Original Article

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%, I^2=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%, I^2=96%, P<0.01), 27% (95% CI: 10–44%, I^2=93%, P<0.01), and 8% (95% CI: 0–16%, I^2=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

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 I^2 statistic (23). Values of I^2<25%, 25–50%, and >50% indicated low, moderate, and high heterogeneity, respectively. When I^2<50%, a fixed effects model was used; however, when I^2>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).

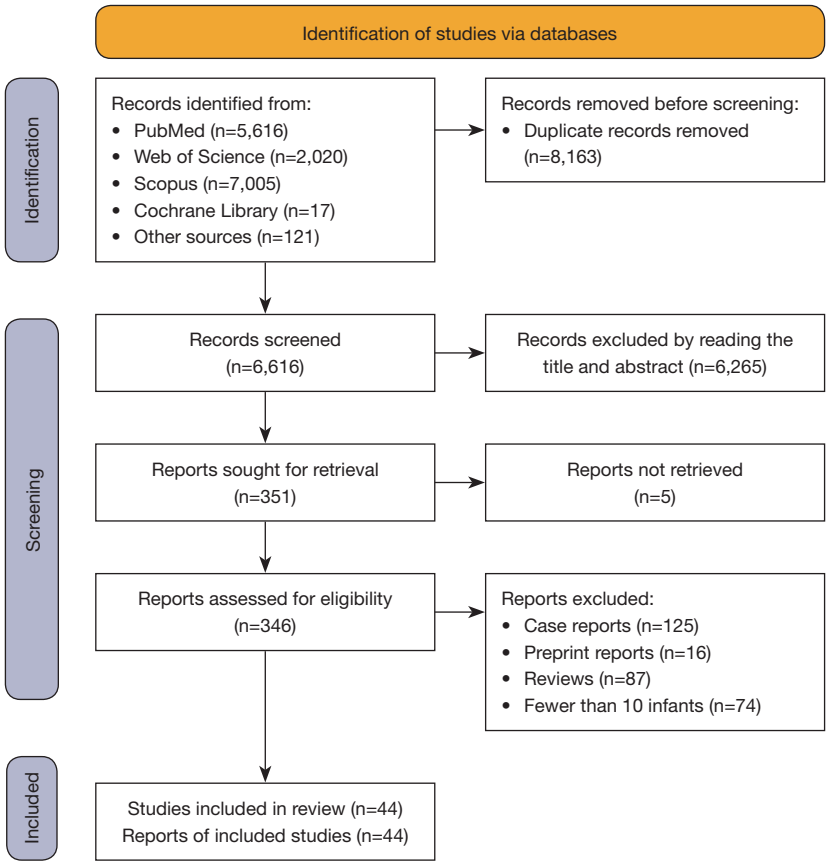

Figure 1 The flowchart of study selection.

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%, I^2=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%, I^2=96%, P<0.01, *Figure 2B*), moderate symptoms was 27% (95% CI: 10–44%, I^2=93%, P<0.01, *Figure 3A*), and severe symptoms was 8% (95% CI: 0–16%, I^2=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),

Table 1 Clinical features of included studies

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
Díaz-Corvillón *et al.* [2020] (25)	37	Mixed	16/37	18/21	–	3/21	–	–	–	–	–	–	–	–
Schwartz *et al.* [2022] (26)	22	Neonate	2/22	–	–	–	15/22	–	5/22	3/22	1/22	–	–	1/22
Sun *et al.* [2020] (27)	36	Mixed	1/36	–	–	–	–	6/36	17/36	28/36	9/36	4/36	–	–
Mithal *et al.* [2020] (28)	18	Mixed	1/18	–	–	–	1/18	5/18	14/18	8/18			1/18	5/18
Bellino *et al.* [2020] (29)	528	Mixed	43/528	104/528	–	21/528	–	–	–	–	–	–	–	–
Parri *et al.* [2020] (36)	61	Mixed	5/39	26/61	7/39	1/39	–	–	–	–	–	–	–	–
Maltezou *et al.* [2020] (30)	23	Mixed	5/23	6/23	11/23	1/23	–	–	–	–	–	–	–	–
Gale *et al.* [2021] (38)	66	Neonate	7/66	–	–	28/66	24/66	26/66	35/66	11/66	4/66	–	2/66	33/66
Biko *et al.* [2021] (39)	82	Mixed	17/82	–	–	–	13/82	29/82	42/82	37/82	10/82	12/82	–	8/82
Peng *et al.* [2021] (40)	41	Mixed	3/41	–	–	–	–	–	–	–	–	–	–	–
Soysal *et al.* [2021] (41)	27	Mixed	3/27	8/27	1/27	–	–	–	–	–	–	–	–	–
Kulkarni *et al.* [2021] (55)	12	Mixed	4/12	–	–	–	5/12	3/12	7/12	–	–	1/12	–	2/12
Zhang *et al.* [2021] (42)	36	Mixed	2/36	–	–	–	–	–	18/36	13/36	5/36	–	–	–
More *et al.* [2021] (60)	143	Mixed	102/132	–	–	–	–	–	–	–	–	–	–	–
More *et al.* [2021] (60)	39	Mixed	14/27	–	–	–	–	–	–	–	2/39	–	–	–
Paret *et al.* [2021] (54)	22	Mixed	1/22	–	–	–	1/22	2/22	20/22	3/22	–	1/22	2/22	2/22
Shaiba *et al.* [2021] (65)	36	Mixed	2/36	25/36	5/36	–	–	–	25/34	–	–	–	–	–
Ochoa *et al.* [2022] (61)	86	Mixed	30/86	–	–	–	–	–	–	–	–	–	–	–
Akin *et al.* [2022] (62)	176	Neonate	19/176	–	–	–	33/176	14/176	113/176	38/176	14/176	–	3/176	45/176
Iijima *et al.* [2022] (63)	13	Mixed	1/13	–	–	–		9/13	8/13	7/13	–	2/13	–	7/13
Funk *et al.* [2022] (68)	829	Mixed	14/829	–	–	–		–	–	–	–	–	–	–
Albuali *et al.* [2022] (64)	115	Mixed	74/115	–	–	–	13/115	–	71/115	30/115	15/115	–	–	–
Shaiba *et al.* [2022] (65)	898	Mixed	140/898	–	–	–	218/898	219/898	603/898	216/898	217/898	103/898	63/898	158/898
Lu X *et al.* [2020] (37)	31	–	–	6/31	25/31	0/31	–	–	–	–	–	–	–	–
Kainth *et al.* [2020] (31)	19	–	–	14/19	5/19	0/19	–	–	–	–	–	–	–	–

Table 1 (*continued*)

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 *et al.* [2020] (32)	27	–	–	24/27	–	–	–	–	22/27	–	–	–	–	–
Drouin *et al.* [2021] (58)	97	Mixed	–	25/97	17/97	10/97	14/97	22/97	44/97	17/97	12/97	15/97	6/97	21/97
Bayesheva *et al.* [2021] (44)	156	–	–	–	20/156	0/156	–	–	–	–	–	–	–	–
Zachariah *et al.* [2020] (34)	14	Mixed	–	–	–	–	1/14	–	–	–	–	–	–	–
Kanburoglu *et al.* [2020] (33)	37	Neonate	–	–	–	–	9/37	2/37	18/37	10/37	2/37	–	1/37	6/37
Leung [2021] (50)	749	Neonate	–	–	–	–	187/749	–	402/749	394/749	–	–	–	–
Ouldali *et al.* [2021] (47)	193	Mixed	–	–	–	–	53/189	117/188	162/186	71/188	44/190	24/189	–	7/176
Nanavati *et al.* [2021] (46)	21	Neonate	–	–	–	–	5/21	–	–	–	–	1/21	–	–
Shah *et al.* [2021] (57)	18	Neonate	–	–	–	–	5/18	–	3/18	–	–	–	–	–
Spoulou *et al.* [2021] (48)	14	Mixed	–	–	–	–	2/14	9/14	11/14	3/14	4/14	–	–	3/14
Yaman *et al.* [2022] (49)	12	Neonate	–	–	–	–	5/12	–	5/12	6/12	–	–	–	7/12
Yarden Bilavski *et al.* [2021] (52)	75	Mixed	–	–	–	–	1/75	18/75	–	12/75	6/75	–	3/75	6/75
Munian *et al.* [2021] (51)	19	Neonate	–	–	–	–	7/19	–	–	–	2/19	2/19	–	3/19
Ji *et al.* [2021] (45)	40	Mixed	–	–	–	–	2/40	5/40	30/40	28/40	8/40	4/40	–	–
Marks *et al.* [2022] (67)	1,137	Mixed	–	–	–	–	85/252	135/252	–	119/252	–	40/252	–	75/252
Hassan *et al.* [2021] (53)	41	Neonate	–	–	–	–	–	16/41	36/41	12/41	6/41	3/41	–	9/41
McLaren *et al.* [2020] (35)	20	Mixed	–	–	–	–	–	–	7/20	–	–	–	–	–
Leibowitz *et al.* [2021] (56)	20	Mixed	–	–	–	–	–	–	20/20	–	–	–	–	–
Andina-Martinez *et al.* [2022] (66)	12	Mixed	–	–	–	–	–	–	9/12	–	–	–	–	1/12
Wanga *et al.* [2021] (59)	206	Mixed	–	–	–	–	–	–	–	–	–	–	–	7/176

*, the mixed studies were infants (≤1 year).

Table 2 Results of meta-analysis

Group	Total and subgroup analyses	Subcategories	No. of trials	No. of patients	Model	Proportion	95% CI	I^2	τ2	P	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	6	2,117	Random	0.22	0.04–0.41	99%	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	6	2,678	Random	0.29	0.04–0.55	99%	0.1039	<0.01	NC
	Subgroup by age	Neonate	6	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	–	10	870	Random	0.48	0.30–0.65	96%	0.0752	<0.01	Yes
	Moderate symptoms	–	8	428	Random	0.27	0.10–0.44	93%	0.0579	<0.01	NC
	Severe symptoms	–	9	980	Random	0.08	0–0.16	90%	0.0136	<0.01	NC
Clinical features	Respiration symptoms	–	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	66%	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	6	2,379	Random	0.24	0.18–0.30	80%	0.0761	<0.01	NC
	Subgroup by age	Neonate	9	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	3	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	98%	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	I^2	τ2	P	Publication bias
	Fever		26	2,803	Random	0.64	0.57–0.71	92%	0.061	<0.01	None
	Subgroup by year	2020	6	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	5	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	8	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	5	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	6	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	3	95	Random	0.11	0.01–0.25	71%	0.0184	0.03	NC
		2021	11	699	Random	0.13	0.09–0.17	63%	0.0025	<0.01	None
		2022	3	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	9	523	Fixed	0.11	0.09–0.14	0%	0	0.84	NC
		2022	3	1,163	Fixed	0.13	0.10–0.18	45%	0.032	0.16	NC

Table 2 (*continued*)

Table 2 (*continued*)

Group	Total and subgroup analyses	Subcategories	No. of trials	No. of patients	Model	Proportion	95% CI	I^2	τ2	P	Publication bias
	Subgroup by number	<100	10	383	Fixed	0.13	0.10–0.17	0%	0	0.85	Yes
		≥100	3	1,339	Fixed	0.13	0.10–0.15	34%	0.0002	0.22	NC
	Subgroup by age	Neonate	3	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		8	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	6	315	Fixed	0.04	0.02–0.07	0%	0	0.84	NC
	Subgroup by age	Neonate	3	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	3	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	6	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
		Infants (mixed age)	12	1,671	Random	0.16	0.10–0.23	89%	0.0081	<0.01	None

CI, confidence interval; NC, not conducted.

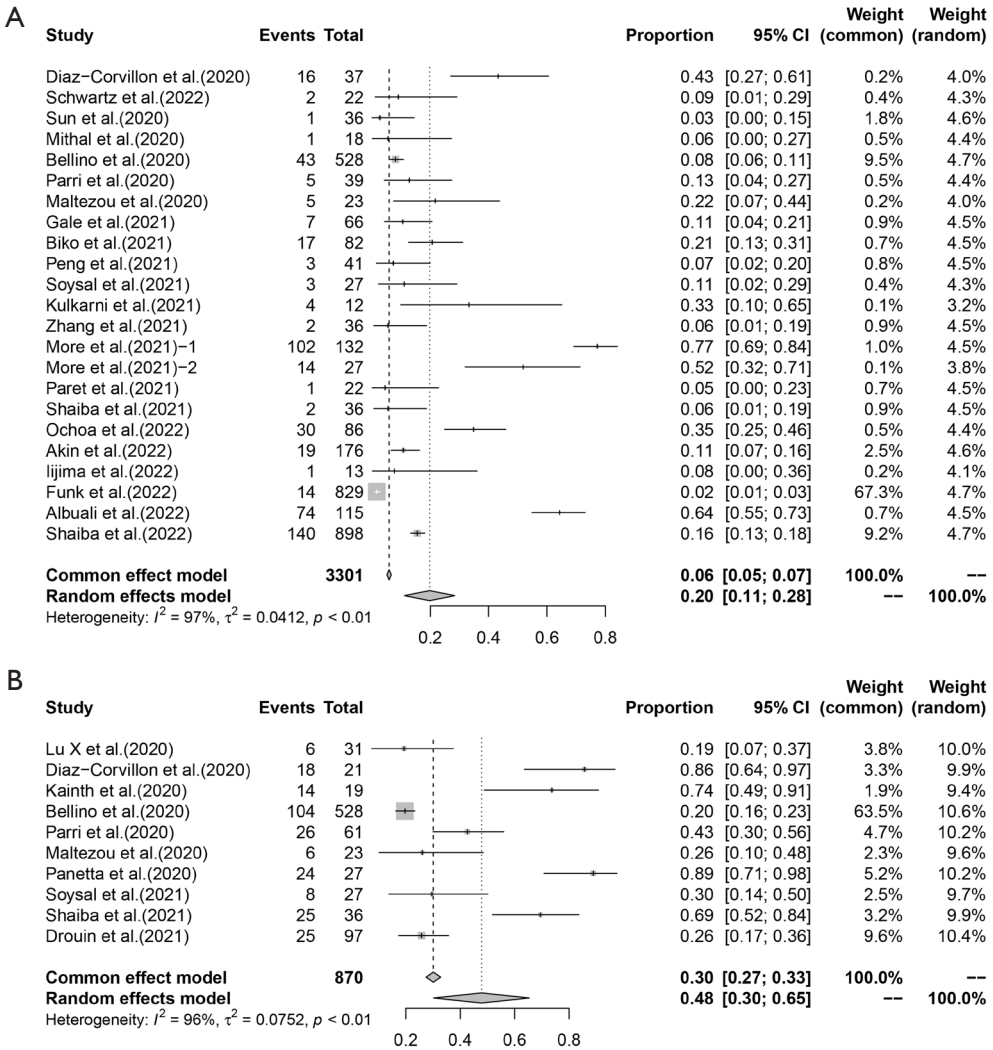

Figure 2 Forest plot of two analyses. (A) Asymptomatic infection analysis; (B) mild symptoms analysis. CI, confidence interval.

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:

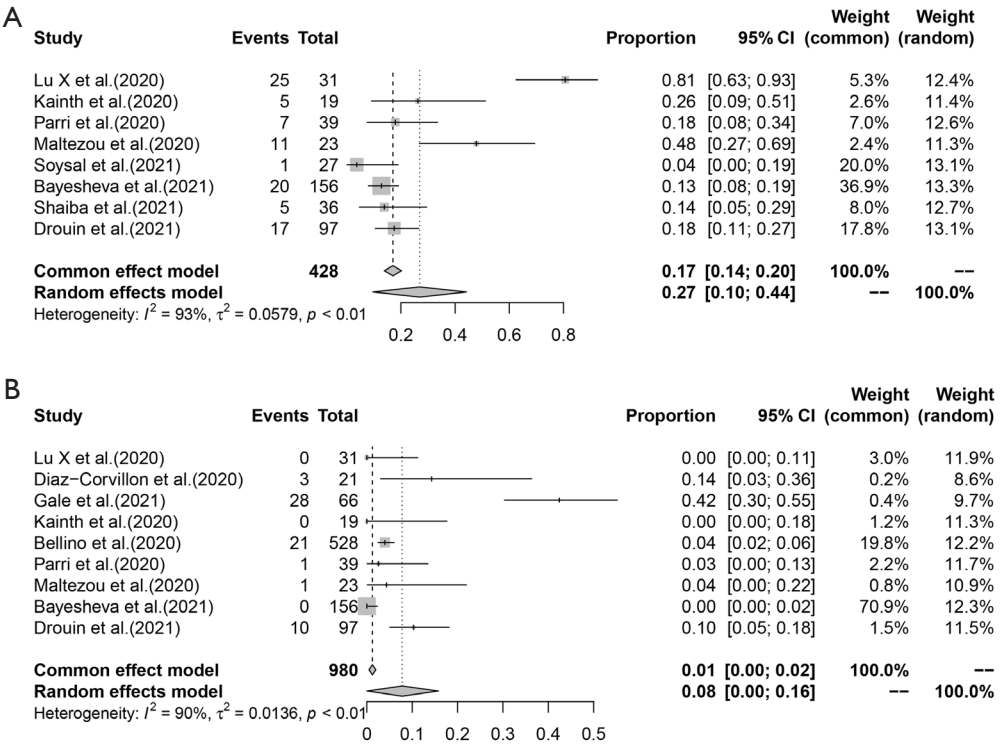

Figure 3 Forest plot of two analyses. (A) Moderate symptoms analysis; (B) severe symptoms analysis. CI, confidence interval.

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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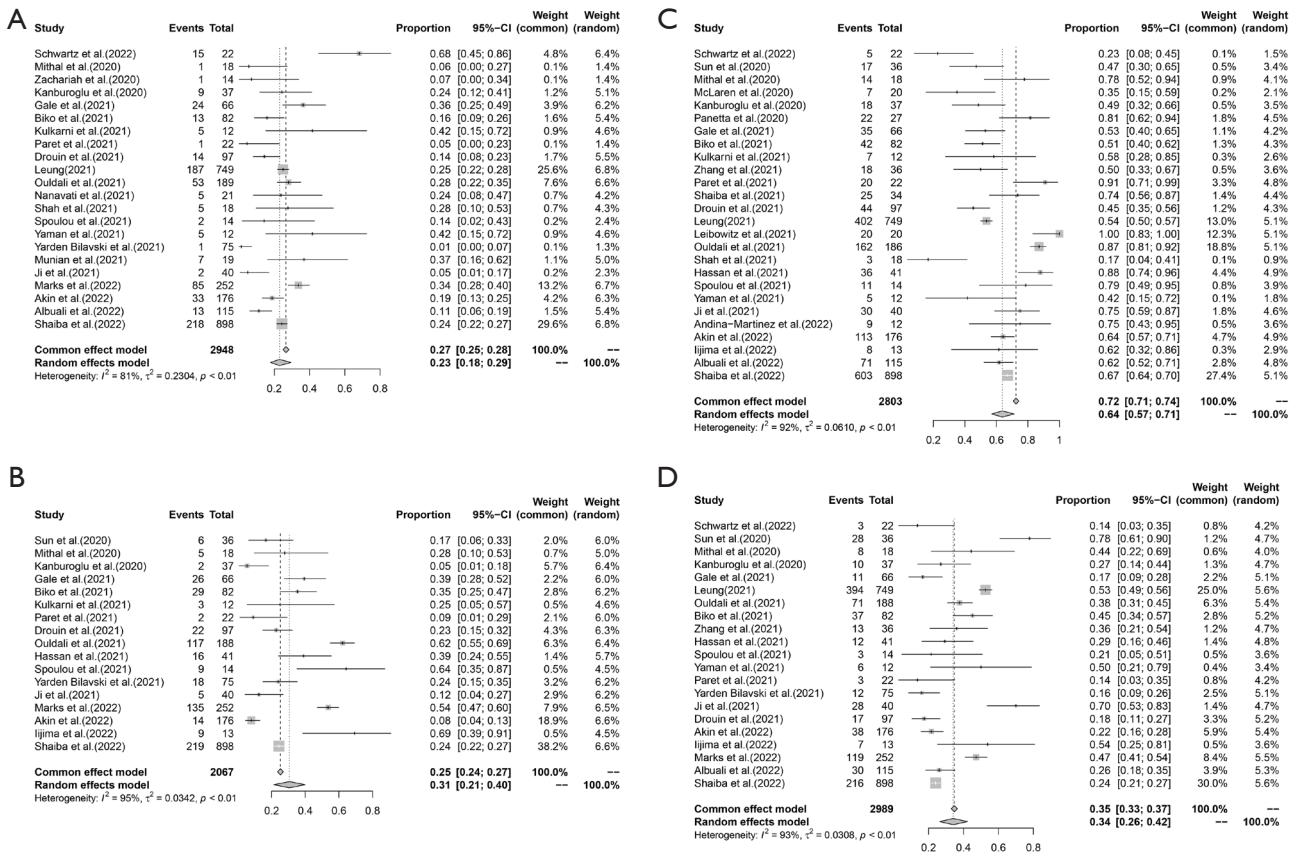

Figure S1 Forest plot of four analyses. (A) Respiratory symptoms; (B) nasal symptoms; (C) fever; (D) cough. CI, confidence interval.

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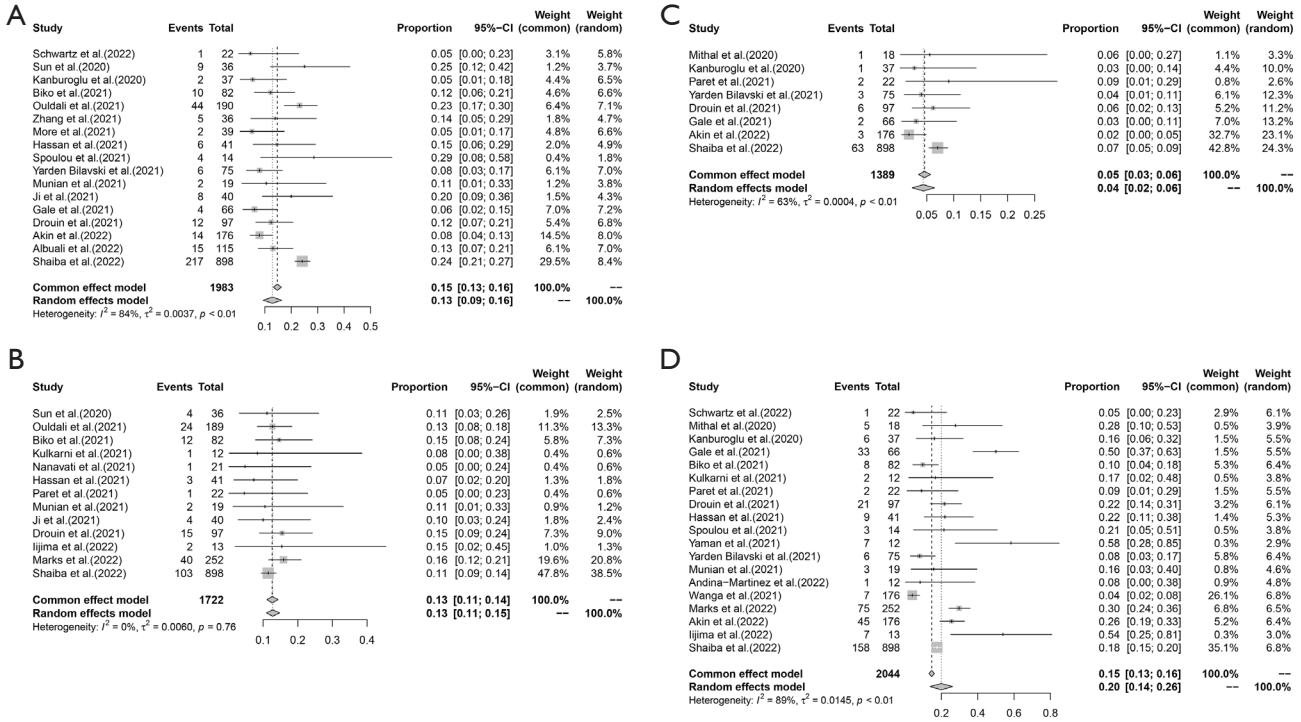

Figure S2 Forest plot of four analyses. (A) Diarrhea; (B) vomit; (C) rash; (D) feeding difficulty. CI, confidence interval.

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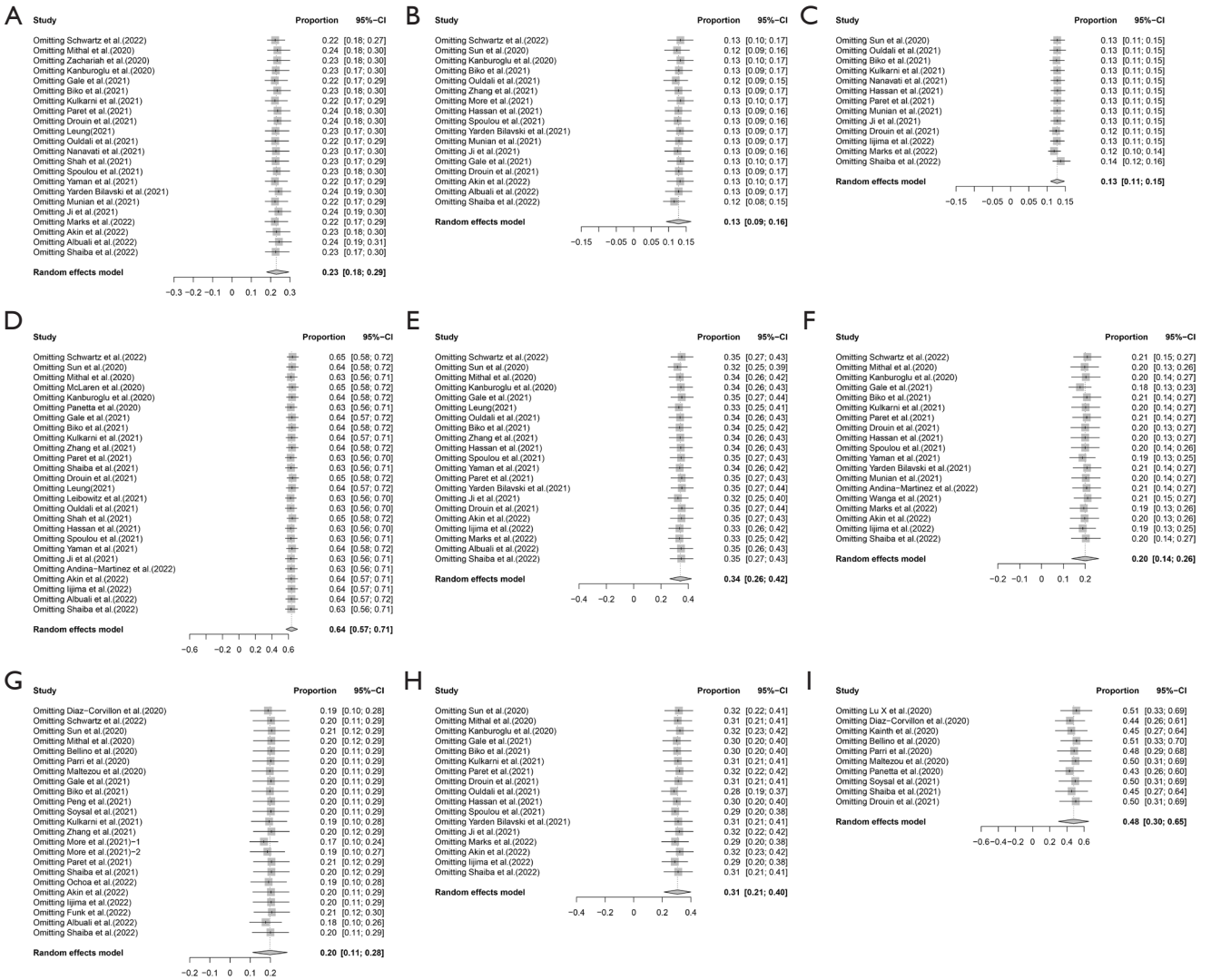

Figure S3 Sensitive analysis. (A) respiratory symptoms; (B) diarrhea; (C) vomit; (D) fever; (E) cough; (F) feeding difficulty; (G) asymptomatic infection; (H) nasal symptoms; (I) mild symptoms. CI, confidence interval.

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

Author	Year	Type of study	Selection	Ascertainment		Causality	Reporting
			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 *et al.*	2020	Case reports and case series	*	*	*	*	*
Sun *et al.*	2020	Case reports and case series	*	*	*	*	*
Mithal *et al.*	2020	Case reports and case series	*	*	*	*	*
Bellino *et al.*	2020	Case reports and case series	*	*	*	*	.
Leung	2021	Case reports and case series	*	*	*	*	*
Parri *et al.*	2020	Case reports and case series	*	*	*	*	*
Biko *et al.*	2021	Case reports and case series	*	*	*	*	.
Maltezou *et al.*	2020	Case reports and case series	*	*	*	*	.
Peng *et al.*	2021	Case reports and case series	*	*	*	*	*
Soysal *et al.*	2021	Case reports and case series	*	*	*	*	*
Ouldali *et al.*	2021	Case reports and case series	*	*	*	*	*
Bayesheva *et al.*	2021	Case reports and case series	*	*	*	*	.
Panetta *et al.*	2020	Case reports and case series	*	*	*	*	*
Kulkarni *et al.*	2021	Case reports and case series	*	*	*	*	.
Zhang *et al.*	2021	Case reports and case series	*	*	*	*	*
Shah *et al.*	2021	Case reports and case series	*	*	*	*	.
More *et al.*	2021	Case reports and case series	*	*	*	*	.
Spoulou *et al.*	2021	Case reports and case series	*	*	*	*	*
Paret *et al.*	2021	Case reports and case series	*	*	*	*	*
Shaiba *et al.*	2021	Case reports and case series	*	*	*	*	.
Munian *et al.*	2021	Case reports and case series	*	*	*	*	.
Ji *et al.*	2021	Case reports and case series	*	*	*	*	*
Drouin *et al.*	2021	Case reports and case series	*	*	*	*	*
Ochoa *et al.*	2022	Case reports and case series	*	*	*	*	.
Wanga *et al.*	2022	Case reports and case series	*	*	*	*	*
Akin *et al.*	2022	Case reports and case series	*	*	*	*	*
Iijima *et al.*	2022	Case reports and case series	*	*	*	*	.
Marks *et al.*	2022	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?

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

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 *et al.*	2020	Retrospective cohort study	****	*	*	6
Kanburoglu *et al.*	2020	Prospective multicentered cohort study	***	*	*	5
Leibowitz *et al.*	2021	Retrospective single-center study	****	**	**	8
Nanavati *et al.*	2021	Retrospective, single-center observational study	***	**	*	6
Hassan *et al.*	2021	Retrospective study	***	**	*	6
Yaman *et al.*	2021	Cohort study	***	*	*	5
Yarden Bilavski *et al.*	2021	Cohort study	***	*	*	5
Andina-Martinez *et al.*	2022	Prospective multicenter cohort	***	**	*	6
Funk *et al.*	2022	Prospective cohort study	****	**	**	8
Albuali *et al.*	2022	Retrospective cohort multicenter study	****	**	*	7
Shaiba *et al.*	2022	Prospective cohort study	***	*	*	5

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

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