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Review Article

Comparison of the Clinical and Laboratory Features of COVID and Influenza in Children

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Abstract. ***Background and Objectives*: Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 and has a clinical presentation ranging from an asymptomatic course to flu-like syndrome up to respiratory failure. Seasonal Influenza, due to the influenza viruses and very common in children, can cause symptoms similar to COVID-19. In order to identify clinical and laboratory characteristics that allow healthcare workers to differentiate COVID-19 from Influenza, we performed a systematic review of the existing literature on the pediatric age. Methods. The research was done via PubMed for articles published from March 2020 to October 2021, combining the MeSH words "COVID-19" and "Influenza" and "Children" and considering the suggestions of the PRISMA Group.**
***Results*: The most frequently described symptoms were fever and cough in both groups. In most studies, high fever, cough, nasal congestion or rhinorrhea, vomiting, and muscle pain were detected more frequently in the Influenza group. Regarding the value of laboratory tests, the results were mixed. Almost all studies reported significantly lower levels of C-reactive protein and procalcitonin in the COVID-19 group than in the Influenza group. In most manuscripts, COVID-19 had a milder course than Influenza.**
***Conclusions*: No symptoms are characteristic of a single infectious agent, with flu-like disorders being the most common. In addition, laboratory tests do not help in the differential diagnosis; however, they show a limited inflammatory response in COVID-19, which could explain the fewer complications compared to adulthood, with a less severe clinical course.**

Keywords: COVID-19; Influenza; Children.

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Introduction. Coronavirus disease 2019 (COVID-19) was first reported in Wuhan in December 2019, spreading to the rest of the world and causing a major pandemic.[1] Actually, about 290 million cases and nearly 5 million deaths have been reported to date.[2] The disease is caused by SARS-CoV-2 and has a clinical presentation ranging from an asymptomatic course to flu-like syndrome up to respiratory failure even at pediatric

age.[3,4]

However, although SARS-CoV-2 was found in children of all ages, including newborns, the infection is generally milder, and the outcome is favorable compared to adults.[5,6]

Adult patients with COVID-19 are characterized by the presence of cough, fever, dyspnoea, and lymphopenia. Men, especially if elderly and with comorbidities, are at higher risk for severe acute respiratory syndrome and death.[7]

The symptoms and mortality from COVID-19 increase proportionally with age in a U-shaped pattern, with the lowest rate described at 3-10 years of age.[6]

Seasonal Influenza is a respiratory infection caused by the influenza viruses. It can cause symptoms similar to COVID-19 and spreads in occasional outbreaks.[8] It can have a serious course, even up to death, in elderly subjects or with chronic diseases.

Given the health, social and economic consequences that COVID-19 is causing in the world, to contain its spread, it would be essential to identify clinical and laboratory characteristics that allow healthcare workers to differentiate it from seasonal Influenza. This differential diagnosis becomes especially important in the pediatric age, a period in which, due to the characteristics of the behavior (with fewer hygiene measures) and the immune system of children, Influenza is very frequent.

To our knowledge, no studies performed a systematic review to compare the clinical and laboratory characteristics between COVID-19 and Influenza in the pediatric age. Consequently, we conducted this research to evaluate children's differences between the two infectious diseases.

Methods. We performed a systematic review of the existing literature considering the suggestions of the PRISMA Group.[9]

Search Strategy. Our literature search strategy was aimed at comparing the clinical and laboratory features of COVID-19 and Influenza in pediatric age (<18 years old).

The systematic search was conducted according to the following PICOS approach: Population, pediatric patients with COVID-19 or Influenza infection; Intervention, study of the clinical features of patients, and execution of blood samples for tests such as blood count, blood chemistry tests, coagulation tests, inflammation indices, heart damage indices; Comparison of clinical features and laboratory tests of children with COVID-19 or Influenza; Outcomes, identify clinical manifestations or laboratory tests allowing to diagnose/suspect COVID-19 or Influenza without waiting for the microbiological confirmation. Study design, all types of studies such as case reports, cohort studies, and retrospective studies.

A systematic search of PubMed was performed from March 2020 to October 2021, combining the MeSH words "COVID-19" and "Influenza" and "Children."

Eligibility criteria and identification of studies, We included in our review only studies aimed at comparing clinical and laboratory characteristics in children with COVID-19 or Influenza.

Observational cohort studies - prospective or retrospective - and case reports were selected, including children under 18 and evaluating the presence of elements useful for a differential diagnosis.

We excluded manuscripts without full free text that were not in English, with studies with different focuses and a population over 18 years of age.

Study selection. All studies published between March 2020 and October 2021 were considered (n= 414). To increase consistency among reviewers, all of them (three seniors) screened the same publications, discussed results, and amended the screening and data extraction before beginning screening for this review. The same reviewers working in pairs then assessed the titles, abstracts, and full text of all publications identified by our searches, and we used an online platform to define which paper should have been included (covidence.org). Finally, we resolved disagreements on study selection and data extraction by consensus and discussion with other reviewers if needed.

Data extraction. Two reviewers independently extracted data from each included study relating to clinical features, laboratory results, and reported outcomes. Results were then checked again across the original manuscript by a third researcher.

Data synthesis. Characteristics of the included (and excluded) studies were presented in a tabulated form on an excel sheet. The study data were collected in columns: citation, year; country; type, retrospective or prospective; number of patients involved; demographic findings; clinical features; laboratory results, and outcome.

Quality assessment in individual studies. The quality of included studies with comments about study limitations, including the age groups which will limit the translation of results to that specific age group, have been assessed by two reviewers.

Possible biases are the inclusion of individual studies and the exclusion from the analysis of manuscripts published in non-indexed journals.

Statistical analyses. A direct comparison was not possible due to few observational and retrospective

studies. Therefore, study results were synthesized between the two groups by comparing the symptoms, and the values reported. A p-value <0.05 was considered significant.

Results. We initially imported 414 studies (**Figure 1**). Three hundred forty-one were excluded after evaluation of title and abstract. After assessment of the full text, a further 62 manuscripts were eliminated: 45 were not relevant to the aim of our study, 15 concerned the adult population, and 2 because the full free text was unavailable. Finally, 1 manuscript was added after the editor's revision. A total of 12 articles were included:[10-21] 8 retrospective studies, 2 cohort studies, 1 cross-sectional study, and 1 case-control study (**Table 1**).

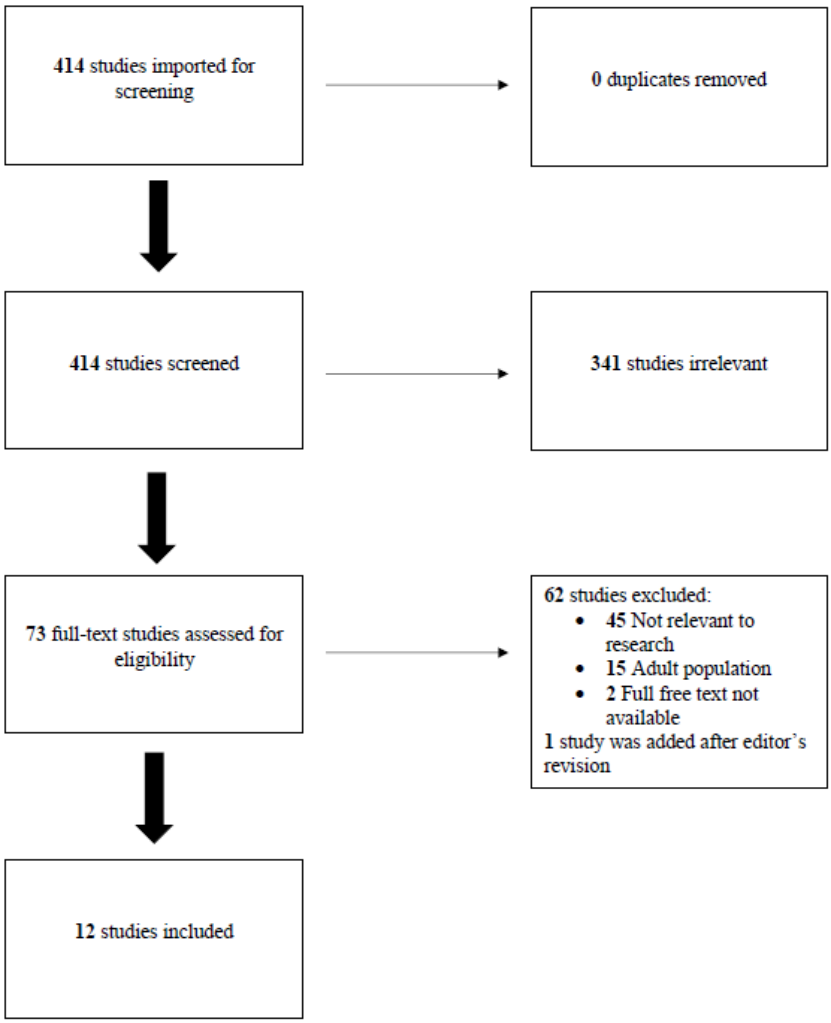

Figure 1. PRISMA guideline flowchart according to the PRISMA guidelines (Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71)

Clinical features in COVID-19 and Influenza (**Table 2**). A comparison of clinical features between COVID-19 and Influenza was reported in 11 of 12 studies.[10-17,19-21]

The most frequently described symptoms were fever and cough in both groups. However, unlike patients with COVID-19, no cases of asymptomatic children were reported in the Influenza group.[15] In most studies, high fever, cough, nasal congestion or rhinorrhea, vomiting, and muscle pain were detected more frequently in the Influenza group than in the COVID-19 group;[10-12,16,17,19] however, the results of the studies were not always statistically significant.

However, Song et al. reported more symptoms (such as fever, cough, dyspnea, chest pain, diarrhea or vomiting, myalgia, and headache) in children with COVID-19 than in those with Influenza.[14] The remaining studies confirmed, although not statistically significant (**Table 2**), that fever, dyspnea, and cough were higher in the Influenza group; however, they found that the frequency of diarrhea was higher in children with COVID-19.[13,15,20] Instead, Yilmaz et al. reported similar rates of diarrhea in the two groups.[11]

Siddiqui et al. statistically confirmed that symptoms such as fever, cough, rhinorrhea, vomiting, and abdominal pain were greater in children with Influenza than in those with COVID-19.[21] Also, in this study,

Table 1. Studies included in the review.

References	Country	Study design	N. of patients (COVID-19/Influenza)
Zhao et al. (9)	China	Case control study	23 / 138
Yilmaz et al. (10)	Turkey	Retrospective study	164 / 46
Vanhems et al. (11)	France	Retrospective study	9 / 31
Sousa et al. (12)	Brazil	Cross sectional study	2570 / 659
Song et al. (13)	United States	Retrospective Cohort study	315 / 1402
Pokorska-Åšpiewak et al. (14)	Poland	Cohort study	15 / 32
Li et al. (15)	China	Retrospective study	57 / 59
Liu X et al. (16)	China	Retrospective study	248 / 337
Liu XP et al. (17)	China	Retrospective study	24 / 67
Liang et al. (18)	China	Retrospective study	71 / 71
Asseri et al. (19)	Saudi Arabia	Retrospective study	73 / 34
Siddiqui et al. (20)	Turkey	Retrospective study	206 / 411

Table 2. Clinical features in COVID-19 and Influenza *(C=COVID-19; I=Influenza; in=inpatients; out=outpatients).*

References	Fever C	Fever I	p-Value	Cough C	Cough I	p-Value	Dyspnea C	Dyspnea I	p-Value	Chest pain C	Chest pain I	p-Value
9 (n./%)	10/43.5	in: 39/56.5 out: 63/91.3	0.278 <0.001	4/17.4	in: 23/33.3 out: 50/72.5	0.234 < 0.001						
10 (n./%)	34/20.7	31/67.4	<.01	38/23.2	37/80.4	<.01						
11 (n./%)	4/44.4	20/64.5	0.99	2/22.2	31/100.0	<0.001						
12 (n./%)	1820/76.9	634/96.6	<0.001	1,544/68.0	603/92.6	<0.001	1,227 /56.3	418/66.0	<0.001			
13 (n./%)	41/76	159/55	0.005	24/48	90/31	0.05	16/30	59/20	0.13	6/11	9/3	0.01
14 (n./%)	7/46.7	31/96.8	0.0001	6/40.0	27/84.3	0.002	1/6.7	3/9.3	0.75	0	2	0.32
15 (n./%)	31/54.4	50/84.7	<0.001	40/70.2	58/98.3	<0.001	2/3.5	5/8.5	0.439			
16 (n./%)	86/34.7	243/72.1		79/31.85	173/51.3	<0.0001	1/0.40	6/1.8	0.0181			
17 (n./%)												
18 (n./%)	32/45.1	41/57.7		23/32.3	38/53.5							
19 (n./%)	70/95.9	33/97.0	0.62	42/57.5	33/97.0	< 0.001	33/45.2	29/85.3	< 0.001			< 0.001
20 (n./%)	166/80.6	388/94.4	0.001	47/22.8	294/71.5	0.001						
References	**Vomiting C**	**Vomiting I**	**p-Value**	**Fatigue C**	**Fatigue I**	**p-Value**	**Diarrhea C**	**Diarrhea I**	**p-Value**	**Nasal Congestion C**	**Nasal Congestion I**	**p-Value**
9 (n./%)	0/0.0	in: 19/27.5 out: 17/24.6	0.012 0.020	1/4.3	in: 16/23.9 out: 9/13.0	0.079 0.439	3/13.0	in: 3/4.4 out: 2/2.9	0.163 0.184	1/4.3	in: 22/31.9 out: 21/30.4	0.018 0.024
10 (n./%)	8/4.9	13/28.9	<.01				11/6.7	6/13	.16			
11 (n./%)												
12 (n./%)	360/18.3	84/14.1	<0.001				360/18.3	84/14.1	<0.001			
13 (n./%)							or vomiting 14/26	36/12	0.01			
14 (n./%)	2/13.3	3/9.4	0.68	0/0.0	3/9.4	0.22	3/20.0	0/0.0	0.009			
15 (n./%)												
16 (n./%)	7/2.82	64/19.0	< 0.0001	3/1.21	4/1.2	0.740	7/2.82	29/8.6	0.0001	8/3.23	92/27.3	<0.0001
17 (n./%)												
18 (n./%)	3/4.2	12/16.9								5/7.0	14/19.7	
19 (n./%)												
20 (n./%)	19/9.2	85/20.7	0.001	22/10.6)	66/16.1	0.072	9/4.4	18/4.4	0.789	4/1.9	0/0	
References	**Rhinorrhea C**	**Rhinorrhea I**	**p-Value**	**Sore throat C**	**Sore throat I**	**p-Value**	**Myalgia C**	**Myalgia I**	**p-Value**	**Headache C**	**Headache I**	**p-Value**

9 (n./%)	1/4.3	in: 20/29.0 out: 19/27.5	0.031 0.041	0/0.0	in: 26/37.8 out: 16/23.2	0.001 0.026	0/0.0	in: 21/30.4 out: 9/13.0	0.006 0.156	1/4.3	in: 12/17.4 out: 10/14.5	0.226 0.354
10 (n./%)	2/1.2	5/10.9	<.01	10/6.1	11/23.9	<.01	31/18.9	34/73.9	<.01	23/14	8/17.4	0.63
11 (n./%)	1/11.1	6/23.1	0.99									
12 (n./%)												
13 (n./%)	Or congestion 9/17	52/18	0.83	3/6	6/2	0.16	12/22	20/7	0.001	6/11	9/3	0.01
14 (n./%)	1/6.7	8/25.0	0.14	0	8/25.0	0.03	0	3/9.4	0.22	0	3/9.4	0.22
15 (n./%)												
16 (n./%)				3/1.21	4/1.2	0.7502	2/0.81	1/0.3	0.7359	2/0.81	10/3	0.3128
17 (n./%)												
18 (n./%)												
19 (n./%)	23/31.5	29/85.3										
20 (n./%)	40/19.4	178/43.3	0.001	45/21.8	68/16.5	0.108	15/7.3	12/2.9	0.012	26/12.6	16/3.9	0.001

diarrhea was more frequent (but non-statistically significant) in the Influenza group than in the one with COVID-19, while headache was a symptom more frequently reported by children with COVID-19.[21]

Interestingly, Sousa et al. described that most patients with severe COVID-19 had no fever or cough at onset, unlike children with Influenza.[13]

Ageusia and anosmia are characteristic symptoms in adult COVID-19 patients.[7] However, almost none of the studies included in the manuscript reported these symptoms in the group of children with COVID-19. Only the study by Siddiqui et al. pointed out that ageusia and anosmia were present respectively in 4.9% and 3.4% of patients with COVID-19, while they were not reported in the Influenza group. Probably this is due to the age of the patients, not yet able to speak or report the presence of symptoms, especially anosmia and ageusia, that are relatively complex to explain for an individual who is not yet autonomous.

Laboratory findings in COVID-19 and Influenza **(Table 3).** A total of 8 out of 12 studies analyzed the differences in laboratory test results between COVID-19 and Influenza.

The results were mixed regarding the value of the white blood cells count (WBC) and the leukocyte formula. Most manuscripts reported a lower WBC in children with COVID-19 than in those with Influenza.[11,16,20] Other studies reported a higher percentage of leukocytopenia in the Influenza group and a greater number of children with leukocytosis than those with COVID-19.[17,21] Some studies described lower neutrophil count in the COVID-19 group than in the Influenza group.[11,16,19] Zhao et al. showed higher

Table 3. Laboratory findings in COVID-19 and Influenza.

Rf	WBC C		WBC I	p-Value	Neu C	Neu I	p-Value	Lym C	Lym I	p-Value
9	6.4±2.2		in: 7.1±3.8 out: 7.8±3.2	0.465 0.067						
10	7.1±1.08		10.9±1.82	<0.05	3.19±0.58	6.04±0.97	<0.05	3.07±0.41	3.40±0.52	0.36
11										
12										
13										
14										
15	7.87±2.87		9.89±4.84	0.027	2.43±1.92	5.16±4.46	<0.001	4.58±2.06	3.56±2.01	0.006
16	**Increase (n/%)** **Decrease (n/%)**	23/9.43 13/5.33	A: 35/18.82; B: 27/18.88 A: 26/13.98; B: 18/12.59	0.0001	33/13.52 13/5.33	A: 67/37.02; B: 39/27.46 A: 13/7.18; B: 10/7.04	<0.0001	24/9.84 8/3.28	A: 21/11.60; B: 11/7.75 A: 23/12.71; B: 21/14.79	0.0006
17	6.6 (3.88-9.57)		6.4 (5.1-9.2)	0.804	3.0 (1.3-5.33)	3.03 (2.13-4.55)	0.546	2.03 (1.21-3.6)	2.46 (1.89-3.55)	0.217
18					2.2 (1.4–4.1)	4.2 (2.8–7.7)	<0.01	3.2 (1.8–5.0)	1.8 (1.0–3.4)	< 0.01
19	9.3 (6.2–14.0)		5.6 (2.8–8.6)	<0.001	3.89 (2.10–7.34)	1.93 (0.96–4.97)	0.002	3.36 (1.85–5.09)	1.85 (0.96–3.47)	0.005
20	**Decrease (n/%)** **Increase (n/%)**	6/8.5 10/14.1	30/22.1 23/16.9	0.029	11/15.5 7/9.9	31/22.8 22/16.2	0.144	4/5.6 14/19.7	24/17.6 13/9.6	0.013

Rf	Hem C	Hem I	p-Value	ALT C	ALT I	p-Value	AST C	AST I	p-Value	LDH C	LDH I	p-Value
9				36.3±37.1	in: 46.0±83.7 out: 24.8±9.4	< 0.001 < 0.001	37.5±56.1	in: 35.5±72.8 out: 28.6±11.1	< 0.001 < 0.001	250.9±81.0	in: 289.7±137.6 out: 307.4±89.9	0.245 0.032
10	12.92±2.95	11.03±2.06	<.01	18.93±5.21	40.89±6.27	<0.01	33.09±5.97	81.35±12.28	<0.01	276.20±42.18	603.46±92.83	<0.01
11												
12												
13												
14												
15	11.7±1.1	11.7±1.2	0.932	36±78	26±25	0.595	57±86	50±30	0.591	319±92	357±154	0.340
16	12.8 (12.0-13.8)	A: 12.2 (11.2-12.8) B: 12.2 (11.3-12.9)	<0.0001	Incr (n/%) 27/11.20	Incr (n/%) A: 15/8.62 B: 7/5.26	0.1536	Incr (n/%) 32/13.28	Incr (n/%) A: 43/24.71 B: 40/29.85	0.0003	Incr (n/%) 54 (22.88%)	Incr (n/%) A: 74 (44.58%) B: 58 (44.27%)	<0.0001
17	12.2 (11.3-13.5)	11.8 (11.3-12.3)	0.094	18.5 (13.7-42.3)	17.5 (13.8-23.2)	0.457	31.5 (20.35-40.0)	46.5 (36-59.3)	<0.001	300.5 (206.0-394.0)	369 (319-467)	0.036
18	12.3 (11.1-12.8)	11.2 (10.1-12.3)	0.094									
19	11.5±2.0	12.4±2.0	0.20	20 (14–26)	29 (21–38)	0.002	23 (18–33)	56 (37–97)	< 0.001			
20												
Rf	**PT C**	**PT I**	**p-Value**	**APTT C**	**APTT I**	**p-Value**	**Fibr C**	**Fibr I**	**p-Value**	**D-Dimer C**	**D-Dimer I**	**p-Value**
9	11.6±0.7	13.3±2.4	0.001	34.6±4.7	31.2±8.6	0.104	244.3±108.8	312.4±83.9	2			
10	13.41±2.16	15.54±2.34	0.06	27.87±3.68	33.64±2.89	<0.01						
11												
12												
13												
14												
15	10.8±0.7	11.2±0.8	0.014	33.4±5.2	34.1±5.9	0.650				0.34±0.29	1.94±2.88	<0.001
16										Increase (n/%) 25/13.81	Increase (n/%) A: 22 (45.83%) B: 19 (52.77%)	<0.0001
17												
18	11.6 (10.7-12.8)	14.0 (12.7-15.1)	< 0.01	35.2 (30.9-40.5)	42.4 (38.7-46.3)	<0.01						
19												
20												
Rf	**Troponin C**	**Troponin I**	**p-Value**	**Albumin C**	**Albumin I**	**p-Value**	**CRP C**	**CRP I**	**p-Value**	**Procalcitonin C**	**Procalcitonin I**	**p-Value**
9							2.2±4.4	in: 48.0±74.8 out: 7.9±9.0	< 0.001 < 0.001			
10							1.0±201.98	4.7±174.79	<0.01	0.1±20.99	2.2±6.7	<0.01
11												
12												
13												
14												
15				4.3±0.7	4.4±0.4	0.964	3.7±6.85	15.1±32.2	0.001	0.09±0.09	0.68±1.82	<0.001

	Increase (n/%)	Increase (n/%)		Increase (n/%)	Increase (n/%)		Increase (n/%)	Increase (n/%)		Increase (n/%)	Increase (n/%)	
16	7/5.93	A: 6/22.22 B:2/15.38	0.0252	12/4.98	A: 25/14.37 B: 28/13.53	0.0022	40/18.60	93/56.71 69/40.64	<0.0001	5/2.05	4/2.23 1/0.70	0.5328
17							1.09 (0.6-3.0)	1.2 (0.3-3.9)	0.870	0.07 (0.05-0.1)	0.31 (0.09-0.63)	0.001
18				4.4 (4.2-4.6)	4.2 (3.9-4.3)	< 0.01	0.9 (0.8-5.0)	5.8 (1.2-20.6)	< 0.01	0.1 (0.1-0.1)	0.4 (0.2-1.0)	< 0.01
19				3.4 (2.8–3.7)	3.5 (3.1–3.6)	0.60	0.8 (0.0–1.6)	0.8 (0.0–1.6)	0.81			
20							Increase (n/%) 28/40	Increase (n/%) 52/38.2	0.550			

C=COVID-19; I=Influenza; A=Influenza A; B=Influenza B; in=inpatients; out=outpatients; WBC=White blood cell count (x10^9 /L, median, SD or IQR); Neu=Neutrophil (x10^9 /L, median, SD or IQR); Lym=Lymphocyte (x10^9 /L, median, SD or IQR; PT=Prothrombin time (s, mean, SD or IQR); APTT (s, mean, SD or IQR); Fibr=Fibrinogen (g/L, mean, SD); D-Dimer (mg/L, median, SD); Troponin (ng/L); Albumin (g/L, median, SD or IQR); CRP (mg/L, median, SD or IQR); Procalcitonin (ng/L, median, SD or IQR).

lymphocyte count in children with COVID-19,[10] while lymphocytopenia was more frequent in children with Influenza.[17,19,21]

Almost all studies reported significantly lower levels of C-reactive protein and procalcitonin in the COVID-19 group than in the Influenza group.[10,11,16,17,19]

No studies found an alteration of the coagulation tests. However, significantly lower values of prothrombin time,[10,11,16,19] aPTT,[11,19] and d-Dimer[16,17] were described in children with COVID-19 matched to those with Influenza.

In the COVID-19 group, compared to the Influenza group, most manuscripts reported significantly lower levels of alanine aminotransferase,[10,11,20] aspartate aminotransferase,[11,18,20] and lactate dehydrogenase.[11,18] However, Zhao et al. described higher levels of aspartate aminotransferase and lactic acid.[10]

Liu et al. reported acute cardiac injury in approximately 7% of patients with COVID-19, 20% with influenza A and 18% with influenza B.[17]

Outcome **(Table 4).** 11 out of 12 studies analyzed the complications and consequences of infections.

In most manuscripts, COVID-19 had a milder course than Influenza.[12,19] Indeed, children with Influenza were characterized by a higher rate of hospitalization duration, need for intensive care, oxygen therapy, ventilatory support, and mortality than those with COVID-19.[10,11,16,17]

Asseri et al. reported that 11% of children in the COVID-19 group were diagnosed with Inflammatory Syndrome in Children (MIS-C), which was not observed in the Influenza group. Furthermore, they noted that children with Influenza had a longer length of stay in the ICU than those with COVID-19, which needed a longer period of oxygen therapy.[20]

Song et al. described that the 2 groups had a similar rate of ICU admission; however, 65% of children with COVID-19 had at least one comorbidity, significantly higher than 42% with Influenza.[14]

Instead, Pokorska-Åšpiewak et al. noted that patients hospitalized with Influenza had a higher number of comorbidities, although not statistically significant.[15]

Contrary to other studies, Sousa et al. reported a worse outcome in the COVID-19 group. Although these children had a lower need for non-invasive ventilatory support, their mortality rate was higher than in the influenza group.[13]

Siddiqui et al. reported no significant differences in oxygen therapy, hospitalization, and mortality between the 2 groups. However, ICU hospitalization was higher in children with COVID-19.[21]

Discussion. Our study compared the clinical characteristics, laboratory findings, and outcomes among children with COVID-19 or Influenza.

A previous unsystematic review reported that SARS-CoV-2 infection is generally mild in children, being asymptomatic or with symptoms of a common viral upper respiratory infection, such as fever, cough, runny nose, diarrhea, and vomiting, not allowing to distinguish COVID-19 from any other community-acquired respiratory virus.[22]

In our study, symptoms such as fever, cough, rhinorrhea, myalgia, and vomiting were described more frequently in the Influenza group, while some studies showed that diarrhea was more frequent in the COVID-19 group. Although these differences have not always been statistically significant and have not been confirmed by all the studies analyzed, they could help to differentiate the two etiological agents (perhaps by combining them with other elements) and could be explained by the different distribution of the receptors of the 2 viruses.

Table 4. Outcomes in COVID-19 and Influenza.

Rf	ICU C	ICU I	p-Value	Mortality C	Mortality I	p-Value	Comorb C	Comorb I	p-Value	O2 therapy C	O2 therapy I	p-Value
9 (n./%)				0/0.0	in: 1/1.4 out: 0	0.499						
10 (n./%)	3/ 1.8	19/ 41.3	<.01	2/1.2	7/15.2	<.01	3	13/28		3/1.8	20/43.4	<.01
11 (n./%)				0/0.0	1/3.3	0.99						
12 (n./%)	644/ 31.0	188/ 31.0	0.008	353/15.2	27/4.5	<0.001				Inv. 298/13.7 Noninv. 637/29.3	70/12.1 197/34.1	<0.001 <0.001
13 (n./%)	18/ 5.7	98/ 7.0	1.0	0	2/0.1		35/65	121/42	2			
14 (n./%)	0	0					1	7	20	0	1	0.57
15 (n./%)	2/ 3.5	4/ 6.7	0.679							1/1.7	7/11.8	0.061
16 (n./%)				1	0	0	39/15.7	108/32		Noninv. 3/1.21 Inv. 4/1.61	A: 28/14.89 B: 15/10.07 A: 6/3.19 B: 2/1.34	<0.0001 0.4164
17 (n./%)												
18 (n./%)	1	4										
19 (n./%)												
20 (n./%)	5/ 2.4	2/ 0.5	0.045	1/0.5	0	0.334	19/9.2	28/6.8	0.287	6/2.9	18/4.4	

C=COVID-19; I=Influenza; A=Influenza A; B=Influenza B; in=inpatients; out=outpatients; ICU=Intensive Care Unit; Comorb=Comorbidities; O2=Oxygen; Inv=Invasive; Noninv=Noninvasive.

In fact, the Influenza virus uses sialic acid to penetrate inside human cells.[23] This receptor is mainly expressed in the upper respiratory tract,24 explaining the greater frequency of flu symptoms and the rarity of neurological and gastrointestinal symptoms.

Instead, the SARS-CoV-2 receptor is represented by angiotensin-converting enzyme 2 (ACE2). This metallopeptidase has a ubiquitous distribution, including intestinal and alveolar epithelial cells and central nervous system endothelial cells.[25] This datum would justify the higher incidence of pneumonia, gastrointestinal and neurological symptoms (including anosmia and ageusia not described in Influenza) in patients with SARS-CoV-2 infection.

As described in adulthood,[26] the presence in a patient of fever, cough, rhinorrhea, myalgia, and arthralgia does not allow to distinguish between the 2 infectious diseases, but the addition of diarrhea, perhaps associated with anosmia or ageusia, should lead to a preponderance towards COVID-19.

An extensive systematic review conducted in adulthood[27] showed that rhinorrhea, sore throat, dyspnoea, nausea, and vomiting were less common in COVID-19 patients than in those with Influenza, confirming our data. Still, they found no differences in gastrointestinal symptoms between the 2 groups. Therefore, an analysis of more data is needed to ensure the importance of diarrhea in the diagnosis of pediatric COVID-19.

Laboratory findings did not show specific changes in a single infectious agent.

Some studies reported lower neutrophils in the COVID-19 pediatric groups,[11,16,19] like that observed in adulthood.[26]

Lymphocytopenia, described in the general population affected by severe COVID-19,[26] was not a diagnostic marker either:[28] it does not appear to be a peculiar feature of this infection and does not allow to distinguish SARS-CoV-2 pneumonia from influenza pneumonia. However, lymphopenia seems to be associated with disease severity for both conditions in adulthood.

Lymphocytopenia seems to be generated by the direct infection of the lymphocytes and by the damage consequent to the "cytokine storm",[26] a characteristic generally not present in the pediatric age.[25] All this could explain the different values found in the leukocyte formula and the absence of elevated inflammatory markers. Our review, in fact, found lower levels of CRP and Procalcitonin in the COVID-19 group compared to Influenza. They are acute phase proteins produced after inflammatory stimuli following an infection. While severe COVID-19 in adulthood is associated with high levels of proinflammatory cytokines, acute phase proteins, and consequent tissue damage,[26] the low values of pediatric age testify to a less exuberant immune

response and a milder clinical course. Therefore, the alteration of hemostasis and the hypercoagulability characteristic of severe COVID-19 are not present, as confirmed by the finding of normal coagulation tests. The lack of the cytokine storm would also justify the lower levels of transaminases, lactate dehydrogenase, and indices of myocardial damage.

These data are also confirmed by numerous pediatric COVID-19 studies, where the white blood cell count and inflammation indices are normal in most cases. Instead, although not specific to SARS-CoV-2 infection, lymphocytopenia and an increase in C-reactive protein, procalcitonin, D-dimer, muscle enzymes, and liver enzymes were described in the most severe rare cases,[29,30] infrequently included in our study. Therefore, although not useful in diagnosis, these altered laboratory tests could be useful in defining the prognosis of the infection.

Regarding the outcome, both infectious agents can lead to ARDS and death. Although affected by the timing and by the region (the quality of the care offered varies according to the phase of the pandemic, the "preparedness" of the health system and the economic level of the country), COVID-19 showed higher mortality or worse outcomes than Influenza in adulthood.[26,28,31-33]

During the pediatric age, the SARS-CoV-2 infection is rarely fatal.[34] In 2020, the mortality rate was two cases per million in England.[35] A systematic review reported a good prognosis in children under five years, with less than 10% of cases of severe COVID-19.[36]

Nearly all of the studies included in our review reported lower severity of SARS-CoV-2 infection compared to Influenza, both for ICU admission and mortality. However, only Sousa et al. described, albeit rare, a higher death rate in COVID-19. This contradictory finding could be caused by a large number of cases in Brazil, associated with disparities in the socio-economic level and provision of health care in different regions.[13]

Instead, in our study, we did not find a greater number of complications secondary to an infection, as evidenced in adulthood, in the COVID-19 group compared to that with Influenza, such as thrombosis[37] and acute kidney injury.[38]

The lower severity of the infection in the pediatric population could be explained by the presence of a more "plastic" immune system, able to offer better performance against a new infectious agent, in contrast to the predominantly "memory" response of the adult immune system. Additionally, children have an increased ability to control the immune response and repair tissue damage.[39]

Oualha et al. highlighted the existence of severe COVID-19 even at pediatric age, with a non-negligible death rate (18%) in an observational study conducted in a pediatric intensive and high-dependency care unit (PICU) in an urban hospital in Paris, mostly in children with comorbidities but even in children without comorbidities. Furthermore, they suggested the presence of a cytokine storm with subsequent prothrombotic events, as described in adult patients.[40]

A greater number of complications from COVID-19 compared to Influenza, such as hospitalization and the need for oxygen therapy, were also reported by a large international study.[41] Although this manuscript included approximately 250,000 children with COVID-19 and 2 million with Influenza, due to the presence of electronic data collected for administrative purposes, not completely available to our literature research and with unclear statistical analysis, it was excluded from our review.

Wei described a case fatality rate of SARS-CoV-2 pneumonia in children aged <5 years lower than that of respiratory syncytial virus (RSV) pneumonia but higher than those of Influenza pneumonia.[42]

Piroth et al. reported a 3-times greater mortality from COVID-19 in the general population than from Influenza, with twice the likelihood of being hospitalized in ICU and receiving invasive mechanical ventilation. In addition, a subgroup analysis found that in-hospital mortality of children with COVID-19 was more than four times higher than those with Influenza.[43]

Consequently, studies with a large number of children are needed to evaluate the outcome of SARS-CoV-2 infection in pediatric age compared to Influenza infection. The initial estimates that predicted a better outcome in the COVID-19 group would probably be revised with the increase in cases in the pediatric population initially spared from infection in the early stages of the pandemic.

Several studies described typical radiological features of COVID-19, both via chest CT and ultrasound.[44,45] However, we decided not to include this topic in our review given the limited data comparing chest CT (limited use due to minor disease severity and to save exposure to ionizing radiation in pediatric age) and chest ultrasound (limited use in pre-pandemic years) in SARS-CoV-2 and Influenza infections.

In fact, although chest CT was used for COVID-19 patients in the early stages of the pandemic, radiological exams are not routine tests for children with respiratory symptoms.[34] They do not modify the first level assistance or therapy, and, to avoid the potential damage caused by ionizing radiation, they are not used unless clinical worsening and the onset of complications. Therefore, it is rare to find its use in data on children with Influenza. Pulmonary ultrasound was employed in diagnosing and monitoring pneumonia; this new method was used for the advantage of being carried out bedside during the pandemic,[46] but there are few data from previous years in the Influenza group.

Our systematic review has several limitations. The number of studies included and the sample size are limited due to the lower incidence of pediatric infection recorded in the early stages of the pandemic. Furthermore, the presence of retrospective studies, with data on Influenza reported from previous-search databases, could potentially influence the results. Due to the greater survival of chronic diseases and syndromes, the number of comorbidities and risk factors has increased, requiring a comparison between epidemic seasons of the same year. The lack of information on SARS-CoV-2 and Influenza infections in out-of-hospital settings and in primary care may have generated bias in the comparison between the two groups. The included studies did not analyze the different variants of the two viruses. The spread of more infectious variants could increase the number of pediatric cases and a greater significance of previously considered rare events.

Finally, the use of only articles with data available and open-access and the initial selection through abstracts may have led to the omission of some manuscripts.

Conclusions. Our study compares clinical and laboratory characteristics between COVID-19 and Influenza in children. To our knowledge, it is the only systematic review carried out at the pediatric age. No symptoms are characteristic of a single infectious agent, with flu-like disorders being the most common. However, the presence of diarrhea could be a discriminating factor. Laboratory tests do not help in the differential diagnosis but show a limited inflammatory response in COVID-19. This is reflected in complications, with a less severe clinical course and rare fatal events.

Prospective studies are needed, with a larger sample size and comparison from the hospital and non-hospital cases to confirm our observations.

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