

Sađlıklı Çocukta COVID-19 ve Gastrointestinal Sistem

DOÇ.DR.ZÜMRÜT ŞAHBUDAK BAL
ÇOCUK ENFEKSİYON HASTALIKLARI BD
EGE ÜNİVERSİTESİ TIP FAKÜLTESİ

COVID-19

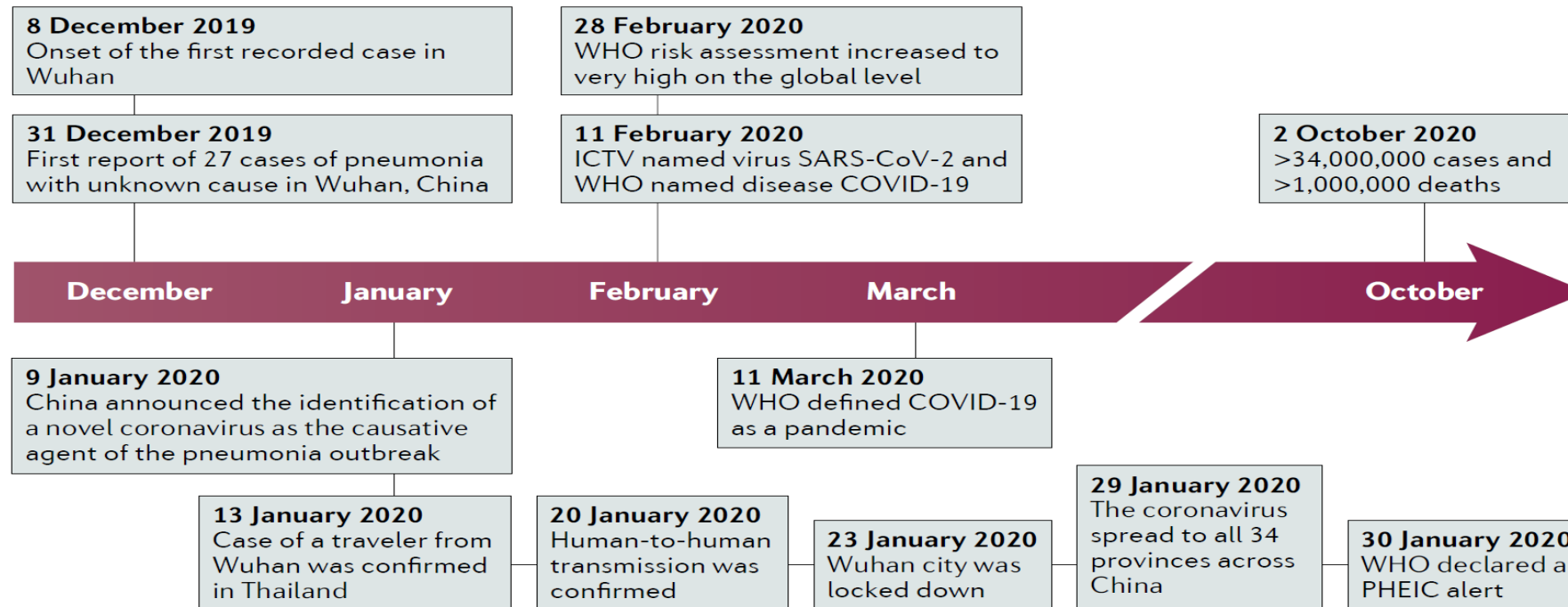


Fig. 1 | **Timeline of the key events of the COVID-19 outbreak.** The first recorded cases were reported in December 2019 in Wuhan, China. Over the course of the following 10 months, more than 30 million cases have been confirmed worldwide. COVID-19, coronavirus disease 2019; ICTV, International Committee on Taxonomy of Viruses; PHEIC, public health emergency of international concern; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

COVID-19



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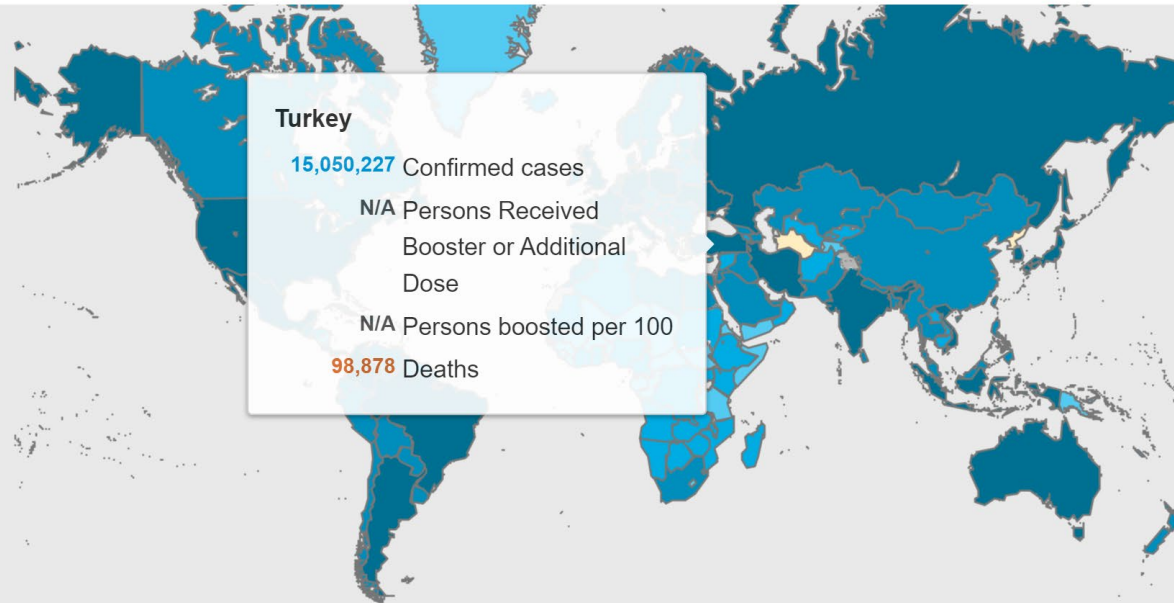
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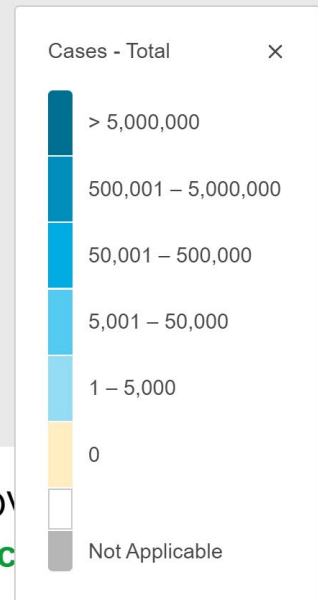


Cases
Total

567,618
new cases in last 24hrs

517,648,631
cumulative cases

6,261,708
cumulative deaths



Globally, as of 3:39pm CEST, 13 May 2022, there have been 517,648,631 confirmed cases of COVID-19, including 6,261,708 deaths, reported to WHO. As of 9 May 2022, a total of 11,655,356,423 vaccine doses have been administered.

SARS-CoV-2

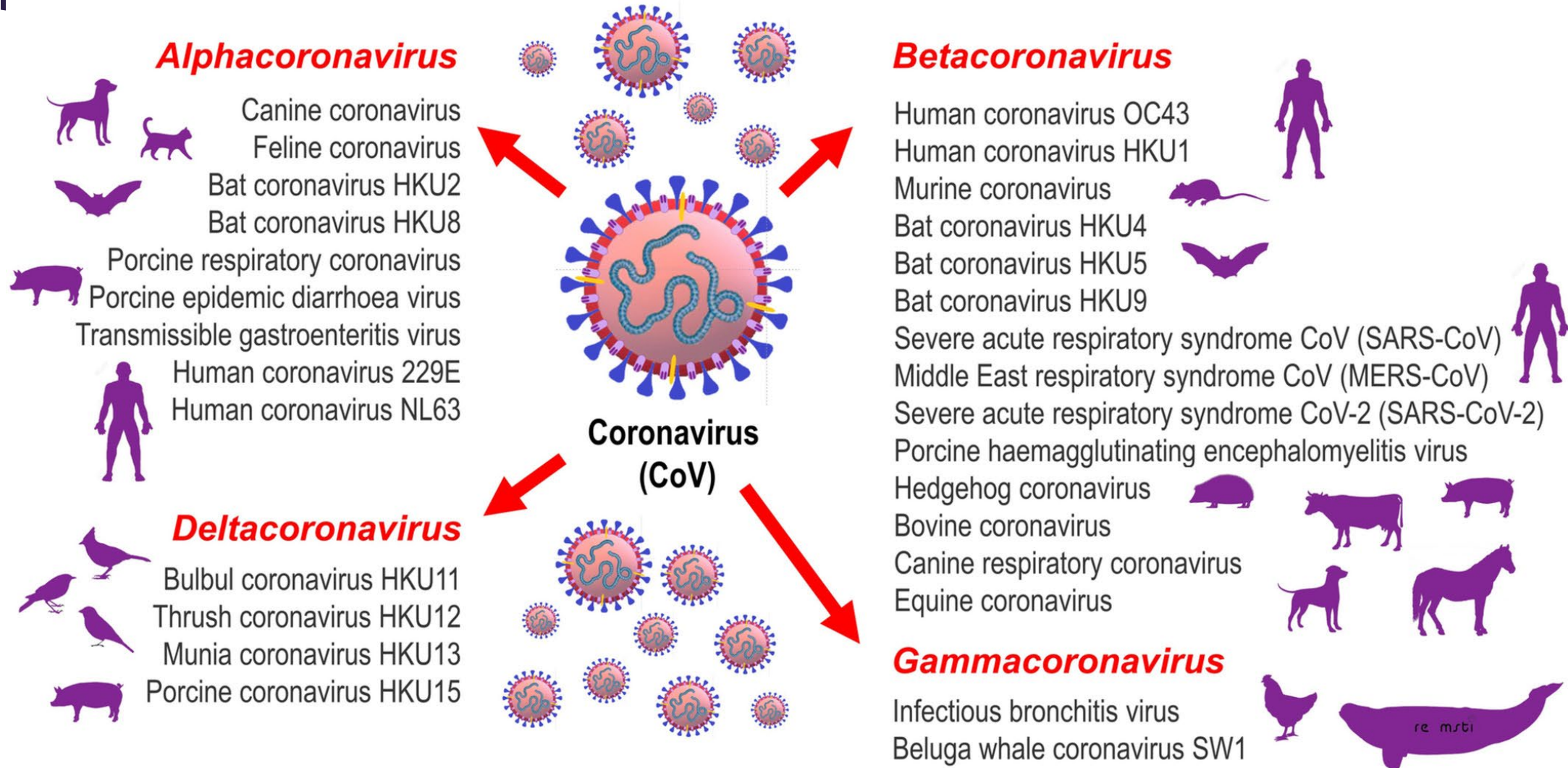
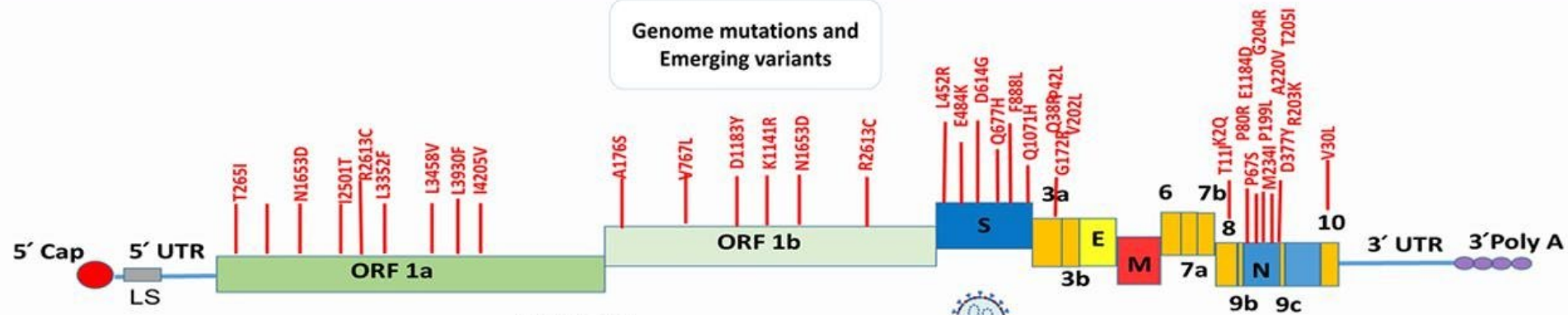


Table 2 | Comparison of SARS-CoV-2, SARS-CoV and MERS-CoV infection

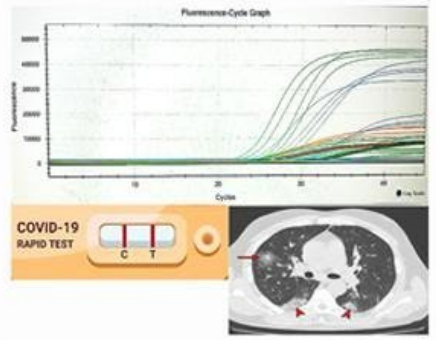
Characteristics	SARS-CoV-2 (REFS ^{4,30,83})	SARS-CoV ^{36,40}	MERS-CoV ^{36,43}
<i>Epidemiology</i>			
Confirmed cases	105,658,476 ^a	8,096	2,519
Mortality (%)	2.2 ^a	9.6	34.4
Incubation period (days)	1–14	2–14	2–14
<i>Gastrointestinal characteristics</i>			
Nausea (%)	7.8	20–35	21.0
Vomiting (%)	7.8	20–35	21.0
Diarrhoea (%)	7.7	20–25	26.0
Percentage of patients with positive faecal samples	55.0	97.0	14.5 ^b

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. ^aAs of 8 February 2021 according to the WHO. ^bPercentage of faecal samples tested positive.

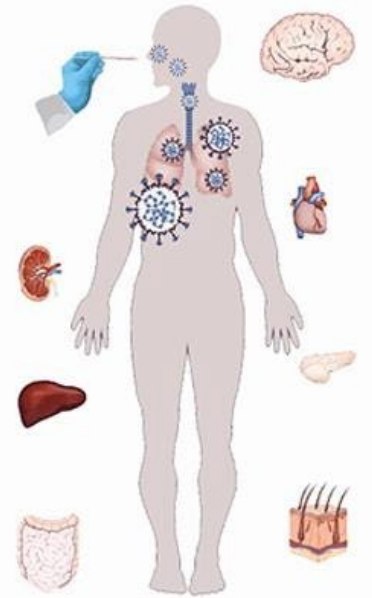


- Variants of Concern (VOC)**
- Alpha (B.1.1.7)
 - Beta (B.1.351)
 - Gamma (P.1)
 - Delta (B.1.617.2)
- Variants of interest (VOI)**
- Epsilon (B.1.427/B.1.429)
 - Zeta (P.2)
 - Eta (B.1.525)
 - Theta (P.3)
 - Iota (B.1.526)
 - Kappa (B.1.617.1)
 - Lambda (C.37)
 - Mu (B.1.621)

Diagnostic tests



Immune Responses and COVID-19 Pathogenesis



COVID-19 vaccine candidates



COVID-19 treatment strategies

- Anti-viral therapy
- RNA Interference (RNAi)
- Anti-inflammatory agents
- Immunotherapy
- Cellular therapy

SARS-CoV-2: Current trends in emerging variants, pathogenesis, immune responses, potential therapeutic, and vaccine development strategies

SARS-CoV-2 Variants

SARS-CoV-2 Variants of Concern



Alpha Variant (B.1.1.7)

Detected in the United Kingdom in September 2020



Beta Variant (B.1.351)

Detected in South Africa in October 2020



Gamma Variant (P.1)

Detected in Brazil in November 2020



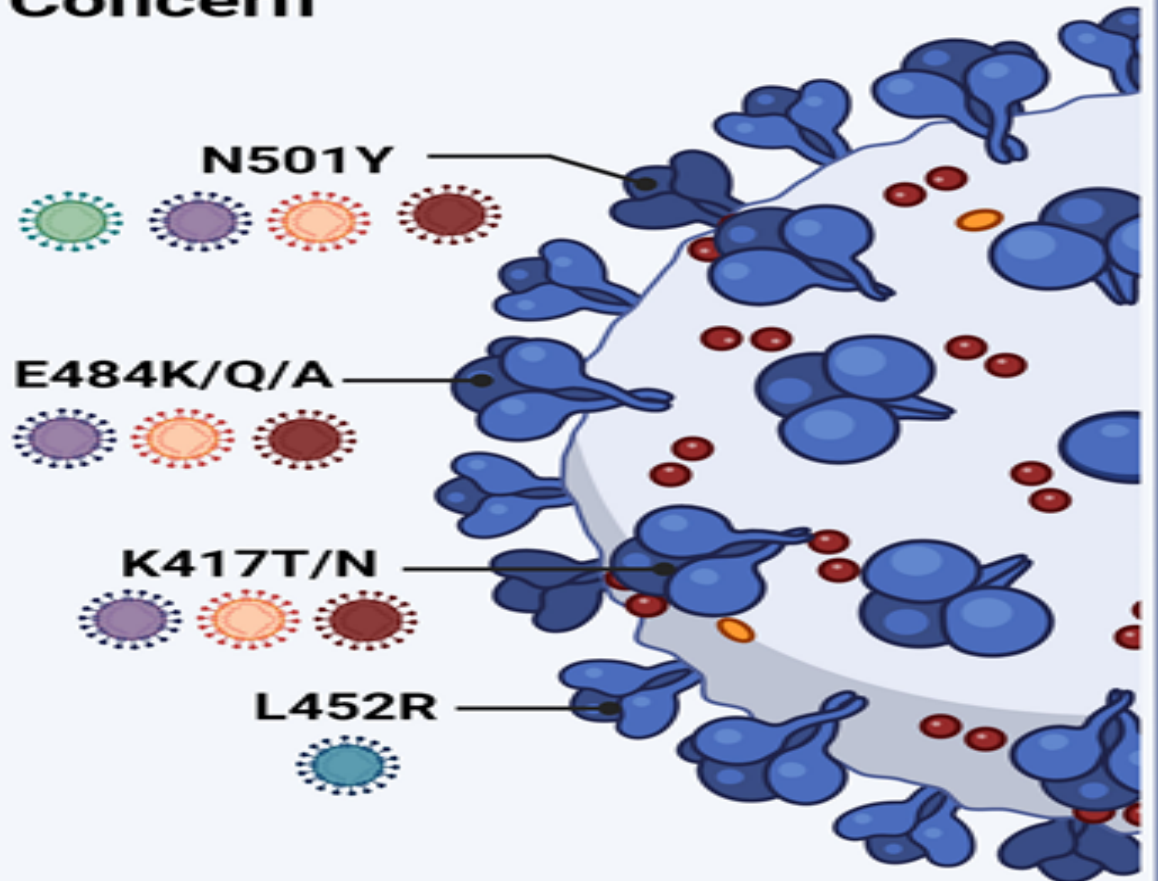
Delta Variant (B.1.617.2)

Detected in India in December 2020



Omicron Variant (B.1.1.529)

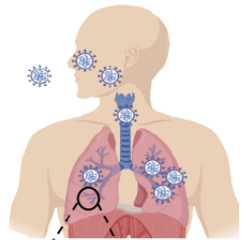
Detected in South Africa in November 2021



Omicron varyantı (B.1.1.529)

- ▶ İlk olarak Güney Afrika'da görülmüş, diğer varyantlar ile karşılaştırıldığında yayılma hızı oldukça yüksek olan bu virüs 26 Kasım 2021 de DSÖ tarafından ***Variant of Concern (VOC)*** olarak tanımlanmıştır.
- ▶ Artan bulaşıcılık ve enfeksiyon veya aşı kaynaklı bağışıklıktan kısmi kaçış ile ilişkili Omicron varyantı, ***Aralık 2021'in sonlarında çok sayıda ülkede baskın varyant olarak Delta'nın yerini almıştır***
- ▶ Omicron varyantında *genom, viral spike proteini ve reseptör bağlanma bölgesi* dahil olmak üzere 50'den fazla mutasyon tanımlanmıştır.

Çocuklar neden şanslı?



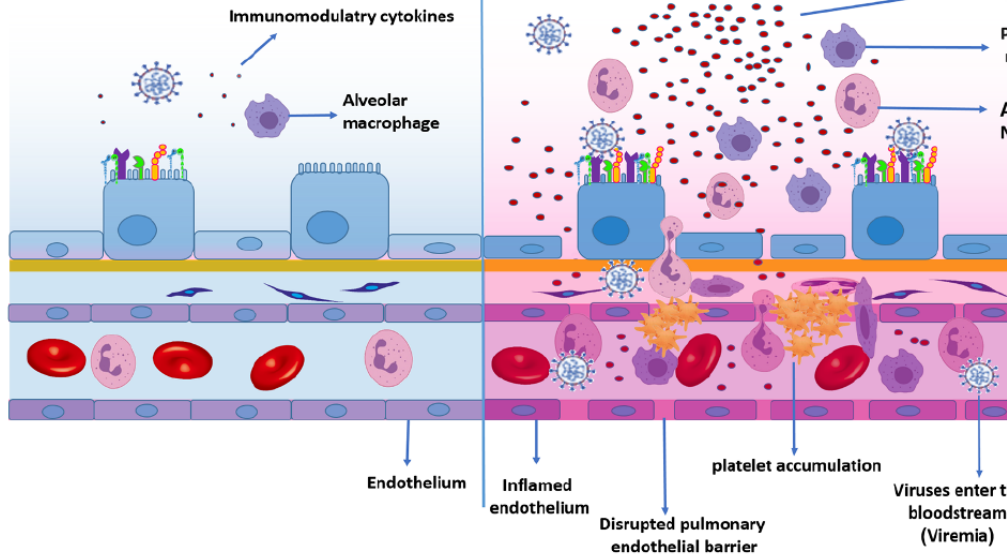
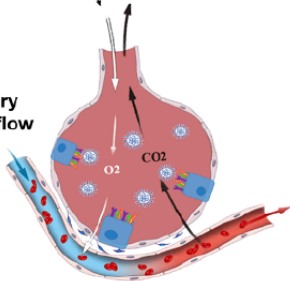
Mild infection (Pediatric lung)

- ✓ Decreased epithelial expression of ACE-2 and TMPRSS2
- ✓ Increased immunomodulatory cytokines: TGF- β , IL-10, IL4, IL-5, IL-13
- ✓ Decreased production of pro-inflammatory cytokines
- ✓ Decreased neutrophil infiltration
- ✓ Preserved pulmonary endothelial barrier
- ✓ High capacity to recover and repair after viral infection

Severe infection (Adult lung)

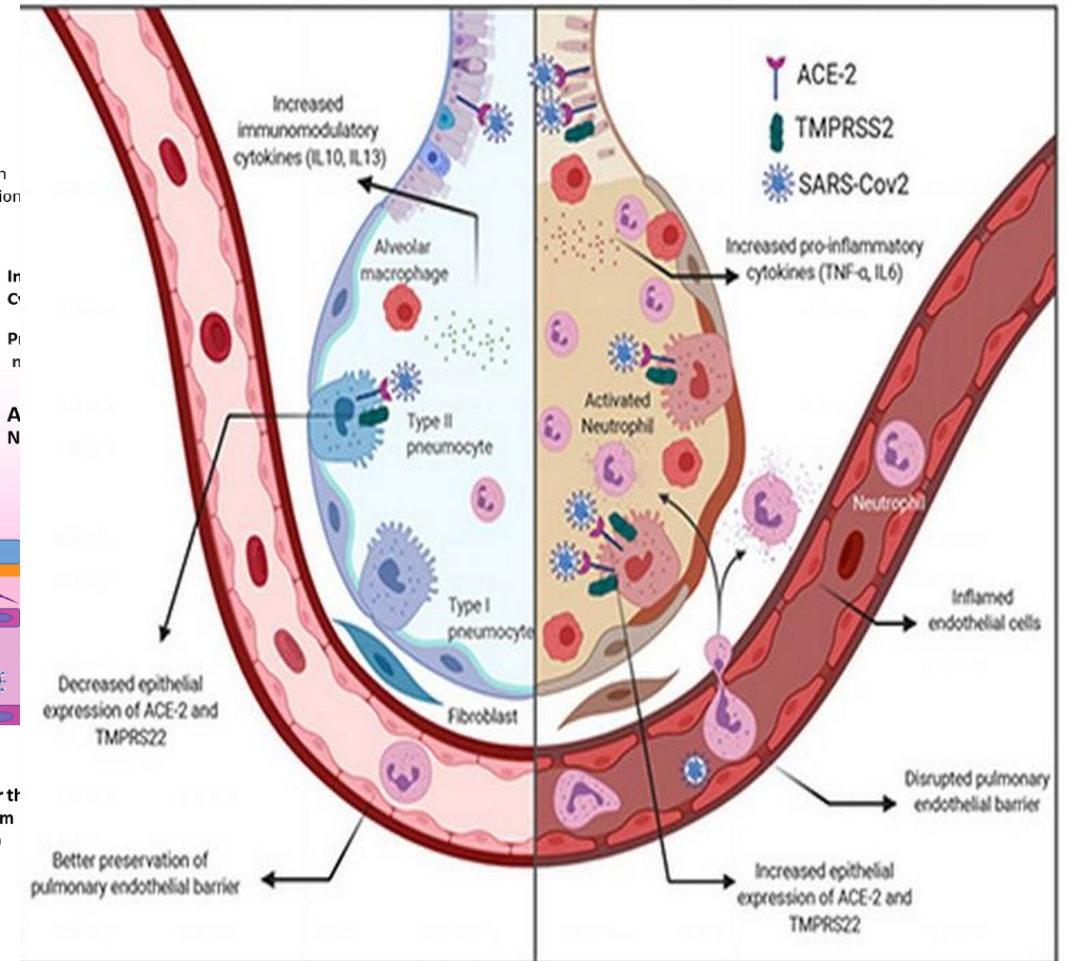
- ✓ Increased epithelial expression of ACE-2 and TMPRSS2
- ✓ Increased pro-inflammatory Cytokines: IL-1 β , IL-6, IL-2, TNF- α , IFN- γ , IL-17 and IL-8
- ✓ Apoptosis and necrosis of alveolar cells
- ✓ Endothelial and epithelial permeability and Fluid Accumulation
- ✓ Platelet thrombus (platelet adhesion, activation, and aggregation)
- ✓ Respiratory failure and acute respiratory distress syndrome (ARDS)
- ✓ Cytokine storm
- ✓ Systemic inflammation and distant organs damage

Capillary blood flow



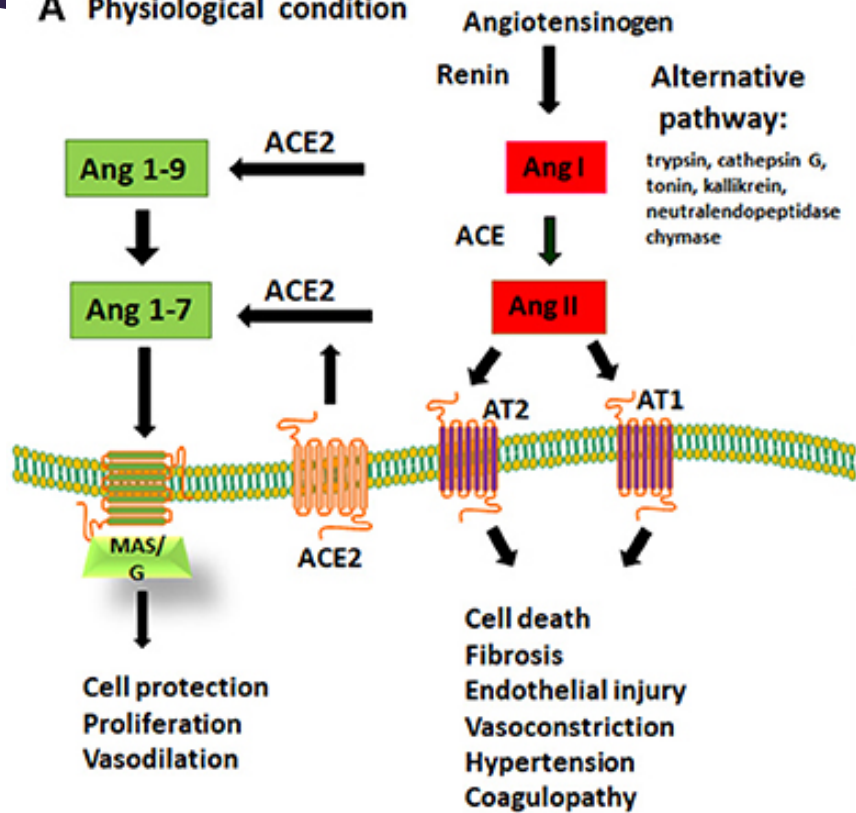
Pediatric Lung

Adult Lung

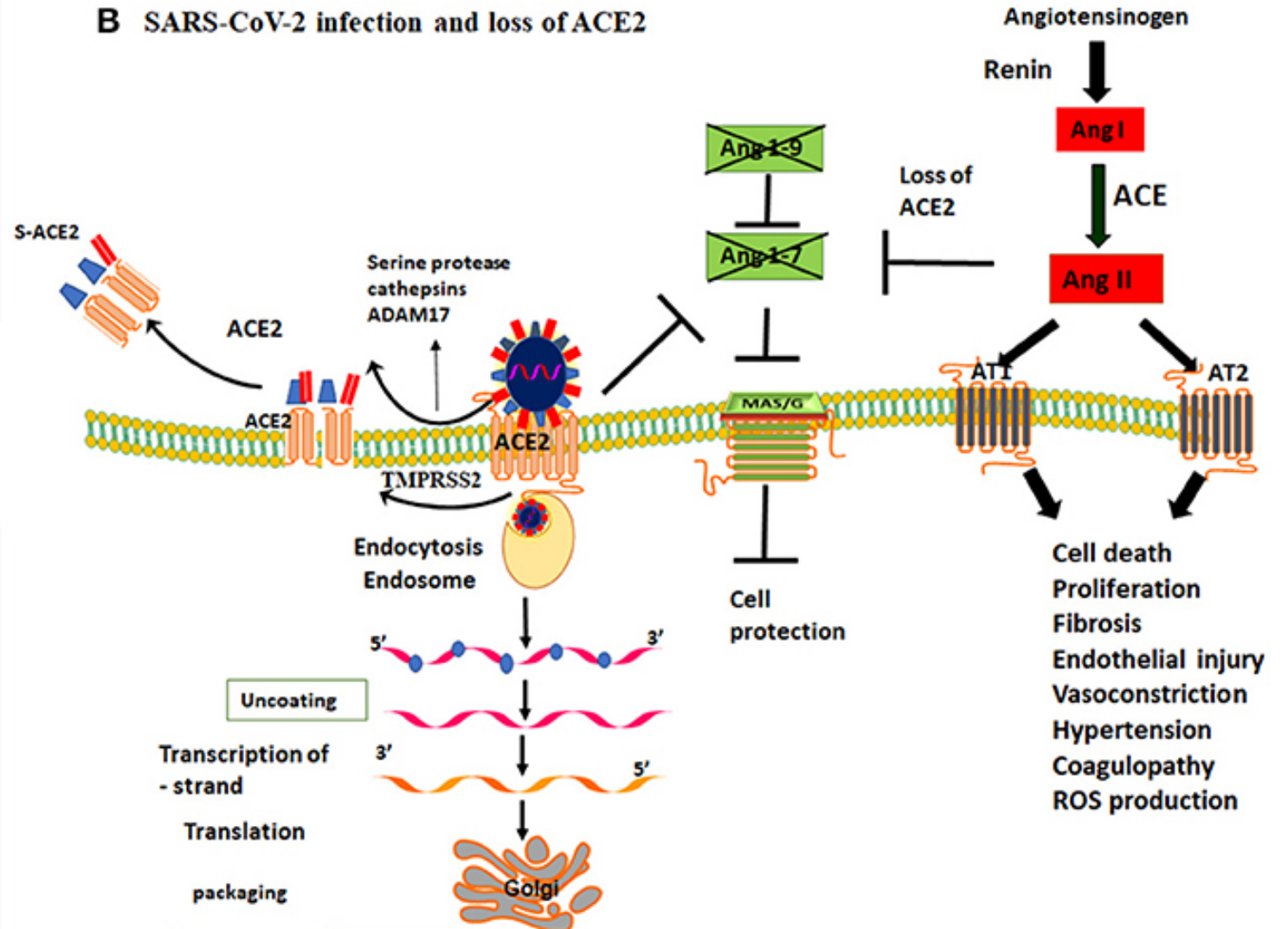


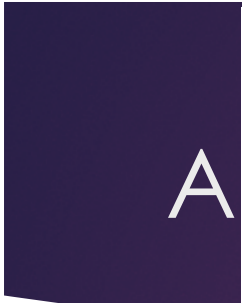
Patofizyoloji

A Physiological condition

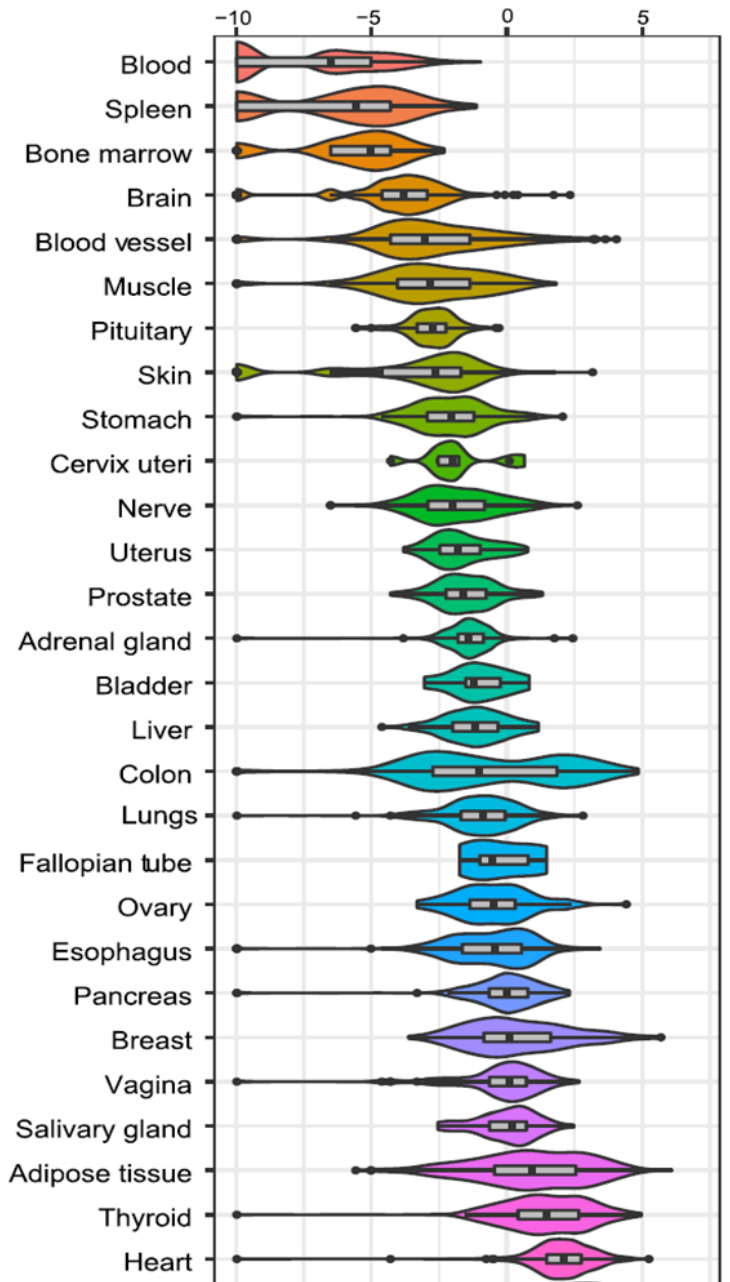


B SARS-CoV-2 infection and loss of ACE2





a ACE2 expression level (log2-transformed)



Hypomethylation →

Zinc deficiency →

ACE2 SNPs →

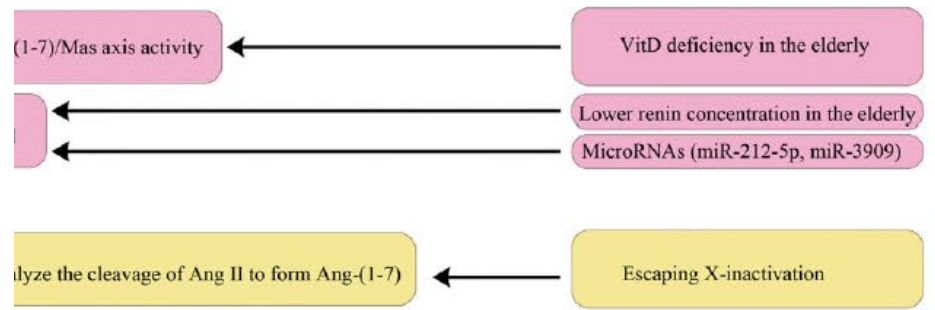


FIGURE 2 | The

The Impact of ACE2 Polymorphisms on COVID-19 Disease: Susceptibility, Severity, and Therapy

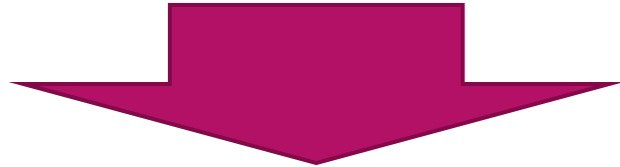
TMPRSS2

- ▶ TMPRSS2'yi kodlayan gen, 21q22.3 lokusunda bulunur, 3450 baz çifti uzunluğundadır ve 14 ekzon içerir.
- ▶ Androjen reseptörü (AR) bağlanır. Androjenler, AR ekspresyonunu artırır. Dolayısıyla androjenlerin TMPRSS2 ekspresyonunu artırdığı bildirilmiştir
- ▶ Yaş ile de ekspresyon artmıştır
- ▶ Yaşlılarda ve erkeklerde daha ciddi seyretmesinde etkilidir

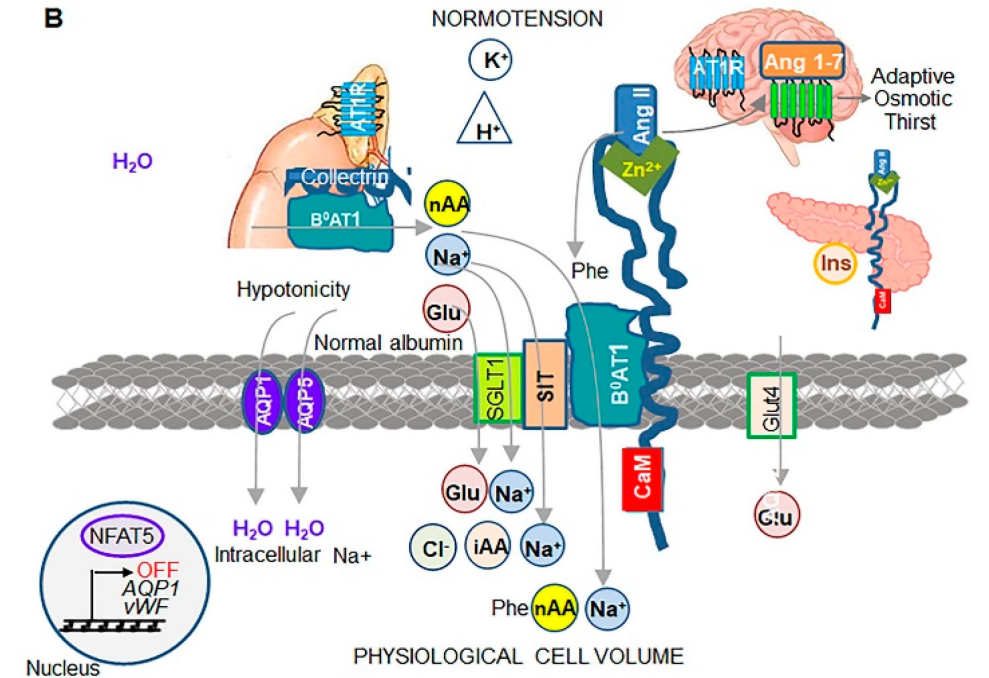
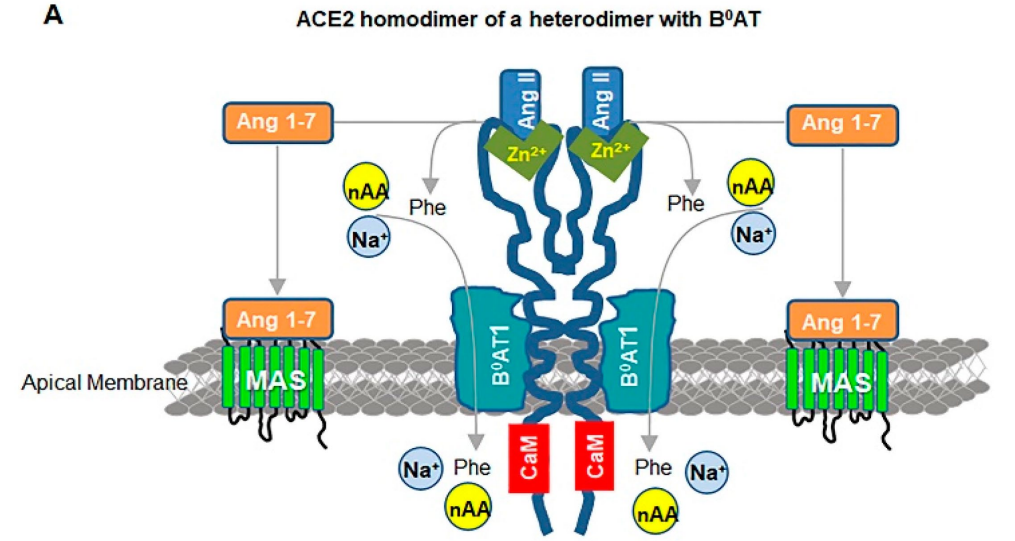
SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

Gastrointestinal Sistem

- ▶ RAAS''dan bağımsız olarak B0AT1
- ▶ Na bağımlı nötral aminoasitlerin transportu
- ▶ Özellikle triptofan ve glutamin

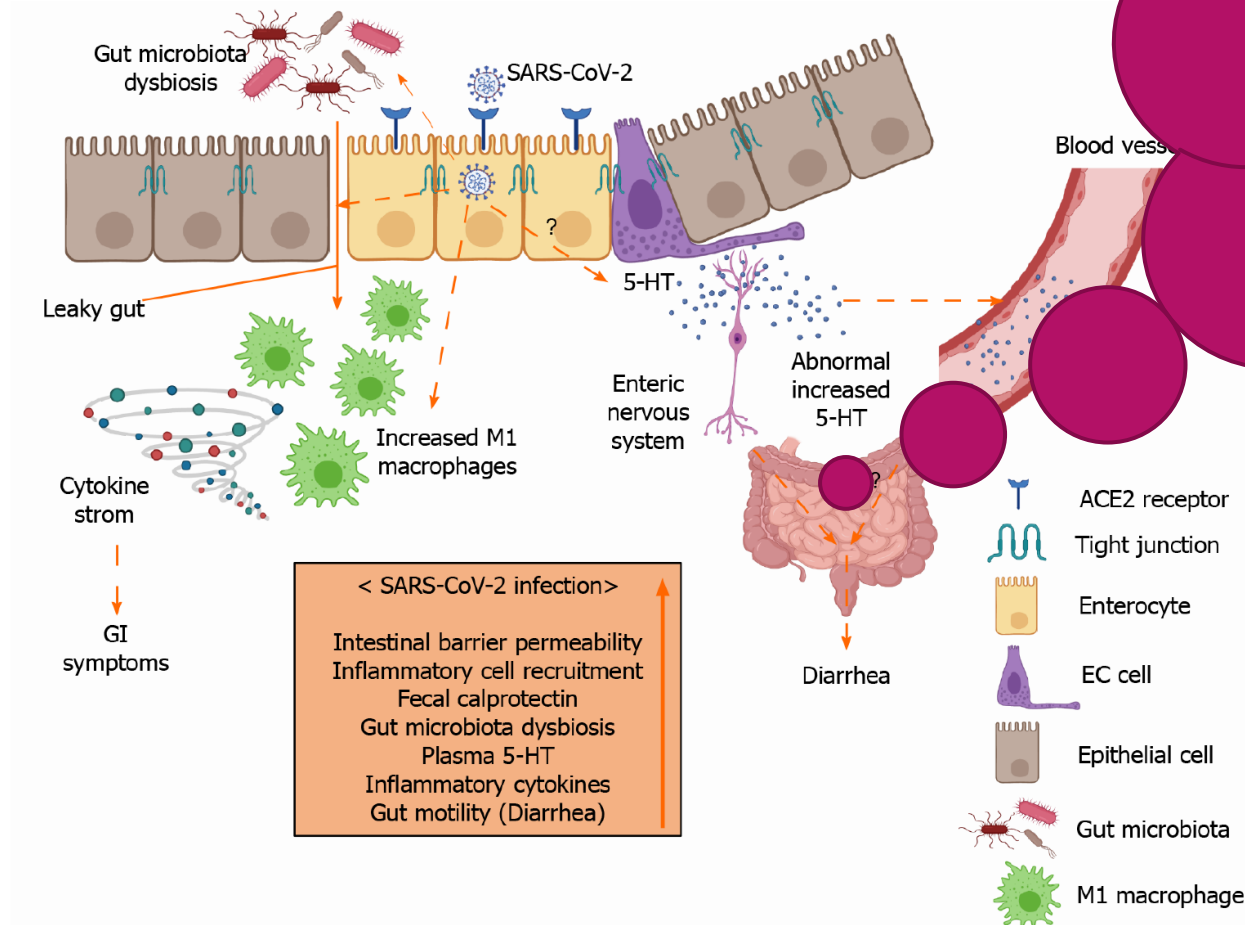


- ▶ Downregulate lenfoid proinflamatuvar sitokinler
- ▶ Intestinal tight junctionların stabilitesi
- ▶ Antimikrobiale aktivite



Serotonin Metabolizması

Jin B *et al.* GI symptoms of COVID-19



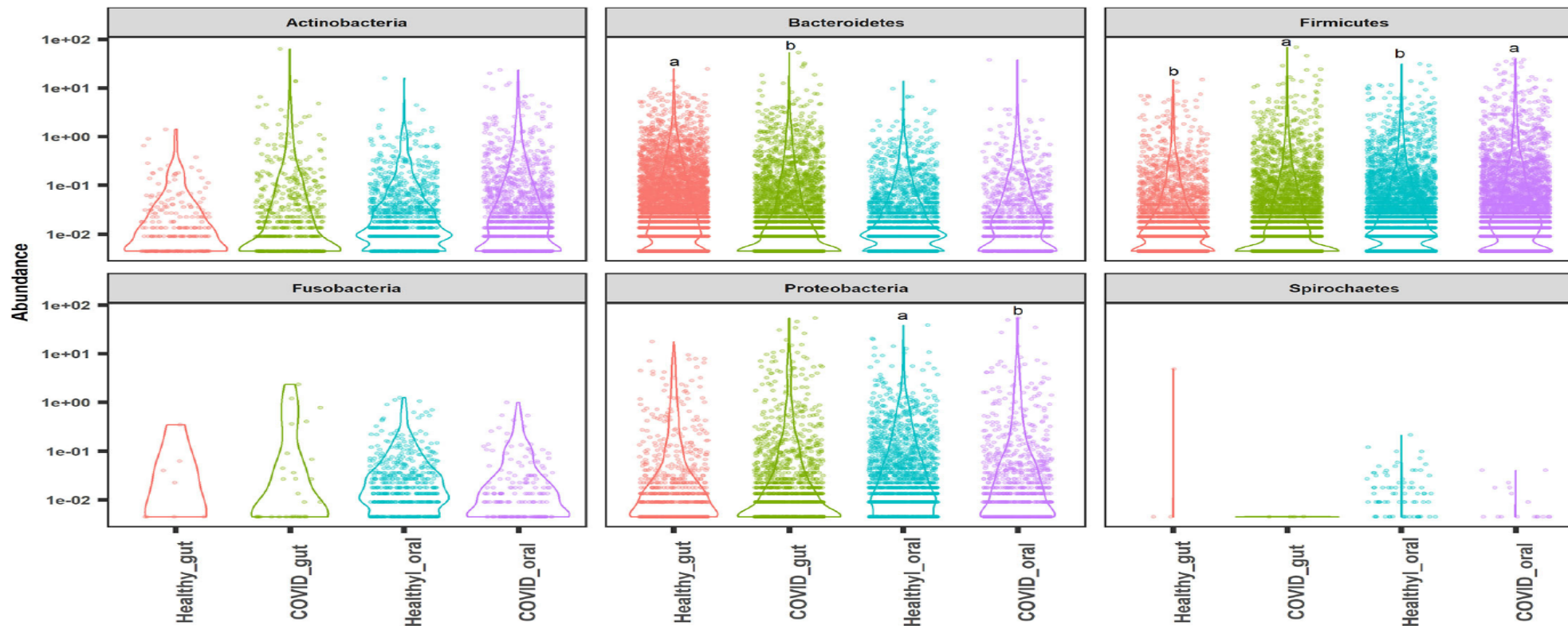
5-HT düzeyindeki değişiklikler İBS ilişkili

COVID-19 hastalarında 5-HT düzeyinde artış

Alterations in serotonin metabolism in COVID-19 patients

We have reported that plasma serotonin (5-hydroxytryptamine, 5-HT) levels were elevated in COVID-19 patients with diarrhea[12]. 5-HT is a hormone and neurotransmitter that has a monoamine structure. 5-HT synthesis begins with the amino acid L-tryptophan, which is converted to 5-hydroxytryptophan (5-HTP) *via* the rate-limiting enzyme tryptophan hydroxylase (TPH). 5-HTP is then rapidly decarboxylated by aromatic L-amino acid decarboxylase to produce 5-HT[26,27]. 5-HT either circulates in our body or is absorbed by the cells that express serotonin reuptake transporter to act or decompose, resulting in 5-hydroxyindoleacetic acid (5-HIAA)[28]. TPH is an enzyme specifically found in 5-HT producing cells, and there are two different isoforms, TPH1 and TPH2[29,30]. TPH1 dependent 5-HT synthesis occurs in entero-

Barsakta disbiyozis



to healthy controls. We report that SARS-CoV-2 infection significantly reduced richness and evenness in the gut and oral microbiomes despite higher unique operational taxonomic units in the gut. The gut samples of the patients with COVID-19 included 46 opportunistic bacterial genera. *Escherichia*, *Shigella*, and *Bacteroides* were detected as the signature genera in the gut of patients with COVID-19 with diarrhea, whereas a relatively higher abundance of *Streptococcus* was found in patients with COVID-19 having breathing difficulties and sore throat (BDST). The patients with COVID-19 had a significantly lower abundance of *Prevotella* in the oral cavity, compared to healthy controls and patients with COVID-19 without diabetes, respectively. The altered

Dysbiosis of Oral and Gut Microbiomes in SARS-CoV-2 Infected Patients in Bangladesh: Elucidating the Role of Opportunistic Gut Microbes

Managing the Inevitable Surge of Post-COVID-19 Functional Gastrointestinal Disorders

Table 2. Proposed diagnostic criteria for post-COVID-19 FGIDs/DGBI

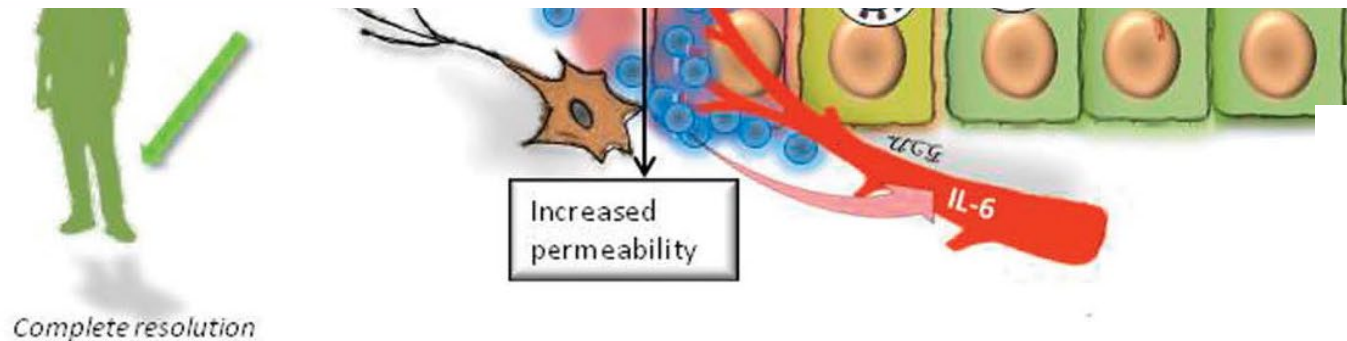
Fulfilling Rome IV criteria for any FGID/DGBI in the past 3 mo, with symptom onset at least 6 mo before diagnosis associated with:

Previous COVID-19 infection confirmed by SARS-CoV-2 real-time PCR performed at regional reference laboratories

Symptom development immediately after resolution of acute COVID-19 infection

Should not meet criteria for FGIDs before onset of acute illness

COVID-19, coronavirus disease 2019, DGBI, disorders of gut-brain interaction; FGID, functional gastrointestinal disorder; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.



Gut inflammation in COVID-19 patients with diarrhea

Fecal calprotectin (FC) has evolved as a reliable fecal biomarker allowing detection of intestinal inflammation in inflammatory bowel disease (IBD) and infectious colitis[25]. Previous studies have shown that COVID-19 patients with diarrhea without IBD had high FC compared to patients without diarrhea, indicating that the infection evokes a significant intestinal inflammatory process[25]. Furthermore, FC levels correlated significantly with the pro-inflammatory interleukin - 6 (IL-6) serum concentrations, and a murine study showed that deficiency of ACE2 results in highly increased susceptibility to intestinal inflammation induced by epithelial damage[21]. Collectively, the aforementioned studies highlighted that GI inflammation was overrepresented in patients with COVID-19 that also had functional GI disorders (FGIDs) or post-infection (PI) GI disorders.

Intestinal Host Response to SARS-CoV-2 Infection and COVID-19 Outcomes in Patients With Gastrointestinal Symptoms

0.0 2.5 5.0 7.5

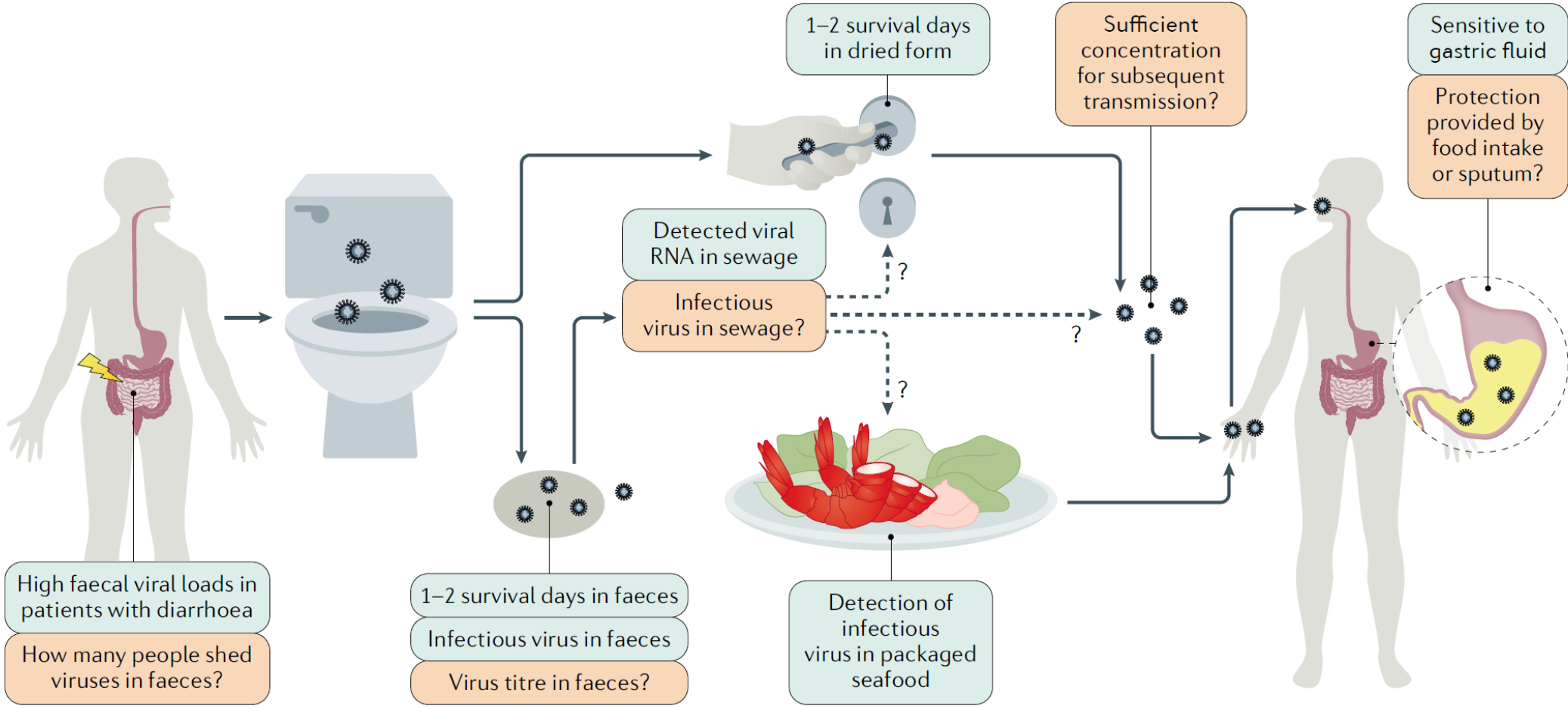


See editorial on page 2251.

BACKGROUND & AIMS: Given that gastrointestinal (GI) symptoms are a prominent extrapulmonary manifestation of COVID-19, we investigated intestinal infection with SARS-CoV-2, its effect on pathogenesis, and clinical significance. **METHODS:** Human intestinal biopsy tissues were obtained from patients with COVID-19 (n = 19) and uninfected control individuals (n = 10) for microscopic examination, cytometry by time of flight analyses, and RNA sequencing. Additionally, disease severity and mortality were examined in patients with and without GI symptoms in 2 large, independent cohorts of hospitalized patients in the United States (N = 634) and Europe (N = 287) using multivariate logistic regressions. **RESULTS:** COVID-19 case patients and control individuals in the biopsy cohort were comparable for age, sex, rates of hospitalization, and relevant comorbid conditions. SARS-CoV-2 was detected in

small intestinal epithelial cells by immunofluorescence staining or electron microscopy in 15 of 17 patients studied. High-dimensional analyses of GI tissues showed low levels of inflammation, including down-regulation of key inflammatory genes including *IFNG*, *CXCL8*, *CXCL2*, and *IL1B* and reduced frequencies of proinflammatory dendritic cells compared with control individuals. Consistent with these findings, we found a significant reduction in disease severity and mortality in patients presenting with GI symptoms that was independent of sex, age, and comorbid illnesses and despite similar nasopharyngeal SARS-CoV-2 viral loads. Furthermore, there was reduced levels of key inflammatory proteins in circulation in patients with GI symptoms. **CONCLUSIONS:** These data highlight the absence of a proinflammatory response in the GI tract despite detection of SARS-CoV-2. In parallel, reduced mortality in patients with COVID-19 presenting with GI symptoms was observed. A potential role of the GI tract in

Potential intestinal infection and faecal–oral transmission of SARS-CoV-2



Çocuklarda Epidemiyoloji

- **Irksal farklılıklar erişkin çalışmalara benzer şekilde gösterilmiştir**
 - Asya ırklarında ve siyahi ırkta hastaneye yatış ihtiyacı, beyaz ırktan daha yüksek bulunmuştur
- **Kız ve erkek çocuklar eşit oranda etkilenmektedir**
- **Ağırlıklı ortalama yaş: 7.6 'dır.**

KLİNİK BULGULAR

- ▶ COVID-19, çocuklarda yetişkinlere göre daha hafif seyretmekte, ancak ciddi vakalar da bildirilmiştir
 - ▶ Akut miyokardit ve solunum yetmezliği
 - ▶ HLH ve Karaciğer yetmezliği
 - ▶ ARDS ve solunum yetmezliği
- ▶ 1/3'ü asemptomatik

Çocuklarda GIS bulguları

Studies on paediatric patients

Xu et al. ⁷⁹	Guangdong, China	Until 20 Feb 2020	10	Diarrhoea 30%; vomiting 0	On admission	NA
Cai et al. ⁸¹	China	Jan 19 to 3 Feb 2020	10	Diarrhoea 0%	During hospitalization	NA
Lu et al. ¹⁷⁰	Wuhan, China	28 Jan to 26 Feb 2020	171	Diarrhoea 8.8%; vomiting 6.4%	No distinction made	NA
Fakiri et al. ¹⁷¹	Marrakesh, Morocco	2 Mar to 1 Apr 2020	74	Diarrhoea 5.4%	No distinction made	NA
de Ceano-Vivas et al. ¹⁷²	Madrid, Spain	11 Mar to 9 Apr 2020	58	Diarrhoea 12.1%; vomiting 15.5%	No distinction made	NA
Mahmoudi et al. ¹⁷³	Tehran, Iran	7 Mar to 30 Mar 2020	35	Diarrhoea 26%; vomiting 29%; abdominal pain 11%	No distinction made	NA
CDC COVID-19 Response Team ¹⁷⁴	USA	12 Feb to 2 Apr 2020	291	Diarrhoea 13%; nausea and/or vomiting 11%; abdominal pain 5.8%	No distinction made	NA
Parri et al. ¹⁷⁵	Italy	3 Mar to 27 Mar 2020	100	Diarrhoea 9%; nausea or vomiting 10%	No distinction made	NA



Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis

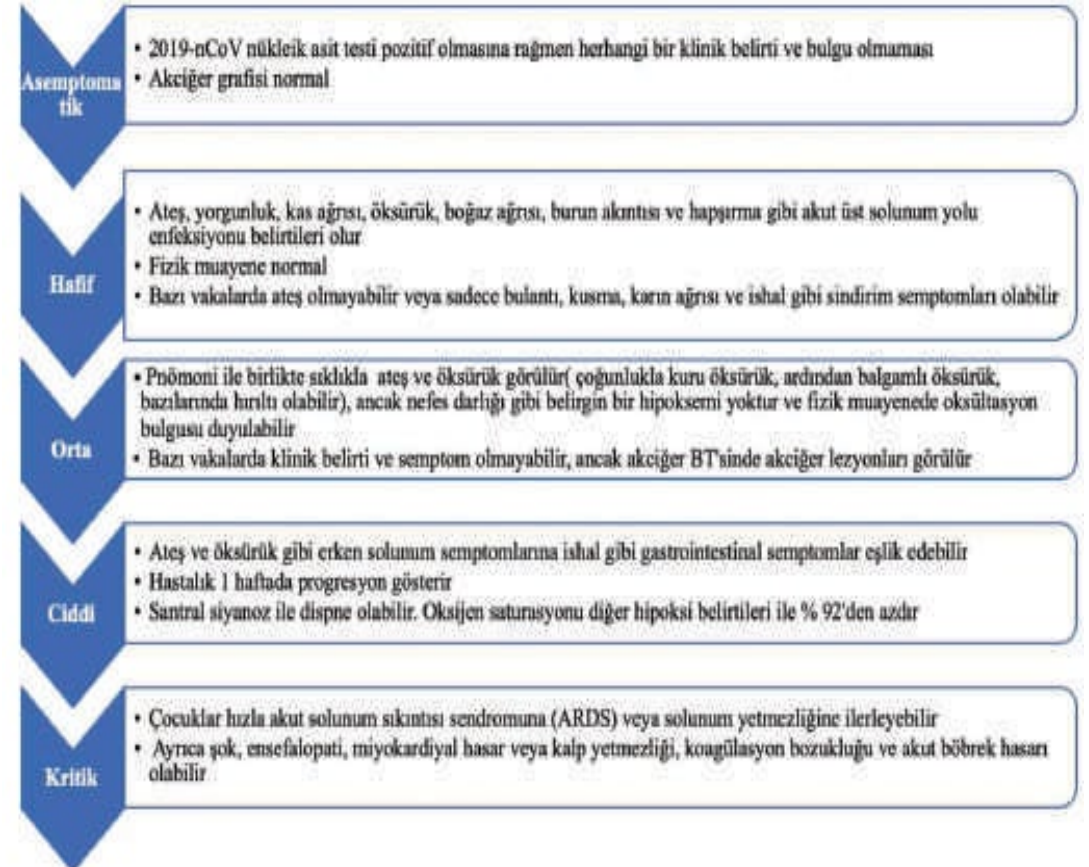
Table 1 Clinical symptoms among reported paediatric COVID-19 cases

Characteristics	Events/total patients	Mean proportion % (95% CI)	Heterogeneity I ² (%)
Comorbidity	1590/6086	27.1 (23.1 to 31.5)	37.6
Fever	3576/6296	63.3 (58.6 to 68.4)	34.9
Cough	1807/5261	33.7 (29.6 to 38.1)	34.4
Nausea/vomiting	880/4243	20.0 (16.5 to 24.0)	25.7
Diarrhoea	796/4884	19.6 (16.1 to 23.7)	13.4
Dyspnoea	879/5332	17.5 (14.4 to 21.1)	23.7
Nasal symptoms	1080/5406	16.6 (13.9 to 19.7)	10.6
Rashes	744/4387	15.5 (11.9 to 19.9)	25.9
Fatigue	709/4474	15.5 (12.6 to 19.3)	26.3
Abdominal pain	626/4135	15.3 (11.9 to 19.4)	26.5
Kawasaki shock/sign	821/4365	13.3 (9.8 to 17.9)	30.6
Asymptomatic	1114/6084	13.1 (10.4 to 16.3)	15.4
Neurological symptoms	693/5475	12.1 (10.1 to 14.6)	17.6
Conjunctivitis	529/4998	10.5 (7.8 to 14.0)	21.0
Pharyngeal erythema	428/3638	9.0 (6.7 to 12.0)	0.0

Hastalık şiddeti

- ▶ Asemptomatik %15
- ▶ Hafif %42
- ▶ Orta %39 → Hipoksemi olmadan pnömoninin klinik veya radyografik kanıtı
- ▶ Ciddi %2 → Dispne, santral siyanoz, hipoksemi
- ▶ Kritik %0.7 → akut solunum sıkıntısı sendromu, solunum yetmezliği, şok

Acute COVID-19		COVID-19-associated MIS-C		
Mild	Severe	Febrile inflammatory state	KD-like illness	Severe MIS-C
In most children, COVID-19 causes no or only mild symptoms.	A small minority of children present with severe acute COVID-19 manifestations, including respiratory failure, ARDS, neurologic symptoms, coagulopathy, and shock. This occurs most commonly in children with underlying medical conditions. Some children with severe acute COVID-19 may develop signs of cytokine storm.	Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers may be elevated, but signs of severe multisystem involvement are lacking.	Some children meet criteria for complete or incomplete KD and do not develop shock and severe multisystem involvement.	Children with severe MIS-C have markedly elevated inflammatory markers and severe multisystem involvement. Cardiac involvement and shock are common.



GASTROINTESTINAL SYMPTOMS IN SEVERE COVID-19 CHILDREN

Characteristics	Asymptomatic, mild, or moderate		Severe or critical		<i>P</i> ^a	Not ICU		ICU		<i>P</i> ^a
	N = 107		N = 20			N = 111		N = 8		
	N	%	n	%		N	%	n	%	
Age median (IQR, y)	1.6 (0.3, 7.9)		4.3 (0.3, 10.1)		0.393 ^b	1.6 (0.3, 7.9)		5.5 (0.4, 10.1)		0.497 ^b
Age group					0.845					0.854
Newborn	5	4.7	1	5.0		6	5.4	0	0.0	
Infant	44	41.1	7	35.0		44	39.6	3	37.5	
Children	42	39.2	8	40.0		46	41.4	3	37.5	
Adolescent	16	15.0	4	20.0		15	13.5	2	25.0	
Male	68	64.2	14	70.0	0.799	71	64.5	5	62.5	1.000
Presentation										
Fever	85	79.4	20	100.0	0.023	92	82.9	8	100.0	0.352
Respiratory symptoms	68	63.6	14	70.0	0.799	74	67.3	4	50.0	0.441
Respiratory symptoms only	46	43.0	7	35.0	0.624	44	39.6	2	25.0	0.468
Cough	52	48.6	9	45.0	0.812	57	51.4	2	25.0	0.812
Rhinorrhea	43	40.2	6	30.0	0.460	46	41.4	0	0.0	0.022
Wheezing	4	3.7	0	0.0	1.000	3	2.7	0	0.0	1.000
Dyspnea	5	4.7	5	25.0	0.009	7	6.4	2	25.0	0.114
GI symptoms	26	24.3	10	50.0	0.029	31	27.9	4	50.0	0.232
GI symptoms only	13	12.1	5	25.0	0.160	14	12.6	3	37.5	0.087
Vomit	6	5.6	6	30.0	0.004	6	5.4	6	75.0	0.004
Diarrhea	20	18.7	8	40.0	0.044	20	18.0	8	100	0.044
Abdominal pain	6	5.6	2	10.0	0.611	8	7.2	0	0.0	1.000



Epidemiological, Clinical, and Laboratory Features of Children With COVID-19 in Turkey

TABLE 2 | Clinical features.

	<i>N</i>	%	Duration (median) (IQR)
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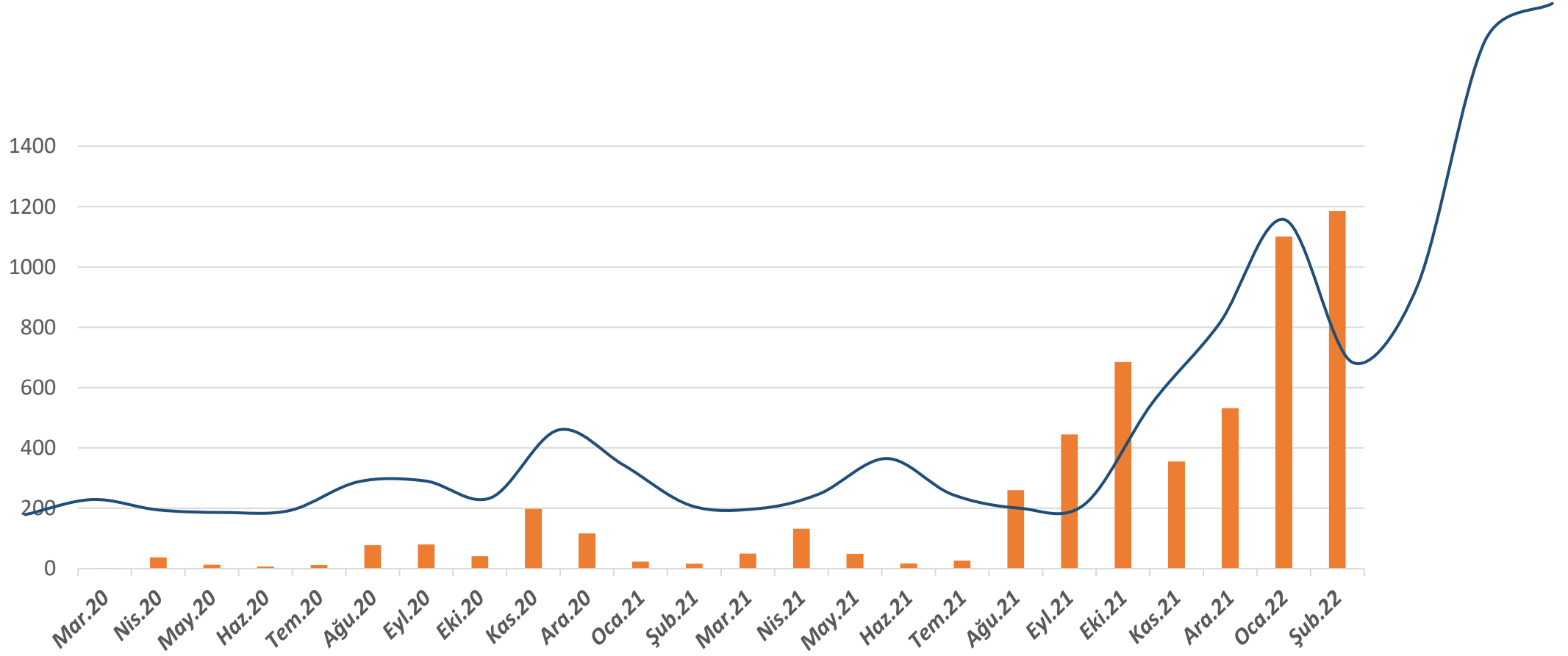
TABLE 6 | Laboratory findings.

	Total Cases	Symptomatic Cases	Asymptomatic Cases	<i>p</i>
	Median (IQR)	Median (IQR)	Median (IQR)	
Hemoglobin (g/dL)	12.9 (12-14)	12.8 (11.9–13.9)	13.0 (12.1–14.0)	0.09
Leukocyte count (/uL)	6,615 (5,222–9,187)	6,780 (5,275–9,560)	6,219 (5,157–8,260)	0.009
Lymphocyte count (/uL)	2,200 (1,490–3,285)	2,100 (1,435–3,300)	2,320 (1,700–3,235)	0.09
Thrombocyte (/uL)	248,000 (207,000–306,750)	245,000 (204,000–306,000)	262,500 (219,000–312,000)	0.13
C-reactive protein (mg/L)	2.73 (2.73–7.78)	3.1 (1.0–10.7)	1.1 (0.7–3.0)	<0.001
Aspartate transaminase (U/L)	28 (21–37)	27 (20.7–35)	28 (22.0–33.5)	0.6
Alanin transaminase (U/L)	17 (13–24)	15 (12–21)	17 (13.0–24.0)	0.9
Creatin kinase (U/L)	89 (65–121)	89 (63–123)	91 (68–115)	0.8
Troponin (ng/L)	0.1 (0.1–2.3)	0.1 (0.1–2.7)	0.1 (0.1–2.3)	0.6
Sore throat*	+	143	12.4	2 (1–3)
	–	980	84.7	

Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, July 2021–January 2022

- Omicron varyantı baskın olduğu dönem ile delta varyantı dominant dönem karşılaştırılmış ve çocuk ve adolasan yaş grubunda hastaneye yatış oranlarında x4 kat artış saptanmış.
- Özellikle 0-4 yaş grubunda hastaneye yatış oranları x5 kat artarak en ciddi artışı göstermiştir.
- Hastaneye yatan hastalarda YBÜ yatış oranlarında ve MV ihtiyacında azalma gözlenmiştir.

Ege Üniversitesi Tıp Fakültesinde SARS-CoV-2 PCR pozitif çocuk sayısı



Omicron Öncesi
(1 Ekim -15 Aralık)

Omicron Sonrası
(16 Aralık –28 Şubat)

0-4 yaş

102 (%7,9)

472 (%17,1) x 4,6 kat

5-9 yaş

328 (%25,4)

679 (%24,4)

10-14 yaş

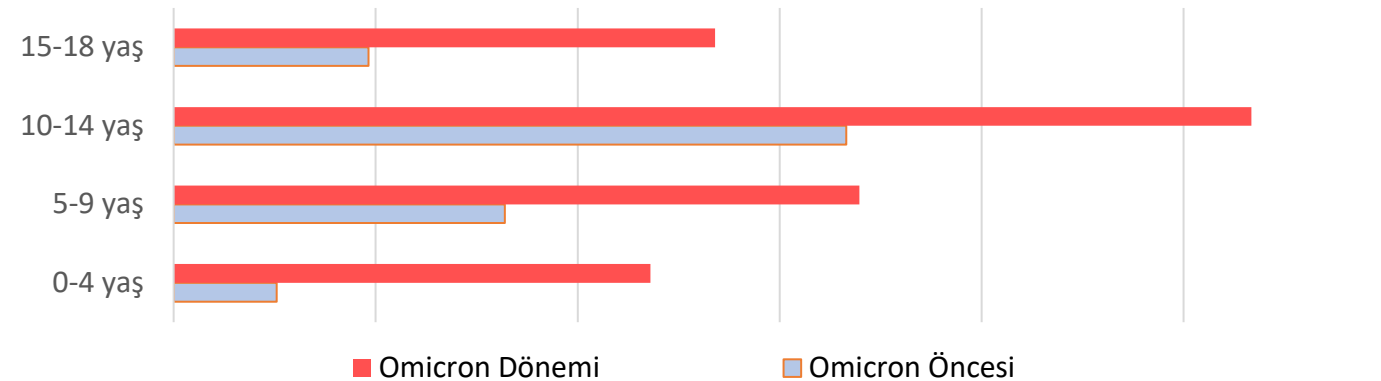
666 (%51,7)

1067 (%38,7)

15-18 yaş

193 (%15)

536 (%19,5)



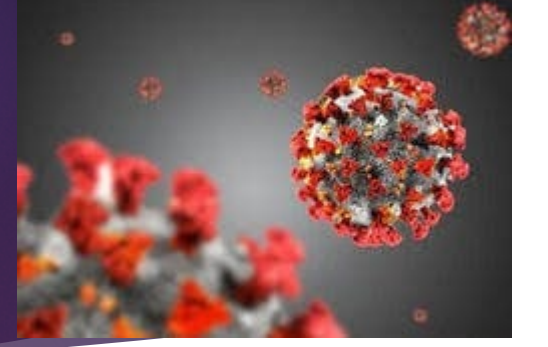
HLH ve Karaciğer nakli

- ▶ 2 yaş erkek hasta
- ▶ COVID-pozitif saptanmış
- ▶ KCFT'lerinde yükseklik (AST: 1500IU ve ALT: IU 1350)
- ▶ T.bil: 2.7 D.bil:2.1,hiperamonyemi
- ▶ Pansitopenisi, LDH yüksekliği, Trigliserid yüksekliği
- ▶ Hipofirinojenemi
- ▶ Kemik iliği: Hemofagositoz

**HLH,
karaciğer
yetmezliği**

Plazmaferez

Çocuklarda multisistemik inflamatuvar sendrom" (MIS-C)



- Nisan 2020'de Birleşik Krallık ve sonrasında İtalya ve ABD'de Kawasaki Hastalığı veya Toksik Şok Sendromu benzeri vakalarda artış



- Nisan 2020'de çocuklarda ve ergenlerde SARS-CoV-2 enfeksiyonu ile muhtemel ilişkisi olan "**çocuklarda multisistemik inflamatuvar sendrom" (MIS-C)** olarak adlandırılan yeni bir sendrom

[Comment](#) > [Lancet](#). 2020 May 23;395(10237):1607-1608. doi: 10.1016/S0140-6736(20)31094-1. Epub 2020 May 7.

Hyperinflammatory shock in children during COVID-19 pandemic

Shelley Riphagen ¹, Xabier Gomez ², Carmen Gonzalez-Martinez ³, Nick Wilkinson ³, Paraskevi Theocharis ³

Patogeneez???

Trends in Microbiology

CellPress
REVIEWS

T lymphocytes, with an overall undisturbed distribution of naïve and effector B and T cell populations in MIS-C compared with healthy pediatric controls [8]. Neutrophils and nonclassical monocytes from MIS-C patients showed elevated CD64 (FcγRI), as reported previously [7], and higher CD54 (ICAM1), both consistent with myeloid cell activation.

Autoantibodies have been implicated in KD [10], and several research groups have looked for autoreactive antibodies in MIS-C patient serum or plasma. Using panels of human antigens (protein arrays) to screen for autoantibodies, Consiglio *et al.* and Gruber *et al.* both highlight the presence of autoantibodies in acute MIS-C patients [6,8]. Although the overall antibody binding to human peptide antigens in MIS-C is similar to that in healthy pediatric controls, KD, and pediatric COVID-19 re-

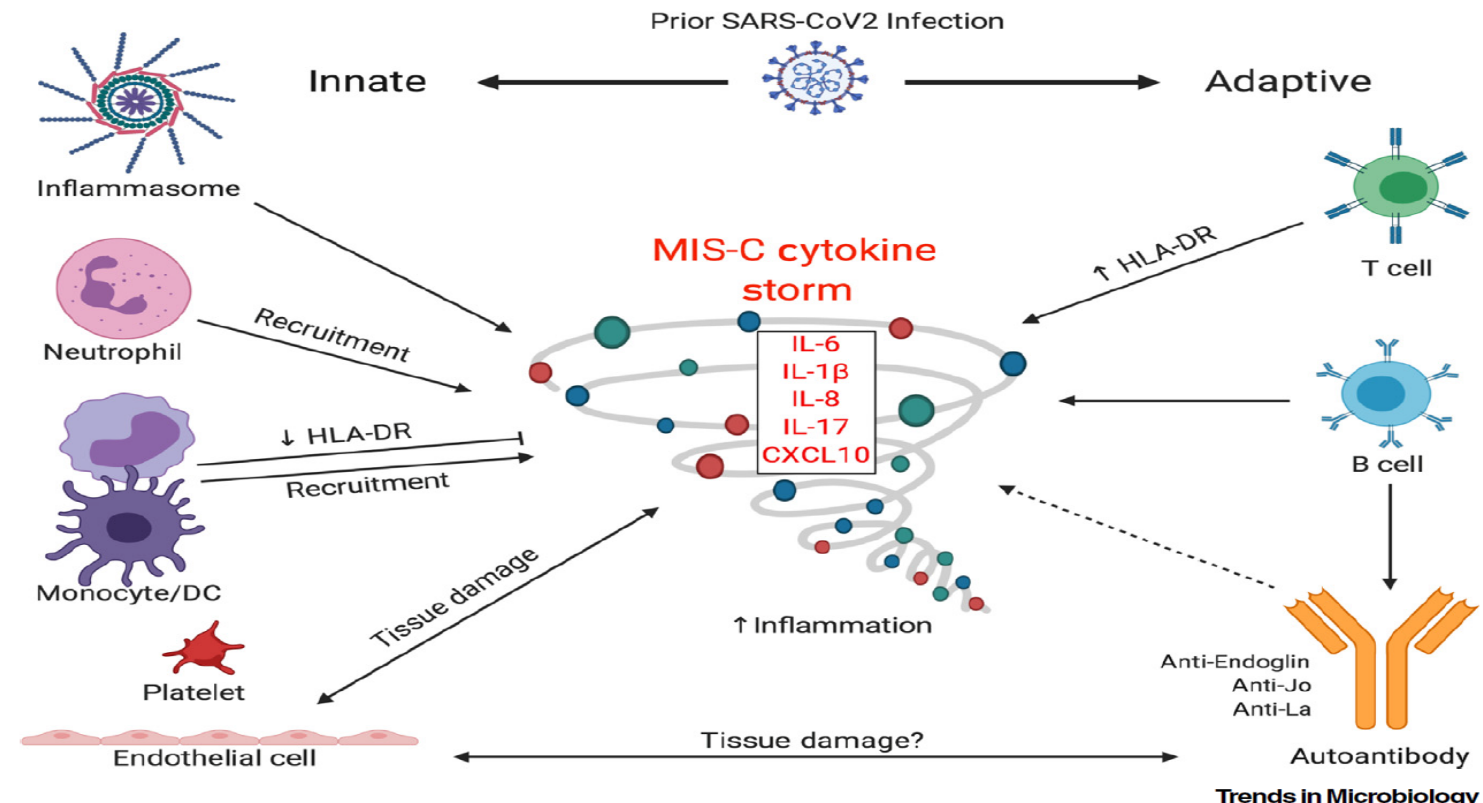


Figure 1. MIS-C Occurs 4–6 Weeks after SARS-CoV-2 Infection in Children and Adolescents and Is Characterized by a Cytokine Storm Involving Innate and Adaptive Immune Cells. The self-limiting

Trends in Microbiology

MIS-C Tanımı (CDC, 13 Mayıs 2020)

(1) <21 yaş olguda:

(2) Klinik kriterler:

- ▶ Minimum 24 saatlik subjektif veya objektif ateş öyküsü $\geq 38^{\circ}\text{C}$ **VE**
- ▶ Hastaneye yatmayı gerektiren ağır hastalık **VE**
- ▶ Etkilenen iki veya daha fazla organ sistemi (örn., Kalp, renal, respiratuvar, hematolojik, dermatolojik ve GİS tutulumu)

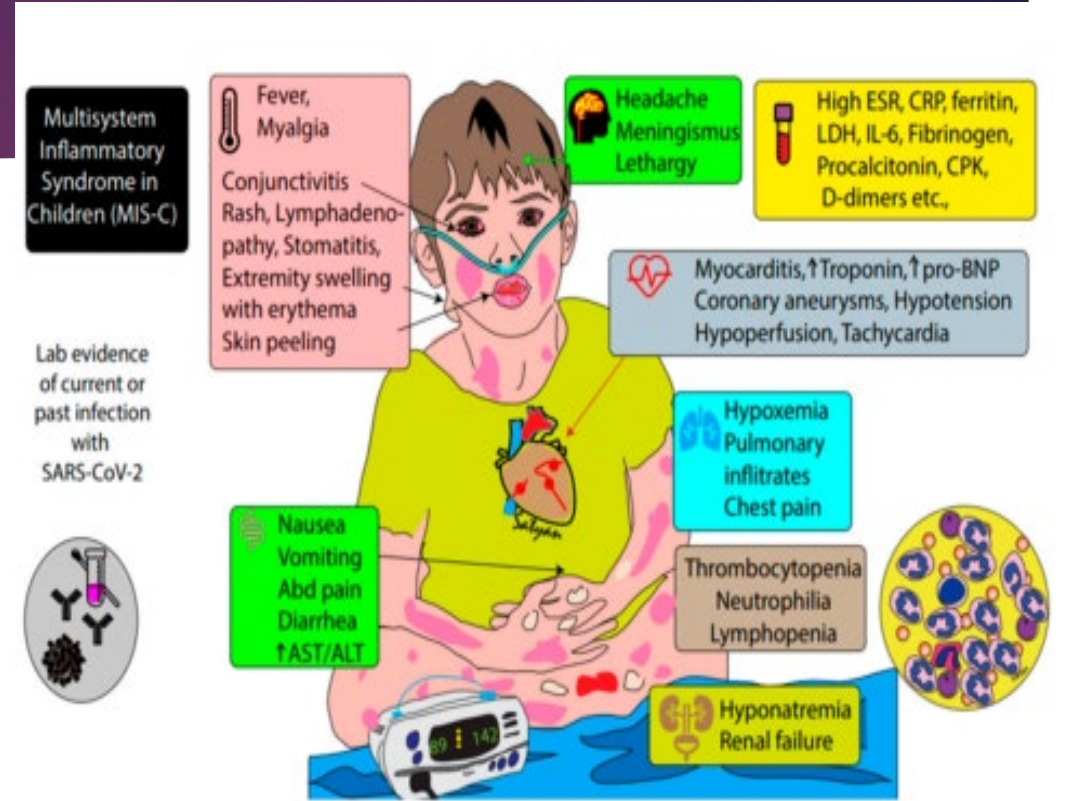
(3) Enflamasyonun laboratuvar kanıtı:

- ▶ Aşağıdakilerden biri veya daha fazlası:
 - Yüksek CRP, ESR, PCT, fibrinojen, D-dimer, ferritin, LDH, veya IL-6; yüksek nötrofiller veya azalmış lenfositler; düşük albümin

(4) SARS-CoV-2 enfeksiyonunun laboratuvar veya epidemiyolojik kanıtı:

- RT-PCR veya seroloji ile pozitif SARS-CoV-2 testi **VEYA**
- Semptomların başlamasından önceki 4 hafta içinde COVID-19 maruziyeti

(5) Alternatif tanı olmaması

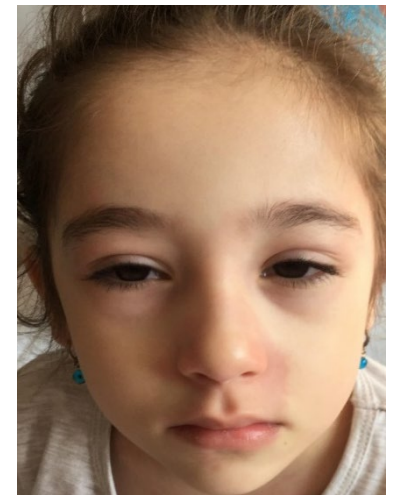


Çocuklarda SARS-CoV-2 ile ilişkili multisistem inflamatuvar sendrom için vaka tanımları

Royal Pediatri ve Çocuk Sağlığı Koleji, İngiltere	Hastalık Kontrol ve Önleme Merkezleri (CDC), ABD	Dünya Sağlık Örgütü (WHO)
<p>* İnatçı ateşle başvuran çocuk (> 38,5 ° C), ve İnflamasyon (nötrofili, yüksek CRP ve lenfopeni) ve Tek veya çoklu organ disfonksiyon kanıtı (şok, kardiyak, solunum, böbrek, gastrointestinal veya nörolojik bozukluğu) ek özelliklerle *</p> <p>*Bu, KH için tam veya kısmi kriterleri karşılayan çocukları içerebilir. *Bakteriyel sepsis, stafilokok veya streptokok şok sendromları, enterovirüs gibi miyokardit ile ilişkili enfeksiyonlar dahil olmak üzere diğer mikrobiyal nedenlerin hariç tutulması (bu araştırmaların sonuçlarını beklemek uzman tavsiyesi almayı geciktirmemelidir). *SARS-CoV-2 RT-PCR test sonuçları pozitif veya negatif olabilir. **Ek özellikler:</p> <p>Klinik: -Çoğu: oksijen ihtiyacı, hipotansiyon -Bazıları: karın ağrısı, konfüzyon, konjunktivit, öksürük, ishal, baş ağrısı, lenfadenopati, mukus zarı değişiklikleri, boyunda şişme, döküntü, solunum semptomları, boğaz ağrısı, şişmiş eller ve ayaklar, senkop kusma;</p> <p>Laboratuvar: -Hepsi: anormal fibrinojen, yüksek D-dimer, yüksek ferritin, hipoalbüminemi; -Bazıları: akut böbrek hasarı, anemi, trombositopeni, koagülopati, yüksek IL-10, yüksek IL-6, proteinüri, yüksek CK, yüksek LDH, yüksek TG, yüksek troponin, transaminaz yüksekliği</p> <p>Görüntüleme: <u>EKO ve EKG:</u> miyokardit, valvülit, perikardiyal efüzyon, koroner arter genişlemesi; <u>AC grafisi:</u> yamalı simetrik infiltratlar, plevral efüzyon; <u>Abdomen USG:</u> kolit, ileit, lenfadenopati, asit, hepatosplenomegali; <u>Göğüs BT:</u> AC grafisinde olduğu gibi, kontrast varsa koroner arter anormalliklerini gösterebilir.</p>	<p>Ateş* ile başvuran 21 yaşından küçük birey ve İnflamasyonun laboratuvar kanıtı **</p> <p>ve</p> <p>Hastanede yatmayı gerektiren klinik olarak ağır hastalık kanıtı, çoklu sistem (≥ 2) organ tutulumları ile (kardiyak, renal, solunum, hematolojik, gastrointestinal, dermatolojik veya nörolojik);</p> <p>VE</p> <p>Hiçbir alternatif teşhis yok;</p> <p>VE</p> <p>Semptomların başlamasından önceki 4 hafta içinde COVID-19 maruziyeti, SARS-CoV-2 enfeksiyonu için mevcut veya yeni RT-PCR, seroloji veya antijen testi pozitifliği</p> <p>Ateş ≥ 38 ° C, ≥ 24 saat, veya 24 saat süren sübjektif ateş raporu.</p> <p>** Şu sıralananlardan birini veya daha fazlasını içerir, ancak bunlarla sınırlı değildir: yüksek CRP, ESR, fibrinojen, prokalsitonin, D-dimer, ferritin, LDH veya IL-6, yüksek nötrofiller, azalmış lenfositler ve hipoalbüminemi.</p> <p>Ek Özellikler:</p> <ul style="list-style-type: none">Bazı kişiler KH için kriterlerini tamamını veya bir kısmını yerine getirebilir, ancak MIS-C için vaka tanımına uyuyorlarsa rapor etmeleri gerekir;SARS-Cov-2 enfeksiyonu kanıtı olan herhangi bir pediatrik ölümden MIS-C'yi düşünün.	<p>Ateşi ≥3 gün olan 0-19 yaş arası çocuklar ve adölesanlar; VE aşağıdakilerden ikisi:</p> <ol style="list-style-type: none">Döküntü veya iki taraflı pürülan olmayan konjunktivit veya mukokutanöz enflamasyon belirtileri (ağız, eller veya ayaklar).Hipotansiyon veya şok.Miyokardiyal disfonksiyon, perikardit, valvülit veya koroner anormalliklerin özellikleri (EKO bulguları veya yükselmiş troponin/NT-proBNP dahil),Koagülopati kanıtı (PT, PTT, yükselmiş D-dimer ile).Akut gastrointestinal problemler (ishal, kusma veya abdominal ağrı). <p>VE</p> <p>ESR, C-reaktif protein veya prokalsitonin gibi artmış inflamasyon belirteçleri.</p> <p>VE</p> <p>Bakteriyel sepsis, stafilokok veya streptokokal şok sendromları dahil başka hiçbir belirgin mikrobiyal enflamasyon nedeni yoktur.</p> <p>VE</p> <p>COVID-19 kanıtı (RT-PCR, antijen testi veya seroloji pozitif) veya COVID-19 hastaları ile olası temas. Tipik veya atipik KH veya toksik şok sendromu özelliklerine sahip çocuklarda bu sendromu düşünün</p>

Bulgular

- ▶ Persistan ateş (ort 4-6 gün) – %100
- ▶ GİS sempt (karın ağrısı, kusma, ishal) – %60- 100
- ▶ Döküntü – %45-76
- ▶ Konjonktivit – %30-81
- ▶ Mukozal membran tutulumu– %27-76
- ▶ Nörokognitif semptomlar (baş ağrısı, laterji, konfüzyon)
- ▶ Respiratuar semptomlar– %21-65
- ▶ Boğaz ağrısı– %10-16
- ▶ Miyalji – %8-17 ,El-ayaklarda şişlik–% 9-16
- ▶ Lenfadenopati – %6-16



Klinik Bulgular

- ▶ Şok – %32-76
- ▶ Komplet Kawasaki Hastalığı ile uyumlu kriterler – %22-64
- ▶ Miyokardial disfonksiyon (EKO ile ve/veya artmış Troponin veya pro-BNP) – %51-90
- ▶ Aritmi – %12
- ▶ Noninvaziv veya invaziv ventilasyon ihtiyacı gerektiren akut respiratuar yetmezlik – %28-52
- ▶ Akut böbrek yetmezliği – %8-52
- ▶ Serözit (plevral, perikardiyal efüzyon ve asit) – %24-57
- ▶ Hepatit veya hepatomegali – %5-21
- ▶ Ensefalopati, nöbet, koma veya meningoensefalit – % 6-7

Laboratuvar

➤ Hemogram bulguları:

- Lenfopeni – %80-95
- Nötrofil – %68-90
- İlimli anemi – %70
- Trombositopeni – %31-80

➤ İnflamatuar belirteç artışı:

- CRP artışı – % 90-100
- ESR – %75-80
- D-dimer – %67-100
- Fibrinogen – %80-100
- Ferritin – %55-76
- Prokalsitonin – %80-95
- IL-6 – %80-100

➤ Artmış kardiyak belirteçler:

- Troponin – %50-90
- BNP ya da N-terminal pro-BNP – % 73-90

➤ Hipoalbüminemi – %48-95

➤ İlimli KCFT artışı – %62-70

➤ LDH artışı – %10-60

➤ Hipertrigliseridemi – %70

OLGU

10 yaş erkek hasta



6 gündür 38.5 °C ateş yüksekliği+halsizlik



Dış merkez → ÜSYE, amoksisilin klavunat başlanmış



1 gün sonra vücutta döküntü ve karın ağrısı



Karın ağrısı nedeniyle çekilen batın USG'de mezenter LAP +, appendiks görülememiş



Apandisit ön tanısı ile operasyonu planlandığı sırada hipotansiyon ve taşikardi gelişmesi üzerine EÜTF YB'a sevk

Fizik Muayene

- ▶ **GD orta**
- ▶ **Kan basıncı:100/35 mmHg**
- ▶ **KTA:145/dk**
- ▶ **Solunum sayısı:35/dk**
- ▶ SpO2: %100
- ▶ **Ateş :38.6°C**
- ▶ Baş boyun: servikal millimetrik LAP, tonsiller hipertrofik, orofarinks hiperemik
- ▶ AC: takipneik, solunum sesleri olağan
- ▶ KVS: Kalp sesleri normal, üfürüm yok
- ▶ **Batın: Organomegali yok yaygın hassasiyet**
- ▶ **Tüm vücutta yaygın basmakla solan makülopalüer döküntü**



Laboratuvar

SGOT(AST)	25		U/L	Protrombin Zamanı (süre)	13.1		sn
SGPT(ALT)	79	Y	U/L	Protrombin Zamanı (aktivite)	84		%
Alkale Fosfataz	165		U/L	INR	1.1		
GGT	68	Y	U/L	APTZ	26.2		sn
Total Protein	51.6	D	g/L	İbrinogen	551	Y	mg/dL
Albümin	30	D	g/L	D-DIMER	3942	Y	µg/L FEU
Total Bilirubin	0.43		mg/dL	CTH (Akşam)	46.6		ng/L
Direkt Bilirubin	0.26	Y	mg/dL	TSH	0.471	D	mU/L
LDH	274		U/L	FT4	1.25		ng/dL
Total Kolesterol	99		mg/dL	Kortizol (Akşam)	39.8	Y	µg/dL
Trigliserid	149	Y	mg/dL	*** TAM KAN SAYIMI ***			
HDL Kolesterol	16	D	mg/dL	Lökosit	12.15		10 ³ /µL
LDL Kolesterol (Friedewald Formülü ile)	53		mg/dL	Nötrofil %	89.1	Y	%
HDL-dışı Kolesterol (Hesap ile)	83		mg/dL	Lenfosit %	6.6	D	%
Glukoz (Açlık)	93		mg/dL	Monosit %	1.3		%
Üre	27		mg/dL	Eozinofil %	2.8		%
Kreatinin	0.37		mg/dL	Bazofil %	0.2		%
eGFR (CKD-EPI)	18 yaşından küçük olduğu için hesaplanamadı.		mL/dak/1.73 m ²	İmmatür Granülosit %	1.4	Y	%
Ürik Asid	3.3		mg/dL	Nötrofil #	10.83	Y	10 ³ /µL
Sodyum	131	D	mEq/L	Lenfosit #	0.8	D	10 ³ /µL
Potasyum	4.2		mEq/L	Monosit #	0.16		10 ³ /µL
Klorür	99		mEq/L	Eozinofil #	0.34		10 ³ /µL
Kalsiyum	8.1	D	mg/dL	Bazofil #	0.02		10 ³ /µL
Fosfor	3.07	D	mg/dL	İmmatür Granülosit #	0.17	Y	10 ³ /µL
Magnezyum	2.25		mg/dL	NRBC%	0		%
CRP	157.49	Y	mg/L	NRBC#	0		10 ³ /µL
Prokalsitonin	2.78	Y	µg/L	Eritrosit	4.81		10 ⁶ /µL
Sedimantasyon 1 saat	33	Y	mm	Hemoglobin	10.5	D	g/dL
				Hematokrit	31.9	D	%
				MCV	66.3	D	fL
				MCH	21.8	D	pg
				MCHC	32.9		g/dL
				RDW-CV	15.8	Y	%
				Trombosit	340		10 ³ /µL
				MPV	11.4	Y	fL
				PCT	0.39		%

Acute Abdomen and Appendicitis in 1010 Pediatric Patients With COVID-19 or MIS-C: A Multinational Experience from Latin America

Hwang *et al.* *BMC Pediatrics* (2021) 21:258
<https://doi.org/10.1186/s12887-021-02724-x>

BMC Pediatrics

CASE REPORT

Open Access

The Great Gut Mimicker: A case report of MIS-C and appendicitis clinical presentation overlap in a teenage patient



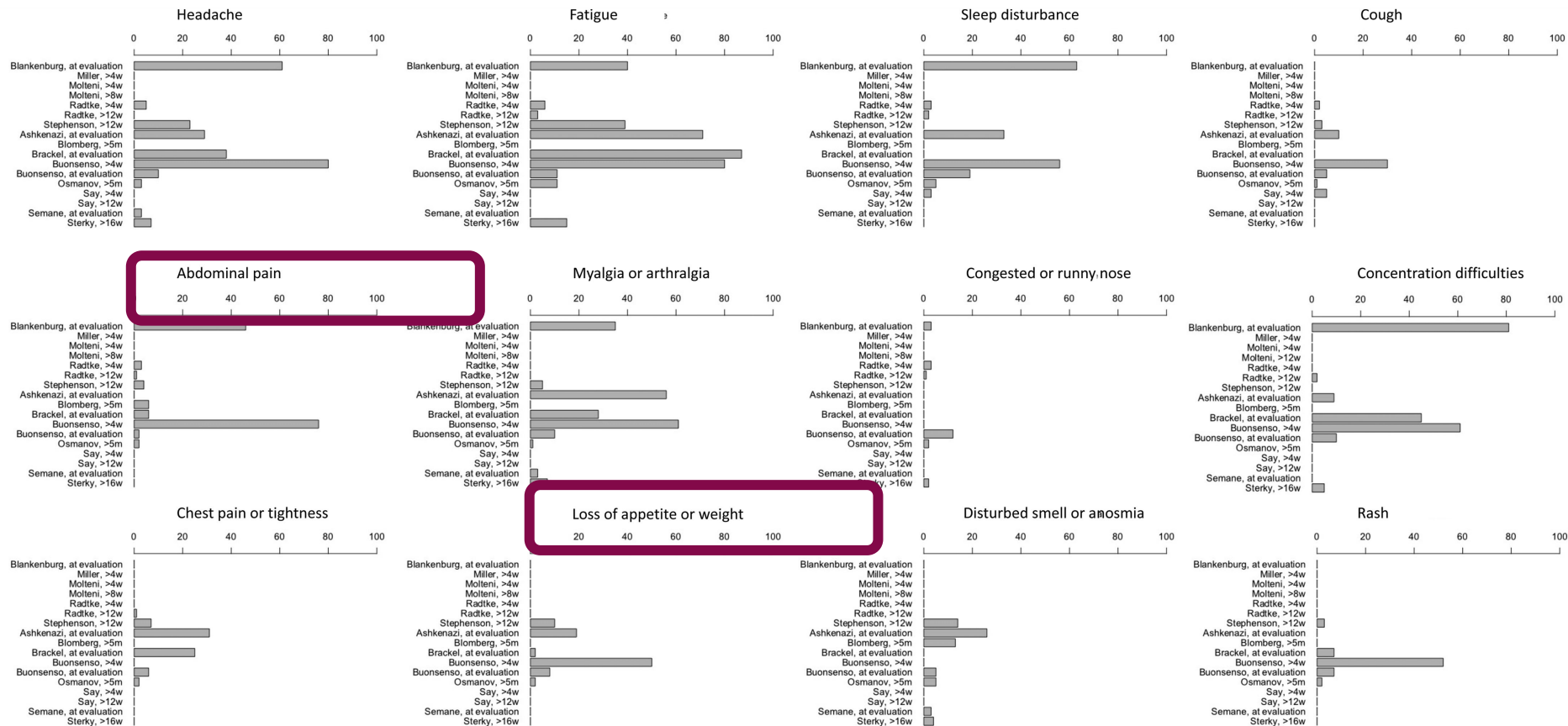
Article

MIS-C-Implications for the Pediatric Surgeon: An Algorithm for Differential Diagnostic Considerations

Uzamis COVID-19

How Common is Long COVID in Children and Adolescents?

Petra Zimmermann, MD, PhD,*†‡§¶ Laure F. Pittet, MD-PhD,‡§¶ and Nigel Curtis, FRCPCH, PhD‡§||





Emergency Preparedness and Response

Resources for Emergency Health Professionals > Health Alert Network (HAN) > HAN Archive > 2022



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Updated Recommendations for Adenovirus Testing and Reporting of Children with Acute Hepatitis of Unknown Etiology

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Update to provide clinicians and public health authorities with updated information about an epidemiologic investigation of pediatric cases of hepatitis of unknown etiology in the United States. This investigation focuses on collecting information to describe the epidemiology, etiology, clinical presentation, severity, and risk factors related to illness and to identify any relationship between adenovirus infection or other factors and hepatitis. As of May 5, 2022, CDC and state partners are investigating 109 children with hepatitis of unknown origin across 25 states and territories, more than half of whom have tested positive for adenovirus with more than 90% hospitalized, 14% with liver transplants, and five deaths under investigation. Because this investigation is ongoing and includes reviewing cases of hepatitis of unknown cause with onset since October 2021, patients under investigation are not limited to current or newly diagnosed pediatric hepatitis illnesses.

Eve götürülecek Mesajlar

- ✓ COVID-19 hastalığı çocuklarda hafif seyirli olmakla birlikte morbidite ve mortaliteye neden olmaktadır
- ✓ Ateş ve karın ağrısı olan çocuklarda diğer sistem bulguları ve laboratuvar değerlendirme yapılmalı ve MIS-C akılda tutulmalı
- ✓ Yeni varyantlar oluşabilir ve COVID-19 azalmakla birlikte hala akılda tutulmalıdır
- ✓ Etiyolojisi bilinmeyen hepatitlerde Adenovirus akılda tutulmalı





Önceliđimiz
koruma