%, $I^2=84\%$, P<0.01, Figure S2A). Vomit was evaluated in 13 studies (27,39,45-47,51,53-55,58,63,65,67), and the

proportion of this symptom was 13% (95% CI: 11–14%, $I^2=0\%$, P=0.76, Figure S2B). Rashes were evaluated in 8 studies (28,33,38,52,54,58,62,65), and the proportion of this symptom was 4% (95% CI: 2–6%, $I^2=63\%$, P<0.01, Figure S2C). Feeding difficulty was evaluated in 19 studies (26,28,33,38,39,48,49,51-55,58,59,62,63,65-67), and the proportion of this symptom was 20% (95% CI: 14–26%, $I^2=89\%$, P<0.01, Figure S2D). Results of subgroup analyses were provided in *Table 2*.

Sensitivity analysis

Sensitivity analysis was performed by excluding individual studies in the overall analysis. Results were as follows:

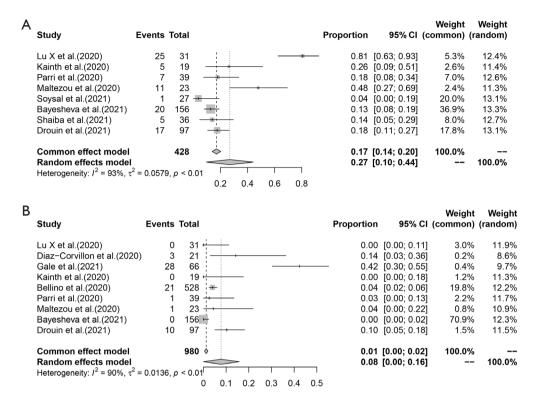


Figure 3 Forest plot of two analyses. (A) Moderate symptoms analysis; (B) severe symptoms analysis. CI, confidence interval.

no study showed a proportion of >1% for respiratory symptoms, diarrhea, and vomit (Figure S3A-S3C); no study showed a proportion of >2% for fever, cough, and feeding difficulty (Figure S3D-S3F); no study showed a proportion of >3% for asymptomatic infection and nasal symptoms (Figure S3G,S3H); and no study showed a proportion of >5% for mild symptoms (Figure S3I).

Publication bias

Publication bias was found in the following analyses: asymptomatic infection; mild symptoms; respiratory symptoms; nasal symptoms; diarrhea; and feeding difficulty (*Table 2*). Fever analysis, cough analysis, and vomit analysis did not show the presence of publication bias (*Table 2*).

Discussion

To the best of our knowledge, this is the most comprehensive systematic review and meta-analysis that summarizes current data on clinical features of infants with SARS-CoV-2 infection. This study found that the prevalence of asymptomatic infection was 20% in infants with SARS-CoV-2 infection. Disease severity were mild in 48% of infants, moderate in 27% of infants, and severe in 8% of infants with COVID-19. Notably, the most common features of SARS-CoV-2 infection in infants were fever (64%), cough (34%), and nasal symptoms (31%).

Infants infected with the SARS-CoV-2 virus are often asymptomatic and present with no clinical symptoms or significant chest imaging findings; however, these asymptomatic infections are still contagious (69). Infants with asymptomatic infection may be a source of transmission, which poses a challenge for infection control and requires timely diagnosis. Studies reported that the rate of asymptomatic infants ranged from 2% to 77% (60,68). By performing a meta-analysis, this study found that the prevalence of asymptomatic infection was 20% in 3,301 infants with SARS-CoV-2 infection. We conducted further subgroup analyses by year, because most of studies did not provide information on the SARS-CoV-2 variant. The subgroup analysis found that the proportion of asymptomatic infection is 13%, 22%, and 22% in 2020, 2021, and 2022, respectively. The proportion of asymptomatic infection was lower in 2020 than in 2021 and 2022. Early in 2020, Dong et al. (15) reported the

asymptomatic rate of infants was 1.9% (7/376) in China. Our study found a higher asymptomatic rate by combining studies published in 2020. This may be attributable to the evolution of virus. On November 30, 2021, the United States designated the Omicron variant as a variant of concern. The variant led to a higher rate of pediatric hospitalizations in children younger than 17 years (70). A recent study reported that 13.5% (14/104) of children (age <3 years) with SARS-CoV-2 infection were asymptomatic cases during the outbreak of Omicron (71). However, the number of published studies of infants infected with the Omicron variant is limited in issued studies. Thus, further investigation into the rate of asymptomatic infections in infants is necessary during the Omicron pandemic.

Our analysis of the combined data found that 48% of infants infected with SARS-CoV-2 had mild disease, 27% had moderate disease, and 8% had severe disease. There are two explanations for the higher incidence of mild/ moderate disease in infants. First, children may have a different qualitative response to the SARS-CoV-2 than adults (72). Second, the angiotensin-converting enzyme-2 receptors bind to SARS-CoV-2 spike protein and promote the incorporation of SARS-CoV-2 into human cells (73). Children have less angiotensin-converting enzyme-2 in the nasal epithelium, which may contribute to the protection against SARS-CoV-2 (74). A recent study reported that by measuring hospitalization rates, children with Omicron variant infection have less severe disease than the Delta variant infection (75). Currently, the number of published studies on infants infected with the Omicron variant is still limited; however, close attention should be given to the infants, regardless of the variant type.

A recent meta-analysis (76) included 215 studies with 132,647 COVID-19 patients that found four common features: fever (76.2%), coughing (60.4%), fatigue (33.6%), and dyspnea (26.2%). Similarly, our study found that fever was the most common clinical feature (64%), followed by cough (34%), and nasal symptoms (31%) in infants with COVID-19. Furthermore, our subgroup analyses found that while most of the clinical features (such as fever, nasal symptoms, and respiratory symptoms) were mild in the neonate group, feeding difficulty were severe; this may be in relation to neonates' vulnerability to feeding difficulties. Moreover, feeding difficulty may be the only present symptom in infants; therefore, the possibility of COVID-19 should not be excluded, particularly when infants have had contact with SARS-CoV-2 infected.

Other features, such as fatigue and myalgia, were not

listed in the included studies. This is most likely because infants have underdeveloped language skills and, therefore cannot communicate symptoms. Notably, a longitudinal cohort study (77) investigated 1,127 COVID-19 survivors with 2 years of follow-up and reported several prevalent symptoms, such as sleep difficulties (31%), fatigue or muscle weakness (31%), and joint pain (18%); none of these symptoms could be mentioned in infants. This raises at least three scientific questions that need to be urgently answered: (I) Will these infants develop complications in the distant future after infection, such as those in adults? (II) Will these complications heal on their own? If so, approximately how long will these symptoms persist in infants? (III) Do these complications affect the infant's brain development, including higher cognitive functioning? These is a need for future longitudinal prospective cohort studies that must respond to these scientific questions, as they are critical to infant development.

Certain limitations should be addressed. First, very few included studies reported the detailed variants of SARS-CoV-2; thus, this study could not conduct subgroup analysis based on variants. Second, there was significant heterogeneity in most of the analyses, and while further subgroup analyses also showed considerable heterogeneity, this may have been due to differences in methods and bias of included studies. However, by sensitivity analysis, we found that no study showed a proportion of more than 5% in the overall analysis, which supports our results' reliability. Third, only published studies were included for meta-analysis, while preprint studies and unpublished data were excluded; therefore, publication bias may be evitable. Fourth, most of the included studies were retrospective designs; therefore, selection bias exists in this study. Fifth, six of the analyses found evidence of publication bias. This may by caused by factors such as language bias and availability bias; however, further subgroup analyses found the proportions were similar in these six kinds of analyses, which supported the reliable of our results. Considering these limitations, well-designed trials are needed in future studies.

In conclusion, this study found that 20% of infants with SARS-CoV-2 infections were asymptomatic, while most infants with COVID-19 presented with mild symptoms. Additionally, fever and cough were the most common clinical features in these infants. This study explores the clinical features of infants infected with SARS-CoV-2 to aid health policymakers in constituting a more logical policy for the COVID-19 pandemic.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm. amegroups.com/article/view/10.21037/apm-22-933/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm. amegroups.com/article/view/10.21037/apm-22-933/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

- Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
- 2. Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med 2021;28:taab124.
- Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science 2021;372:eabg3055.
- Fan Y, Li X, Zhang L, et al. SARS-CoV-2 Omicron variant: recent progress and future perspectives. Signal Transduct Target Ther 2022;7:141.
- Ikuse T, Aizawa Y, Shobukawa Y, et al. Household Secondary Transmission of the Severe Acute Respiratory Syndrome Coronavirus 2 Alpha Variant From a

Community Cluster in a Nursery in Japan. Pediatr Infect Dis J 2022;41:e358-64.

- Garnett L, Tse C, Funk D, et al. Differential Infectivity of Original and Delta Variants of SARS-CoV-2 in Children Compared to Adults. Microbiol Spectr 2022. [Epub ahead of print]. doi: 10.1128/spectrum.00395-22.
- Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet 2022;399:1303-12.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
- Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020;20:911-9.
- Xiao F, Chen B, Xiao T, et al. Children with SARS-CoV-2 infection during an epidemic in China (outside of Hubei province). Ann Transl Med 2020;8:849.
- Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020;370:m3249.
- Docherty AB, Harrison EM, Green CA, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
- Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323:2052-9.
- Al Mutair A, Alhumaid S, Alhuqbani WN, et al. Clinical, epidemiological, and laboratory characteristics of mildto-moderate COVID-19 patients in Saudi Arabia: an observational cohort study. Eur J Med Res 2020;25:61.
- Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020;145:e20200702.
- Kumar J, Kumar P, Saini SS, et al. Clinical characteristics & outcome of SARS-CoV-2 infected neonates presenting to paediatric emergency. Indian J Med Res 2022;155:189-96.
- Zimmermann P, Uka A, Buettcher M, et al. Neonates with SARS-CoV-2 infection: spectrum of disease from a prospective nationwide observational cohort study. Swiss Med Wkly 2022;152:w30185.

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- Cozzi G, Cortellazzo Wiel L, Amaddeo A, et al. Prevalence of SARS-CoV-2 positivity in infants with bronchiolitis: a multicentre international study. Arch Dis Child 2022. [Epub ahead of print]. pii: archdischild-2021-323559. doi: 10.1136/archdischild-2021-323559.
- 19. Raschetti R, Vivanti AJ, Vauloup-Fellous C, et al. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun 2020;11:5164.
- Bhuiyan MU, Stiboy E, Hassan MZ, et al. Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis. Vaccine 2021;39:667-77.
- Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60-3.
- 22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
- 23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
- 24. Xiao F, Yan K, Zhou W. Methadone versus morphine treatment outcomes in neonatal abstinence syndrome: A meta-analysis. J Paediatr Child Health 2019;55:1177-82.
- Díaz-Corvillón P, Mönckeberg M, Barros A, et al. Routine screening for SARS CoV-2 in unselected pregnant women at delivery. PLoS One 2020;15:e0239887.
- 26. Schwartz DA, Mohagheghi P, Beigi B, et al. Spectrum of neonatal COVID-19 in Iran: 19 infants with SARS-CoV-2 perinatal infections with varying test results, clinical findings and outcomes. J Matern Fetal Neonatal Med 2022;35:2731-40.
- 27. Sun D, Chen X, Li H, et al. SARS-CoV-2 infection in infants under 1 year of age in Wuhan City, China. World J Pediatr 2020;16:260-6.
- Mithal LB, Machut KZ, Muller WJ, et al. SARS-CoV-2 Infection in Infants Less than 90 Days Old. J Pediatr 2020;224:150-2.
- Bellino S, Punzo O, Rota MC, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics 2020;146:e2020009399.
- Maltezou HC, Magaziotou I, Dedoukou X, et al. Children and Adolescents With SARS-CoV-2 Infection: Epidemiology, Clinical Course and Viral Loads. Pediatr Infect Dis J 2020;39:e388-92.
- Kainth MK, Goenka PK, Williamson KA, et al. Early Experience of COVID-19 in a US Children's Hospital. Pediatrics 2020;146:e2020003186.
- 32. Panetta L, Proulx C, Drouin O, et al. Clinical

Characteristics and Disease Severity Among Infants With SARS-CoV-2 Infection in Montreal, Quebec, Canada. JAMA Netw Open 2020;3:e2030470.

- 33. Kanburoglu MK, Tayman C, Oncel MY, et al. A Multicentered Study on Epidemiologic and Clinical Characteristics of 37 Neonates With Community-acquired COVID-19. Pediatr Infect Dis J 2020;39:e297-302.
- 34. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA Pediatr 2020;174:e202430.
- McLaren SH, Dayan PS, Fenster DB, et al. Novel Coronavirus Infection in Febrile Infants Aged 60 Days and Younger. Pediatrics 2020;146:e20201550.
- Parri N, Lenge M, Cantoni B, et al. COVID-19 in 17 Italian Pediatric Emergency Departments. Pediatrics 2020;146:e20201235.
- 37. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Engl J Med 2020;382:1663-5.
- 38. Gale C, Quigley MA, Placzek A, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health 2021;5:113-21.
- Biko DM, Ramirez-Suarez KI, Barrera CA, et al. Imaging of children with COVID-19: experience from a tertiary children's hospital in the United States. Pediatr Radiol 2021;51:239-47.
- Peng X, Guo Y, Xiao H, et al. Overview of chest involvement at computed tomography in children with coronavirus disease 2019 (COVID-19). Pediatr Radiol 2021;51:222-30.
- 41. Soysal A, Gönüllü E, Arslan H, et al. Comparison of Clinical and Laboratory Features and Treatment Options of 237 Symptomatic and Asymptomatic Children Infected with SARS-CoV-2 in the Early Phase of the COVID-19 Pandemic in Turkey. Jpn J Infect Dis 2021;74:273-9.
- 42. Zhang Z, Guo L, Lu X, et al. Clinical analysis and pluripotent stem cells-based model reveal possible impacts of ACE2 and lung progenitor cells on infants vulnerable to COVID-19. Theranostics 2021;11:2170-81.
- Shaiba LA, Altirkawi K, Hadid A, et al. COVID-19 Disease in Infants Less Than 90 Days: Case Series. Front Pediatr 2021;9:674899.
- 44. Bayesheva D, Boranbayeva R, Turdalina B, et al. COVID-19 in the paediatric population of Kazakhstan. Paediatr Int Child Health 2021;41:76-82.
- 45. Ji SQ, Zhang M, Zhang Y, et al. Characteristics of immune

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and inflammatory responses among different age groups of pediatric patients with COVID-19 in China. World J Pediatr 2021;17:375-84.

- Nanavati R, Mascarenhas D, Goyal M, et al. A singlecenter observational study on clinical features and outcomes of 21 SARS-CoV-2-infected neonates from India. Eur J Pediatr 2021;180:1895-906.
- Ouldali N, Yang DD, Madhi F, et al. Factors Associated With Severe SARS-CoV-2 Infection. Pediatrics 2021;147:e2020023432.
- Spoulou V, Noni M, Koukou D, et al. Clinical characteristics of COVID-19 in neonates and young infants. Eur J Pediatr 2021;180:3041-5.
- Yaman A, Kandemir I, Varkal MA. Infants infected with SARS-CoV-2 and newborns born to mother diagnosed with COVID-19: clinical experience. Ir J Med Sci 2022;191:1263-8.
- Leung C. The younger the milder clinical course of COVID-19: Even in newborns? Pediatr Allergy Immunol 2021;32:358-62.
- Munian D, Das R, Hazra A, et al. Outcome of Neonates Born to COVID-Positive Women at 6 Months of Age. Indian Pediatr 2021;58:853-6.
- 52. Yarden Bilavski H, Balanson S, Damouni Shalabi R, et al. Benign course and clinical features of COVID-19 in hospitalised febrile infants up to 60 days old. Acta Paediatr 2021;110:2790-5.
- 53. Hassan M, Khalil A, Magboul S, et al. Neonates and Young Infants With COVID-19 Presented With Sepsis-Like Syndrome: A Retrospective Case Controlled Study. Front Pediatr 2021;9:634844.
- Paret M, Lalani K, Hedari C, et al. SARS-CoV-2 Among Infants <90 Days of Age Admitted for Serious Bacterial Infection Evaluation. Pediatrics 2021;148:e2020044685.
- 55. Kulkarni R, Rajput U, Dawre R, et al. Severe Malnutrition and Anemia Are Associated with Severe COVID in Infants. J Trop Pediatr 2021;67:fmaa084.
- 56. Leibowitz J, Krief W, Barone S, et al. Comparison of Clinical and Epidemiologic Characteristics of Young Febrile Infants with and without Severe Acute Respiratory Syndrome Coronavirus-2 Infection. J Pediatr 2021;229:41-47.e1.
- Shah B, Dande V, Rao S, et al. Outcome of Covid-19 Positive Newborns Presenting to a Tertiary Care Hospital. Indian Pediatr 2021;58:177-9.
- Drouin O, Hepburn CM, Farrar DS, et al. Characteristics of children admitted to hospital with acute SARS-CoV-2 infection in Canada in 2020. CMAJ 2021;193:E1483-93.

- Wanga V, Gerdes ME, Shi DS, et al. Characteristics and Clinical Outcomes of Children and Adolescents Aged
 <18 Years Hospitalized with COVID-19 - Six Hospitals, United States, July-August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1766-72.
- More K, Chawla D, Murki S, et al. Outcomes of Neonates Born to Mothers With Coronavirus Disease 2019 (COVID-19) - National Neonatology Forum (NNF) India COVID-19 Registry. Indian Pediatr 2021;58:525-31.
- Ochoa V, Díaz FE, Ramirez E, et al. Infants Younger Than 6 Months Infected With SARS-CoV-2 Show the Highest Respiratory Viral Loads. J Infect Dis 2022;225:392-5.
- 62. Akin IM, Kanburoglu MK, Tayman C, et al. Epidemiologic and clinical characteristics of neonates with late-onset COVID-19: 1-year data of Turkish Neonatal Society. Eur J Pediatr 2022;181:1933-42.
- 63. Iijima H, Funaki T, Kubota M. Clinical features and outcomes of coronavirus disease 2019 in early infants in Japan: A case series and literature review. J Infect Chemother 2022;28:582-6.
- 64. Albuali WH, AlGhamdi AA, Aldossary SJ, et al. Clinical profile, risk factors and outcomes of ric COVID-19: a retrospective cohort multicentre study in Saudi Arabia. BMJ Open 2022;12:e053722.
- 65. Shaiba LA, Hadid A, Altirkawi K, et al. SARS-CoV-2 Positivity in Early Infancy: A National Cohort From Saudi Arabia. Front Pediatr 2022;10:849659.
- 66. Andina-Martinez D, Alonso-Cadenas JA, Cobos-Carrascosa E, et al. SARS-CoV-2 acute bronchiolitis in hospitalized children: Neither frequent nor more severe. Pediatr Pulmonol 2022;57:57-65.
- Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of Infants and Children Aged 0-4 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022. MMWR Morb Mortal Wkly Rep 2022;71:429-36.
- Funk AL, Florin TA, Kuppermann N, et al. Outcomes of SARS-CoV-2-Positive Youths Tested in Emergency Departments: The Global PERN-COVID-19 Study. JAMA Netw Open 2022;5:e2142322.
- 69. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA 2020;323:1406-7.
- Marks KJ, Whitaker M, Anglin O, et al. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, July 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71:271-8.
- 71. Wang X, Chang H, Tian H, et al. Epidemiological and clinical features of SARS-CoV-2 infection in children

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during the outbreak of Omicron variant in Shanghai, March 7-31, 2022. Influenza Other Respir Viruses 2022;16:1059-65.

- 72. Brodin P. Why is COVID-19 so mild in children? Acta Paediatr 2020;109:1082-3.
- 73. Ni W, Yang X, Yang D, et al. Role of angiotensinconverting enzyme 2 (ACE2) in COVID-19. Crit Care 2020;24:422.
- Bunyavanich S, Do A, Vicencio A. Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults. JAMA 2020;323:2427-9.

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- 75. Butt AA, Dargham SR, Loka S, et al. Coronavirus Disease 2019 Disease Severity in Children Infected With the Omicron Variant. Clin Infect Dis 2022;75:e361-7.
- 76. Al Maqbali M, Al Badi K, Al Sinani M, et al. Clinical Features of COVID-19 Patients in the First Year of Pandemic: A Systematic Review and Meta-Analysis. Biol Res Nurs 2022;24:172-85.
- 77. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. Lancet Respir Med 2022;10:863-76.

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Supplementary

A Study Events Total	Weight Weight Proportion 95%-CI (common) (random)	C Study Events Total	Weight Weight Proportion 95%-Cl (common) (random)
Schwartz et al.(2022) 15 22	- 0.68 [0.45; 0.86] 4.8% 6.4%	Schwartz et al.(2022) 5 22	0.23 [0.08; 0.45] 0.1% 1.5%
Mithal et al.(2020) 1 18	0.06 [0.00; 0.27] 0.1% 1.4%	Sun et al.(2020) 17 36	0.47 [0.30; 0.65] 0.5% 3.4%
Zachariah et al.(2020) 1 14	0.07 [0.00; 0.34] 0.1% 1.4%	Mithal et al.(2020) 14 18	0.78 [0.52; 0.94] 0.9% 4.1%
Kanburoglu et al.(2020) 9 37	0.24 [0.12; 0.41] 1.2% 5.1%	McLaren et al.(2020) 7 20	0.35 [0.15; 0.59] 0.2% 2.1%
Gale et al.(2021) 24 66	0.36 [0.25; 0.49] 3.9% 6.2% 0.16 [0.09; 0.26] 1.6% 5.4%	Kanburoglu et al.(2020) 18 37	0.49 [0.32; 0.66] 0.5% 3.5% 0.81 [0.62; 0.94] 1.8% 4.5%
Biko et al.(2021) 13 82	0.16 [0.09; 0.26] 1.6% 5.4% 0.42 [0.15; 0.72] 0.9% 4.6%	Panetta et al.(2020) 22 27 Gale et al.(2021) 35 66	0.81 [0.62; 0.94] 1.8% 4.5% 0.53 [0.40; 0.65] 1.1% 4.2%
Paret et al.(2021) 5 12	0.42 [0.15, 0.72] 0.9% 4.6% 0.05 [0.00; 0.23] 0.1% 1.4%	Biko et al.(2021) 35 66	0.53 [0.40; 0.65] 1.1% 4.2%
Drouin et al.(2021) 14 97	0.14 [0.08; 0.23] 1.7% 5.5%	Kulkarni et al.(2021) 7 12 -	0.58 [0.28; 0.85] 0.3% 2.6%
Leung(2021) 187 749	0.25 [0.22; 0.28] 25.6% 6.8%	Zhang et al.(2021) 18 36	0.50 [0.33; 0.67] 0.5% 3.6%
Ouldali et al.(2021) 53 189	0.28 [0.22; 0.35] 7.6% 6.6%	Paret et al.(2021) 20 22	0.91 [0.71; 0.99] 3.3% 4.8%
Nanavati et al.(2021) 5 21	0.24 [0.08; 0.47] 0.7% 4.2%	Shaiba et al.(2021) 25 34	0.74 [0.56; 0.87] 1.4% 4.4%
Shah et al.(2021) 5 18	0.28 [0.10; 0.53] 0.7% 4.3%	Drouin et al.(2021) 44 97	0.45 [0.35; 0.56] 1.2% 4.3%
Spoulou et al.(2021) 2 14	0.14 [0.02; 0.43] 0.2% 2.4%	Leung(2021) 402 749	······································
Yaman et al.(2021) 5 12 Yarden Bilavski et al.(2021) 1 75 ↔	0.42 [0.15; 0.72] 0.9% 4.6% 0.01 [0.00; 0.07] 0.1% 1.3%	Leibowitz et al.(2021) 20 20 Ouldali et al.(2021) 162 186	1.00 [0.83; 1.00] 12.3% 5.1% 0.87 [0.81; 0.92] 18.8% 5.1%
Munian et al. (2021) 7 19	0.01 [0.00; 0.07] 0.1% 1.3% 0.37 [0.16; 0.62] 1.1% 5.0%	Shah et al.(2021) 162 186	0.17 [0.04; 0.41] 0.1% 0.9%
Ji et al.(2021) 2 40	0.05 [0.01; 0.17] 0.2% 2.3%	Hassan et al.(2021) 36 41	
Marks et al.(2022) 85 252	0.34 [0.28; 0.40] 13.2% 6.7%	Spoulou et al.(2021) 11 14	0.79 [0.49; 0.95] 0.8% 3.9%
Akin et al.(2022) 33 176	0.19 [0.13: 0.25] 4.2% 6.3%	Yaman et al.(2021) 5 12	0.42 [0.15: 0.72] 0.1% 1.8%
Albuali et al.(2022) 13 115 →	0.11 [0.06; 0.19] 1.5% 5.4%	Ji et al.(2021) 30 40	0.75 [0.59; 0.87] 1.8% 4.6%
Shaiba et al.(2022) 218 898 🛨	0.24 [0.22; 0.27] 29.6% 6.8%	Andina-Martinez et al.(2022) 9 12	0.75 [0.43; 0.95] 0.5% 3.6%
		Akin et al.(2022) 113 176	0.64 [0.57; 0.71] 4.7% 4.9%
Common effect model 2948	0.27 [0.25; 0.28] 100.0%	lijima et al.(2022) 8 13	0.62 [0.32; 0.86] 0.3% 2.9%
Random effects model Heterogeneity: $l^2 = 81\%$, $\tau^2 = 0.2304$, $\rho < 0.01$	0.23 [0.18; 0.29] 100.0%	Albuali et al.(2022) 71 115 Shaiba et al.(2022) 603 898	0.62 [0.52; 0.71] 2.8% 4.8% 0.67 [0.64; 0.70] 27.4% 5.1%
Heterogeneity: 7 = 81%, t = 0.2304, p < 0.01 0.2 0.4 0.6 0	8	Shaba et al.(2022) 605 696	0.67 [0.64; 0.70] 27.4% 5.1%
0.2 0.4 0.0 0		Common effect model 2803	0.72 [0.71; 0.74] 100.0%
		Random effects model	0.64 [0.57; 0.71] 100.0%
		Heterogeneity: /2 = 92%, 72 = 0.0610, p < 0.01	
		0.2	0.4 0.6 0.8 1
			0.4 0.6 0.8 1
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В		D	Weight Weight
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B Study Events Total	Weight Weight Proportion 95%-CI (common) (random)	0.2 D Study Events Total	Weight Weight Proportion 95%-Cl (common) (random)
Study Events Total	Proportion 95%-CI (common) (random)	0.2 D Study Events Total	Weight Weight
Study Events Total		0.2 D Study Events Total Schwartz et al.(2022) 3 22 Sun et al.(2020) 28 36 Mithai et al.(2020) 8 18 —	Weight Proportion 95%-CI (common) (random) 0.14 [0.03, 0.35] 0.8% 4.2% 0.78 [0.61; 0.90] 1.2% 4.7% 0.44 [0.22; 0.68] 0.6% 4.0%
Study Events Total Sun et al.(2020) 6 36 Mithai et al.(2020) 5 18 Kanburgoju et al.(2020) 2 37	Proportion 95%-Cl (common) (random) 0.17 [0.06; 0.33] 2.0% 6.0% 0.28 [0.10; 0.53] 0.7% 5.0% 0.05 [0.01; 0.18] 5.7% 6.4%	0.2 D Study Events Total Schwartz et al.(2022) 3 22 Sun et al.(2020) 28 36 Mithal et al.(2020) 8 18 Kanburgglu et al.(2020) 10 37	Weight Weight Proportion 95%-CI (common) (random) 0.14 0.03, 0.35 0.8% 0.78 0.610, 001 1.2% 0.78 0.610, 005 0.6% 0.44 0.22, 068 0.6% 4.0%
Study Events Total Sun et al.(2020) 6 36 Mithal et al.(2020) 5 18 Kanburggiu et al.(2020) 2 37 Gale et al.(2021) 26 66	Proportion 95%-Cl (common) (random) 0.17 [0.06; 0.33] 2.0% 6.0% 0.28 [0.10; 0.53] 0.7% 5.0% 0.05 [0.01; 0.18] 5.7% 6.4% 0.38 [0.28; 0.52] 2.2% 6.0%	0.2 D Study Events Total Schwartz et al.(2022) 3 22 Sun et al.(2020) 28 36 Mithal et al.(2020) 8 18 Kanburogiu et al.(2020) 10 37 Gale et al.(2021) 11 66	Weight Weight Weight Proportion 95%-CI (common) (random) 0.14 [0.03: 0.35] 0.8% 4.2% 0.78 [0.61: 0.90] 1.2% 4.7% 0.41 [0.22: 0.69] 0.6% 4.0% 0.27 [0.44] 1.3% 4.7% 0.07 [0.90; 0.24] 1.3% 4.7%
Study Events Total Sun et al. (2020) 6 36 Mithal et al. (2020) 5 18 Kanburogiu et al. (2021) 2 37 Gale et al. (2021) 26 66 Biko et al. (2021) 29 82	Proportion 95%-Cl (common) (random) 0.17 [0.06; 0.33] 2.0% 6.0% 0.28 [0.10; 0.53] 0.7% 6.4% 0.39 [0.28; 0.52] 2.2% 6.0% 0.39 [0.25; 0.57] 2.2% 6.0%	Study Events Total Schwartz et al.(2022) 3 22 Sun et al.(2020) 28 36 Mithai et al.(2020) 8 18 Kanburglu et al.(2021) 10 37 Gale et al.(2021) 11 66 Leung(2021) 394 749	Weight Weight Proportion 95%-CI (common) (random) 0.14 0.03, 0.35 0.8% 4.2% 0.76 0.610, 0.90 1.2% 4.7% 0.44 0.22, 0.68 0.6% 4.0% 0.71 0.90, 0.22 2.2% 5.1% 0.53 0.49, 0.55 25.0% 5.6%
Study Events Total Sun et al.(2020) 6 36 Mithal et al.(2020) 5 18 Kanburggiu et al.(2021) 2 37 Gale et al.(2021) 26 66 Biko et al.(2021) 29 82 Kulkarri et al.(2021) 3 12	Proportion 95%-Cl (common) (random) 0.17 [0.65:0.3] 2.0% 6.0% 0.28 [0.10:0.53] 0.7% 5.0% 0.05 [0.10:0.53] 5.7% 6.0% 0.05 [0.28:0.52] 2.2% 6.0% 0.39 [0.28:0.52] 2.2% 6.0% 0.35 [0.28:0.52] 2.8% 6.2% 0.25 [0.55:0.57] 0.5% 4.6%	0.2 D Study Events Total Schwartz et al.(2022) 3 22 Sun et al.(2020) 28 36 Mithal et al.(2020) 8 18 Kanburoglu et al.(2020) 10 37 Gale et al.(2021) 11 66 Leung(2021) 134 749 Ouldai et al.(2021) 71 188	Weight Weight Proportion 95%-CI (common) (random) 0.14 [0.03, 0.35) 0.8% 4.2% 0.78 [0.61, 0.90] 1.2% 4.7% 0.41 [0.22, 0.69] 0.6% 4.0% 0.27 [0.44] 1.3% 4.7% 0.07 [0.90, 0.24] 2.2% 5.1% 0.33 [0.45, 0.56] 25.0% 5.6% 0.38 [0.31, 0.45] 6.3% 5.4%
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Study Events Total Sun et al.(2020) 6 36 Mithal et al.(2020) 5 18 Kanburggiu et al.(2021) 2 37 Gale et al.(2021) 29 82 Kikari et al.(2021) 29 82 Paret et al.(2021) 2 22 Poroin et al.(2021) 22 97	Proportion 95%-Cl (common) (random) 0.17 [0.6:0.33] 2.0% 6.0% 0.28 [0.10:0.53] 0.7% 5.0% 0.05 [0.10:0.53] 0.7% 6.0% 0.05 [0.21:0.53] 2.2% 6.0% 0.39 [0.28:0.52] 2.2% 6.0% 0.35 [0.25:0.57] 0.5% 4.4% 0.09 [0.05:0.57] 0.5% 4.6% 0.09 [0.15:0.32] 2.1% 6.0% 0.23 [0.15:0.32] 2.1% 6.3%	0.2 Study Events Total Schwartz et al.(2022) 3 22 Sun et al.(2020) 28 36 Mithai et al.(2020) 8 18 Kanburglu et al.(2021) 10 37 Gale et al.(2021) 11 66 Leung(2021) 134 749 Ouldait et al.(2021) 37 82 Zhang et al.(2021) 13 36	Weight Weight Proportion 95%-C1 (common) (candom) 0.14 [0.30, 0.35) 0.8% 4.2% 0.78 [0.81, 0.80] 1.2% 4.7% 0.78 [0.42, 0.68] 1.2% 4.7% 0.79 [0.44] 1.3% 4.7% 0.71 [0.90, 0.25] 2.2% 5.1% 0.73 [0.44] 1.3% 4.7% 0.74 [0.31; 0.45] 6.3% 5.4% 0.45 [0.34; 0.57] 2.8% 5.2% 0.36 [0.21; 0.54] 1.2% 4.7%
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Figure S1 Forest plot of four analyses. (A) Respiratory symptoms; (B) nasal symptoms; (C) fever; (D) cough. CI, confidence interval.

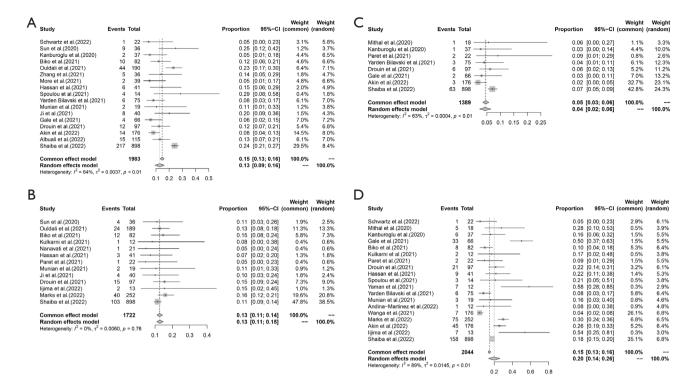


Figure S2 Forest plot of four analyses. (A) Diarrhea; (B) vomit; (C) rash; (D) feeding difficulty. CI, confidence interval.

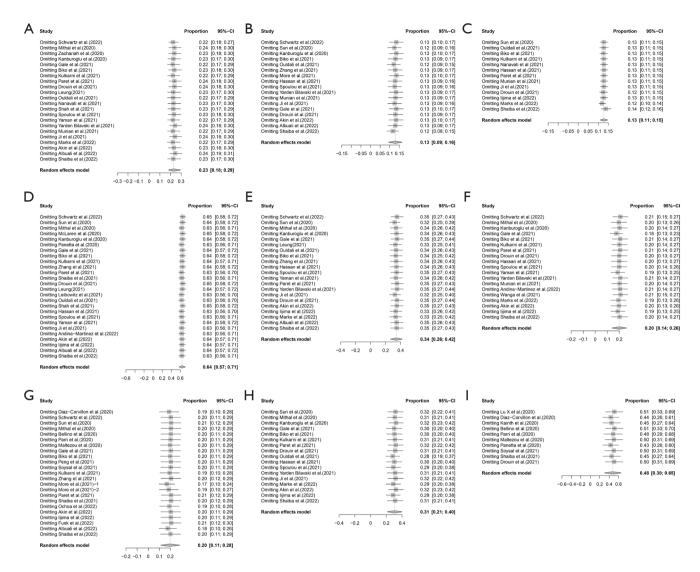


Figure S3 Sensitive analysis. (A) respiratory symptoms; (B) diarrhea; (C) vomit; (D) fever; (E) cough; (F) feeding difficulty; (G) asymptomatic infection; (H) nasal symptoms; (I) mild symptoms. CI, confidence interval.

	Maran	The states is	Selection	Ascert	ainment	Causality	Reporting
Author	Year	Type of study	Q1	Q2	Q3	Q4	Q5
Lu et al.	2020	Case reports and case series	*	*	*	*	
Díaz-Corvillón et al.	2020	Case reports and case series	*	*	*	*	*
Zachariah et al.	2020	Case reports and case series	*	*	*	*	*
McLaren <i>et al.</i>	2020	Case reports and case series	*	*	*	*	*
Sun et al.	2020	Case reports and case series	*	*	*	*	*
Mithal <i>et al.</i>	2020	Case reports and case series	*	*	*	*	*
Bellino <i>et al.</i>	2020	Case reports and case series	*	*	*	*	
Leung	2021	Case reports and case series	*	*	*	*	*
Parri et al.	2020	Case reports and case series	*	*	*	*	*
Biko <i>et al.</i>	2021	Case reports and case series	*	*	*	*	
Maltezou <i>et al.</i>	2020	Case reports and case series	*	*	*	*	
Peng <i>et al.</i>	2021	Case reports and case series	*	*	*	*	*
Soysal <i>et al.</i>	2021	Case reports and case series	*	*	*	*	*
Ouldali <i>et al.</i>	2021	Case reports and case series	*	*	*	*	*
Bayesheva <i>et al.</i>	2021	Case reports and case series	*	*	*	*	
Panetta <i>et al.</i>	2020	Case reports and case series	*	*	*	*	*
Kulkarni <i>et al.</i>	2021	Case reports and case series	*	*	*	*	
Zhang et al.	2021	Case reports and case series	*	*	*	*	*
Shah <i>et al.</i>	2021	Case reports and case series	*	*	*	*	
More <i>et al.</i>	2021	Case reports and case series	*	*	*	*	
Spoulou <i>et al.</i>	2021	Case reports and case series	*	*	*	*	*
Paret <i>et al.</i>	2021	Case reports and case series	*	*	*	*	*
Shaiba <i>et al.</i>	2021	Case reports and case series	*	*	*	*	
Munian e <i>t al.</i>	2021	Case reports and case series	*	*	*	*	
Ji et al.	2021	Case reports and case series	*	*	*	*	*
Drouin <i>et al.</i>	2021	Case reports and case series	*	*	*	*	*
Ochoa <i>et al.</i>	2022	Case reports and case series	*	*	*	*	
Wanga <i>et al.</i>	2022	Case reports and case series	*	*	*	*	*
Akin <i>et al.</i>	2022	Case reports and case series	*	*	*	*	*
lijima et al.	2022	Case reports and case series	*	*	*	*	
Marks <i>et al.</i>	2022	Case reports and case series	*	*	*	*	*

Table S1 Quality assessment of included studies by tool for evaluating the methodological quality of case reports and case series

In the tool for evaluating the methodological quality of case reports and case series, "*" represents "Yes" and "." represents "No". Q1: Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? Q2: Was the exposure adequately ascertained? Q3: Was the outcome adequately ascertained? Q4: Was follow-up long enough for outcomes to occur? Q5. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

Author	Year	Type of study	Selection	Comparability	Exposure	Scores
Gale et al.	2021	Prospective cohort study	***	*	*	5
Schwartz et al.	2022	Retrospective cohort study	***	*	**	6
Kainth <i>et al.</i>	2020	Retrospective cohort study	****	*	*	6
Kanburoglu et al.	2020	Prospective multicentered cohort study	***	*	*	5
Leibowitz <i>et al.</i>	2021	Retrospective single-center study	****	**	**	8
Nanavati <i>et al.</i>	2021	Retrospective, single-center observational study	***	**	*	6
Hassan <i>et al.</i>	2021	Retrospective study	***	**	*	6
Yaman <i>et al.</i>	2021	Cohort study	***	*	*	5
Yarden Bilavski <i>et al.</i>	2021	Cohort study	***	*	*	5
Andina-Martinez et al.	2022	Prospective multicenter cohort	***	**	*	6
Funk <i>et al.</i>	2022	Prospective cohort study	****	**	**	8
Albuali <i>et al.</i>	2022	Retrospective cohort multicenter study	****	**	*	7
Shaiba <i>et al.</i>	2022	Prospective cohort study	***	*	*	5

Table S2 Quality assessment of included studies by Newcastle-Ottawa scale

In Newcastle-Ottawa scale, a "*" represents "a score".