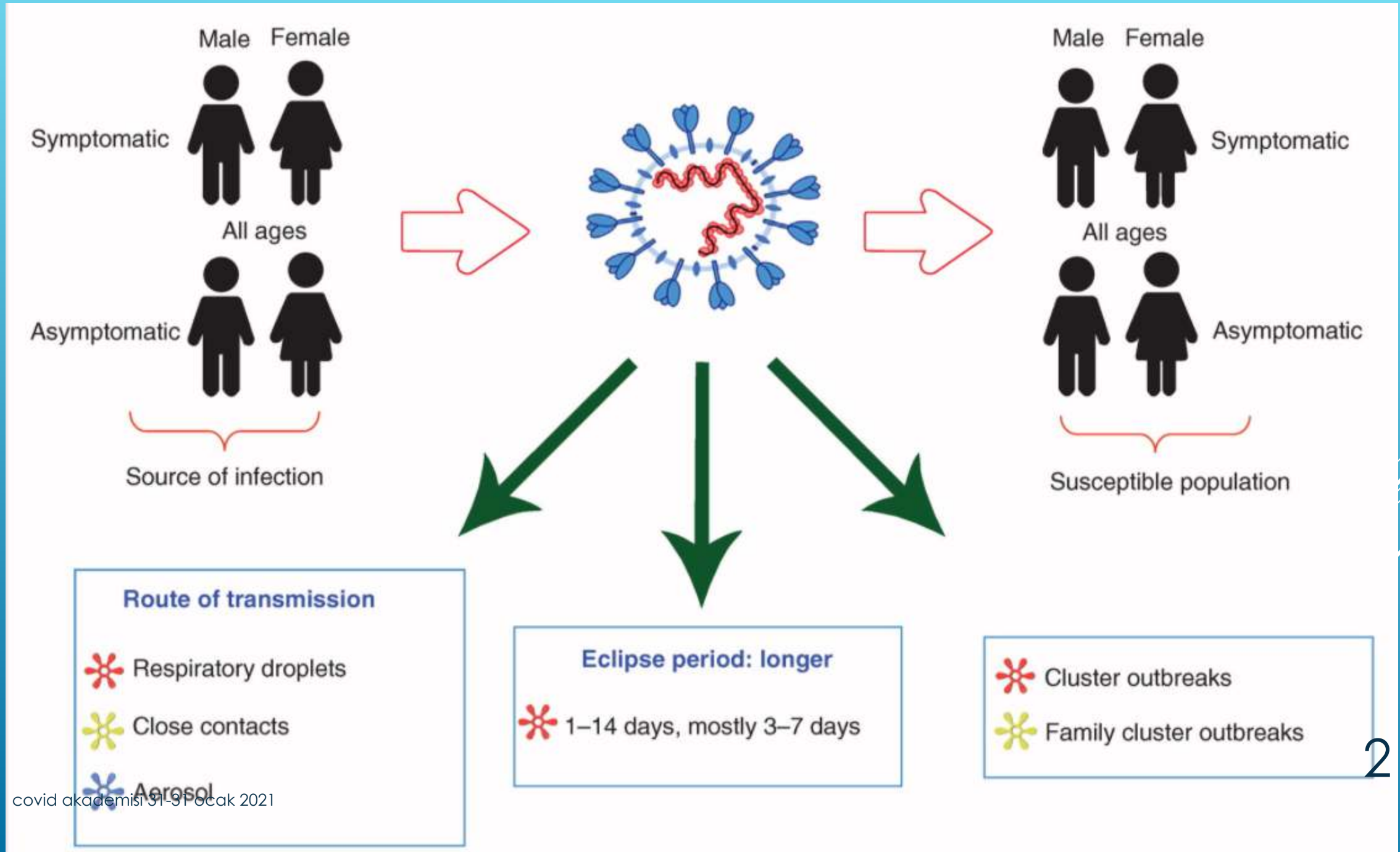
ASEMPTOMATIK VE SEMPTOMATIK HASTALARIN KLINIK YONETIMI

Prof. Dr. FATMA SIRMATEL

21 ocak 2021


Male Female
Symptomatic
All ages
Asymptomatic
Source of infection
Male Female
Symptomatic
All ages
Asymptomatic
Susceptible population
Route of transmission
Respiratory droplets
Close contacts
Aerosol
Eclipse period: longer
1–14 days, mostly 3–7 days
Cluster outbreaks
Family cluster outbreaks

PATOGENEZ

Sars-Cov2
Nazal epitele tutunma

Virusun üst solunum yolundan alt
Solunum yoluna inmesi

Tip II pulmoner alveoler epitel hücresine tutunma

SİTOKİN FIRTINASI

CD4 VE CD8 Aktivasyonu
B hücre uyarımı

Akc de CD8
SİTOTOKSİT ETKİ
Konakçı defansı
ve viral klirens

VİRAL REPLİKASYON

Tip 1 ve tip 2 pnomositlerin harabiyeti

Diffüz alveoler harabiyet
ARDS, SEPSİS, ŞOK

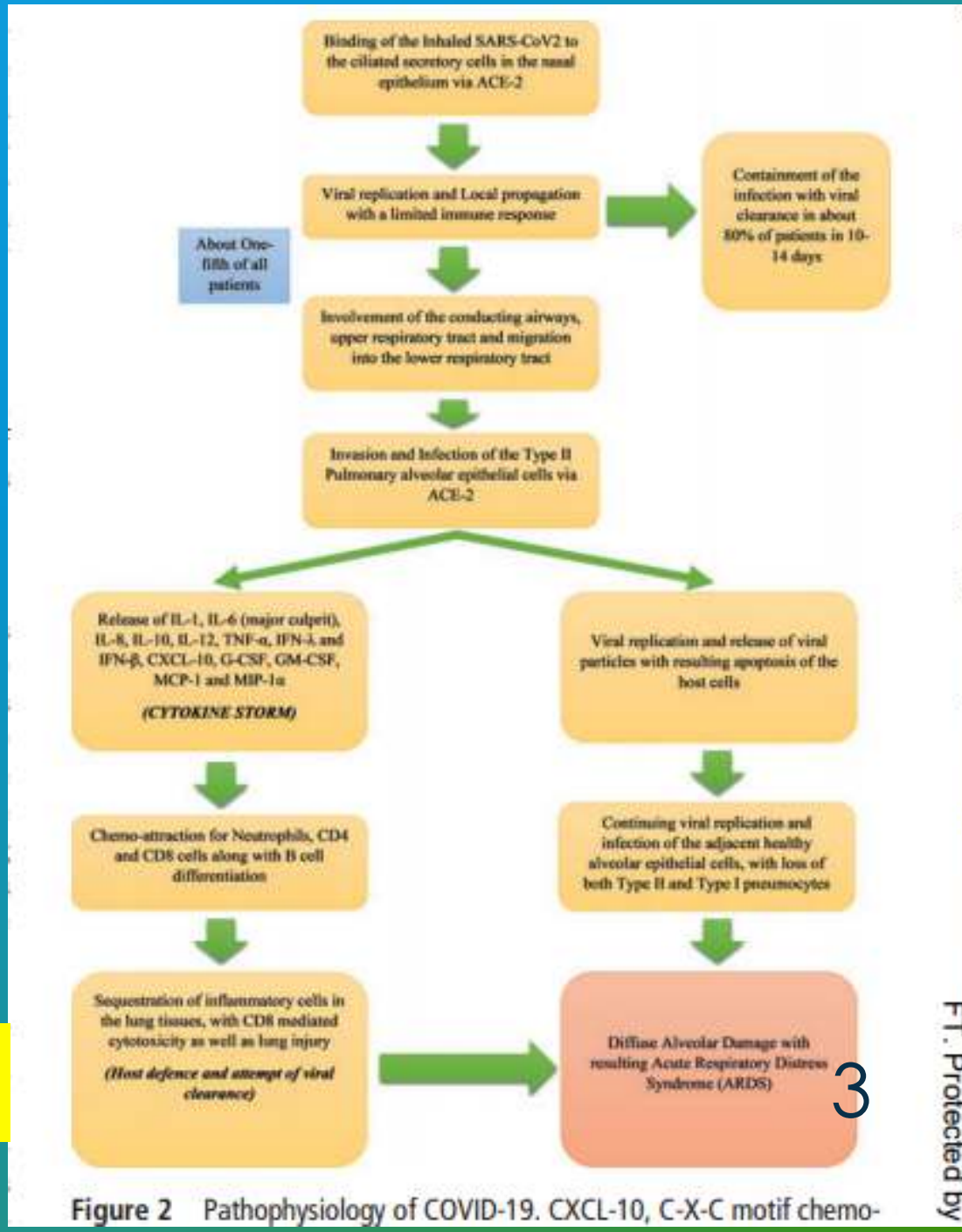
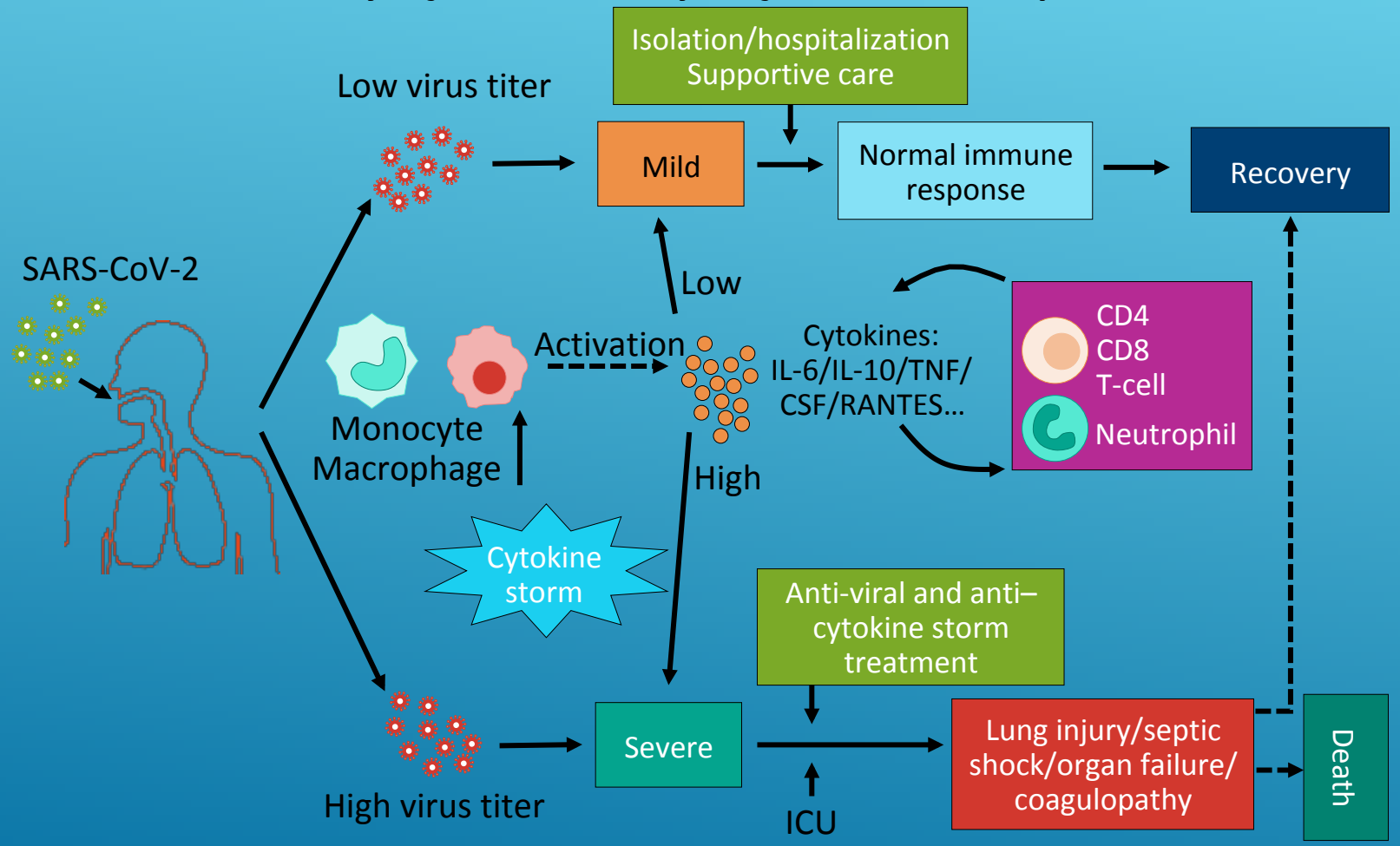


Figure 2 Pathophysiology of COVID-19. CXCL-10, C-X-C motif chemo-

IMMUNE Cevap durumuna göre klinik evreler iyi değerlendirilmelidir

İyileşme ve ölüme yol açan immun cevaptır[1]



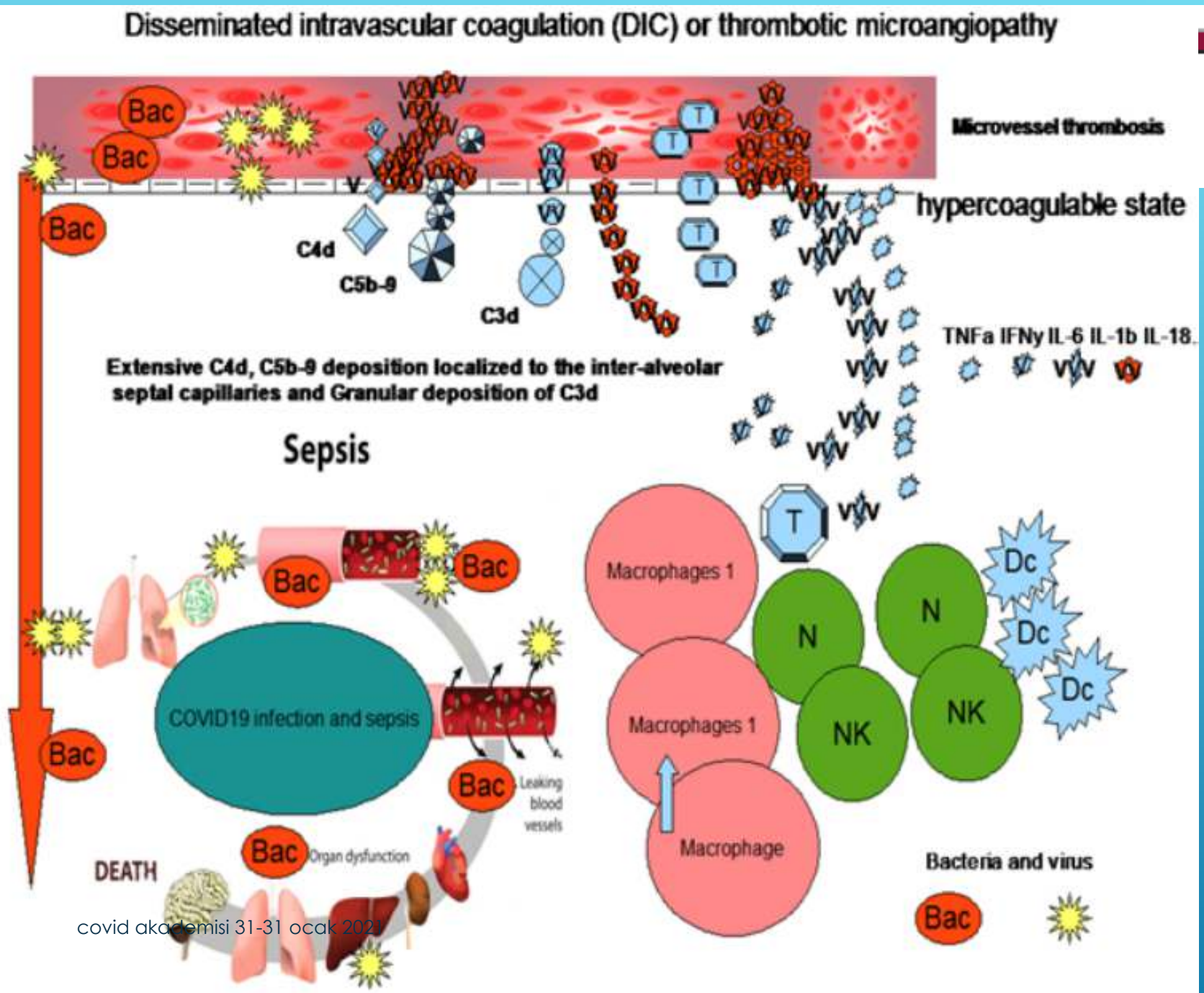
Edinilmiş immun cevap[2]

- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

Kazanılmış immun cevap[2]

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. J Leukoc Biol. 2020;108:17. 2. Sokolowska. Allergy. 2020;75:2445.



Covid-19 endotel duvarında yap
İNFLAMASYON
KOAGULASYON bozukluğu ile
KLİNİK TABLOYU OLUŞTURUR.

International Journal of Environmental Research and Public Health

MDPI

CİDDİ olgular hastaneye yatmalı ve Akc tutulumu olmayanlar 10 gün gözlem altında alınırken >60 yaş ve komorbidite faktörleri ile hasta izlenmeli ve hergün izlenmeli gerekirse HASTANEYE yatırılmalı

Review

Clinical Presentation of COVID-19: Case Series and Review of the Literature

Margherita Macera, Giulia De Angelis, Caterina Sagnelli, Nicola Coppola * and Vanvitelli COVID-19 Group †

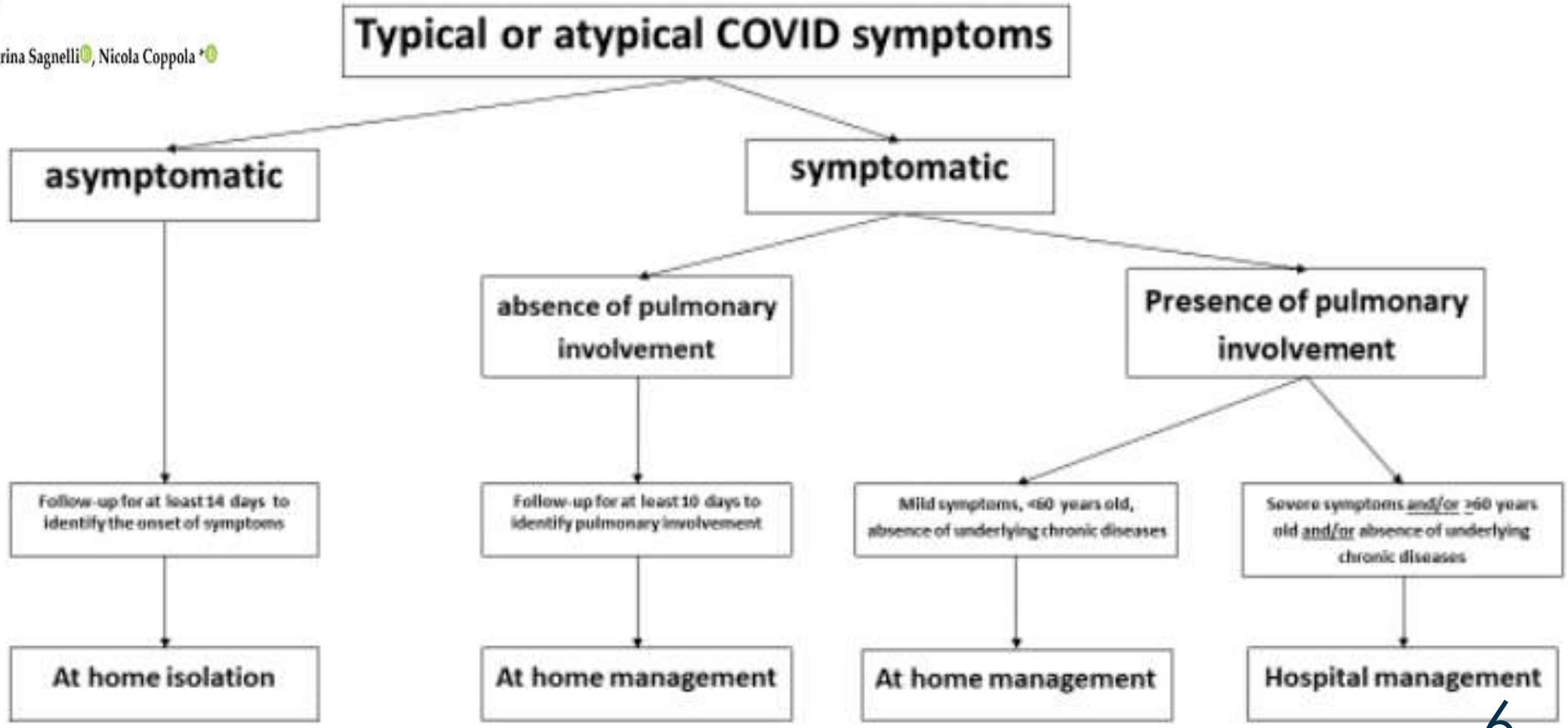


Figure 1. Management of COVID-19 patients according to the clinical presentation.

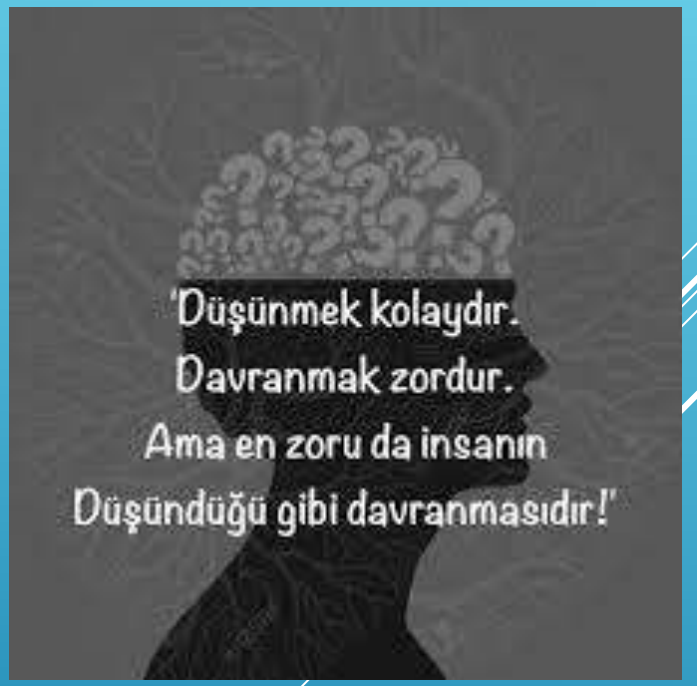
- ASEMPTOMATİK

- PRESEMPTOMATİK-SEMPTOMATİK
- AKCİĞER TUTULUMU
- AKCİĞER DIŞI TUTULUM

SEMPTOMATİK:
Hafif
Orta
Ağır
Ciddi

Semptomların başlama süresi
PCR pozitifliği
Akciğer tomografisinde tutulum
Kalp
Böbrek
Cilt
Nörolojik

- Buzlu cam
- konsolide
- Plevral,perikardiyal,pulmoner arter



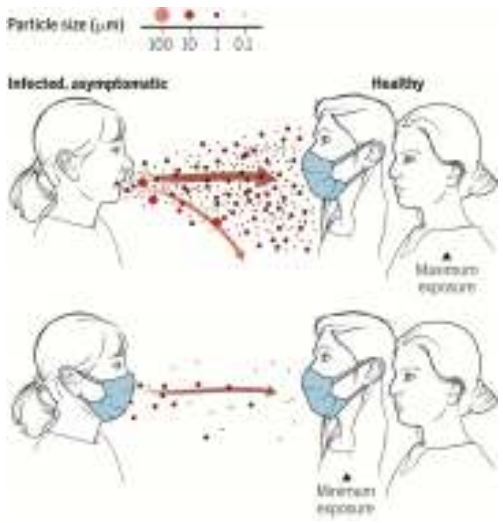
Covid-19 hasta ile temas eden:
-1.5 METREDEN DAHA YAKIN VE 15 DK FAZLA KAPALI ORTAMDA BİRLİKTE BULUNMAK Asemptomatik – Presmptomatik bulgular

- **1420** kişide: hafif ve orta klinik gösteren Avrupa toplumunda Semptomların ortalama süresi(n = 264): **11.5 ± 5.7 gün**
  - Kulak boğaz burun şikayeti **gençlerde**; ateş, iştahsızlık ishal **yaşlı hastalarda**(*P* < .01)
  - Koku kaybı baş ağrısı burun tıkanıklığı boğaz ağrısı halsizlik **kadınlarda**; öksürük ateş **erkeklerde** (*P* < .001)
- Çinde 17 fatal olguda, ortalama semptomların başlamasından ölüme kadar giden süre **14 gün (aralık: 6-41 gün).**
  - **Yaşlılarda : 11.5 gün≥ 70 yrs, 20 gün < 70 yaş(*P* = .033)**

Symptom,[1] %	N = 1420
Headache	70.3
Loss of smell	70.2
Nasal obstruction	67.8
Asthenia	63.3
Cough	63.2
Myalgia	62.5
Rhinorrhea	60.1
Taste dysfunction	54.2
Sore throat	52.9
Fever (> 38°C)	45.4

KLİNİK BULGULAR YAŞ ve CİNSE GÖRE DEĞİŞEBİLİR

1Lechien. J Intern Med. 2020;288:335. 2. Wang. J Med Virol. 2020;92:441.



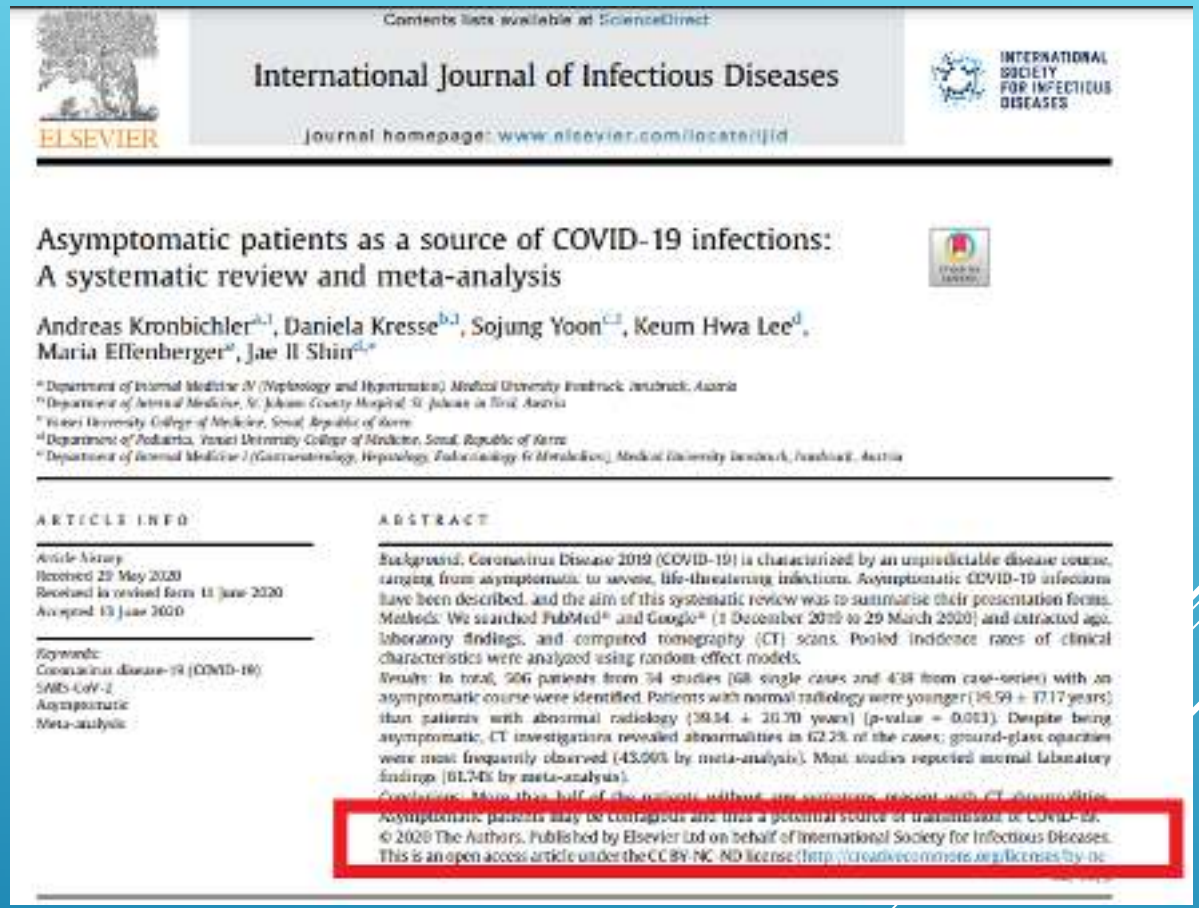
- ASEMPTOMATİK
- PRESEMPTOMATİK
- SEMPTOMATİK (akciğer ve akciğer dışı)
- HAFİF
- ORTA
- CİDDİ
- KRİTİK

Covid-19 klinik


The Hindu
Over 76% of COVID-19 patients in Karnataka are asymptomatic - The Hindu

Asymptomatic, pre-symptomatic, symptomatic: what is the difference?

Asemptomatik Olgular virüsü daha fazla yayarlar



Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

ELSEVIER

Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis

Andreas Kronbichler[a,1], Daniela Kresse[b,1], Sojung Yoon[c,1], Keum Hwa Lee[d], Maria Effenberger[e], Jae Il Shin[d,*]

[a] Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria
[b] Department of Internal Medicine, St. Johann County Hospital, St. Johann in Tirol, Austria
[c] Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[e] Department of Internal Medicine I (Gastroenterology, Hepatology, Endocrinology & Metabolism), Medical University Innsbruck, Innsbruck, Austria

ARTICLE INFO

Article history:
Received 29 May 2020
Received in revised form 11 June 2020
Accepted 13 June 2020

Keywords:
Coronavirus disease-19 (COVID-19)
SARS-CoV-2
Asymptomatic
Meta-analysis

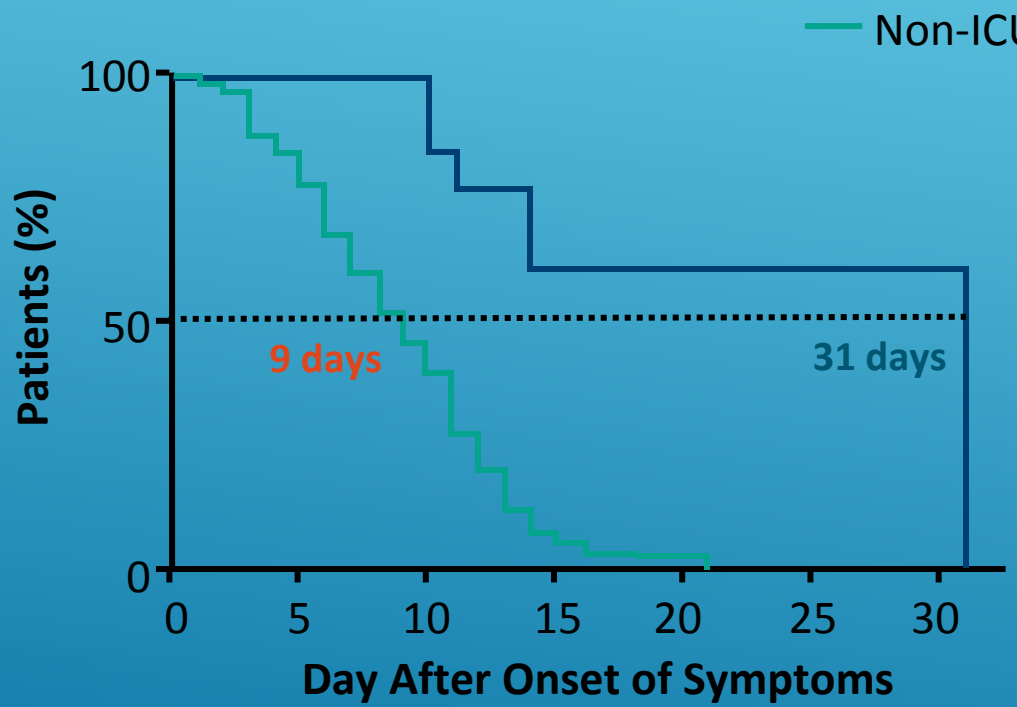
ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is characterized by an unpredictable disease course, ranging from asymptomatic to severe, life-threatening infections. Asymptomatic COVID-19 infections have been described, and the aim of this systematic review was to summarise their presentation forms.
Methods: We searched PubMed® and Google® (1 December 2019 to 29 March 2020) and extracted age, laboratory findings, and computed tomography (CT) scans. Pooled incidence rates of clinical characteristics were analyzed using random effect models.
Results: In total, 506 patients from 54 studies (68 single cases and 438 from case-series) with an asymptomatic course were identified. Patients with normal radiology were younger (16.99 ± 17.17 years) than patients with abnormal radiology (39.84 ± 20.70 years) (p-value = 0.003). Despite being asymptomatic, CT investigations revealed abnormalities in 62.2% of the cases; ground-glass opacities were most frequently observed (45.06% by meta-analysis). Most studies reported normal laboratory findings (61.74% by meta-analysis).
Conclusion: More than half of the patients without any symptoms present with CT abnormalities. Asymptomatic patients may be contagious and thus a potential source of transmission of COVID-19.

YOĞUN BAKIMA GİDENLERDE ATEŞ VE PCR POZİTİFLİĞİ DAHA UZUN sürer

Fever

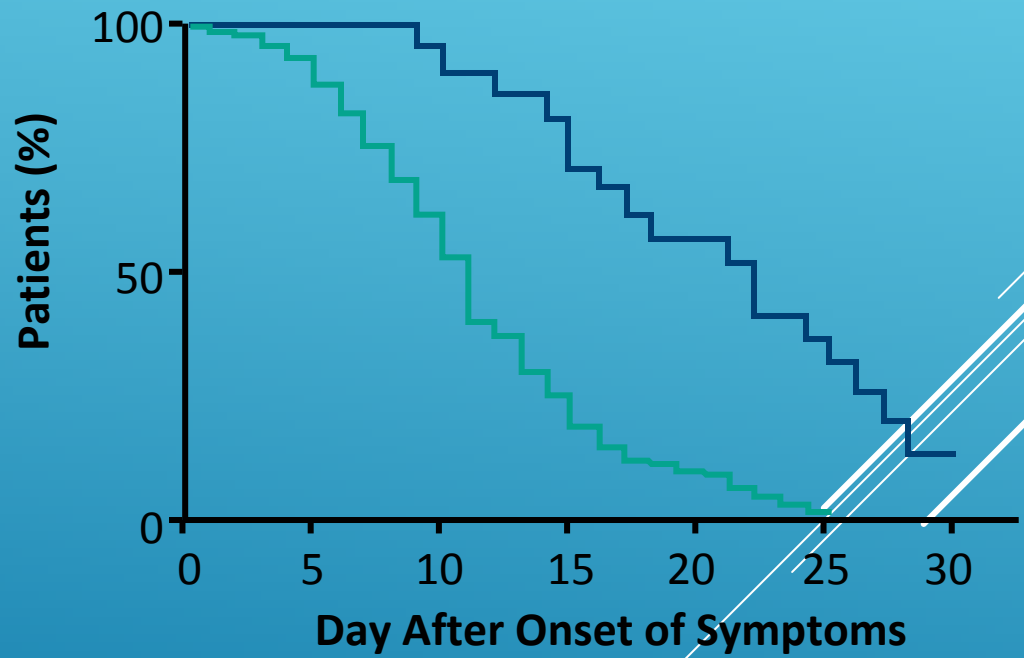
HR: 5.83 (95% CI: 3.86-8.80; *P* < .0001)



Patients at Risk, n			
ICU	22	13	3
Non-ICU	213	93	3

PCR Positivity

HR: 3.17 (95% CI: 2.29-4.37; *P* < .0001)



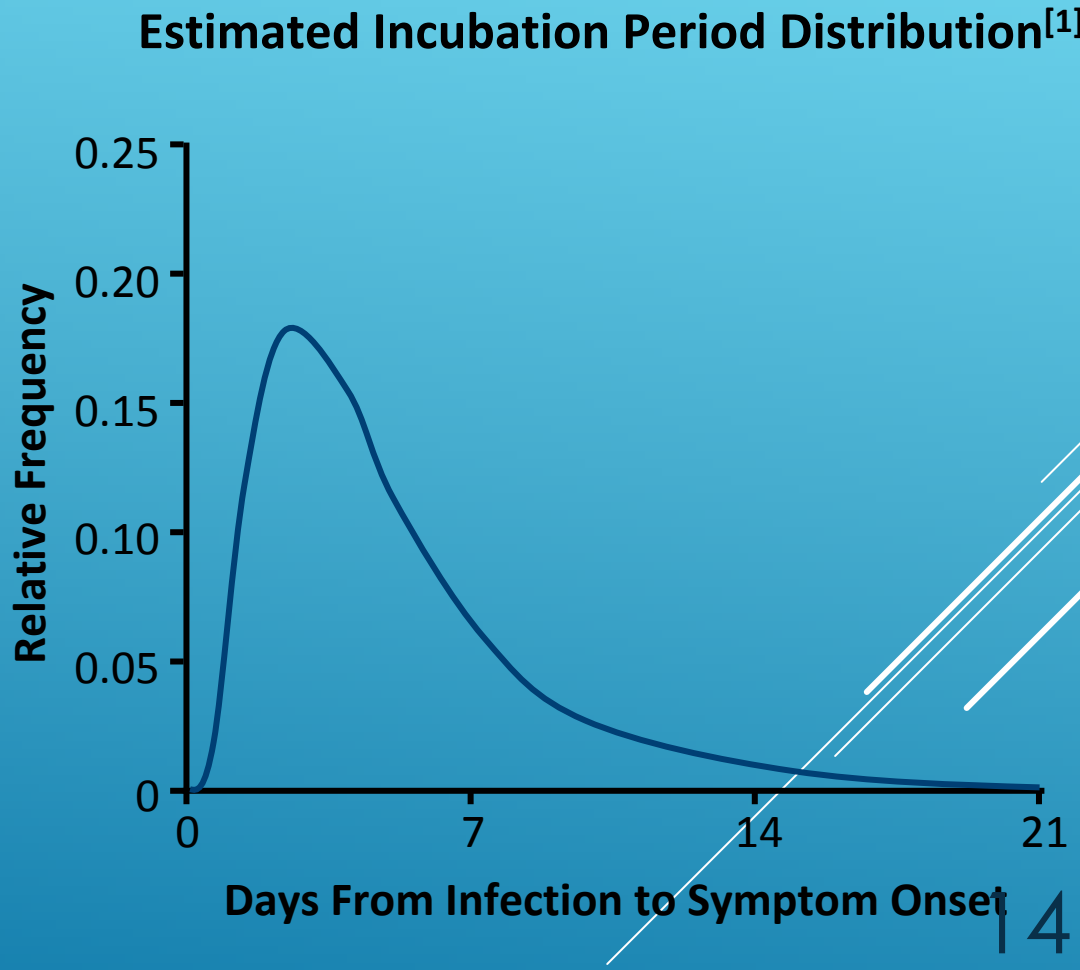
Patients at Risk, n						
ICU	21	21	20	17	12	7
Non-ICU	227	207	149	49	19	1

covid akademisi 31-31 ocak 2021

Chen. J Infect. 2020;80:e1.

COVID-19 INKUBASYON: **İNFEKSİYONDAN SEMPTOMLARA**

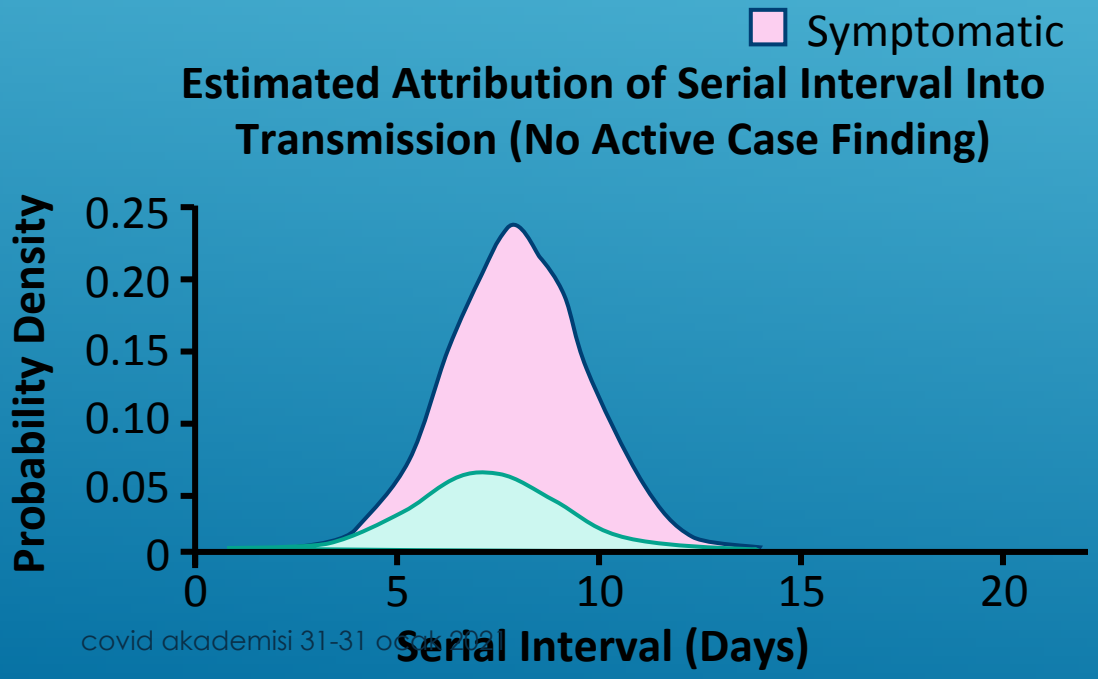
- Ortalama 5.2 gün Wuhan hubei)
  (95% CI: 4.1-7.0)
- Semptomların başlaması %97.5 11.5 gün

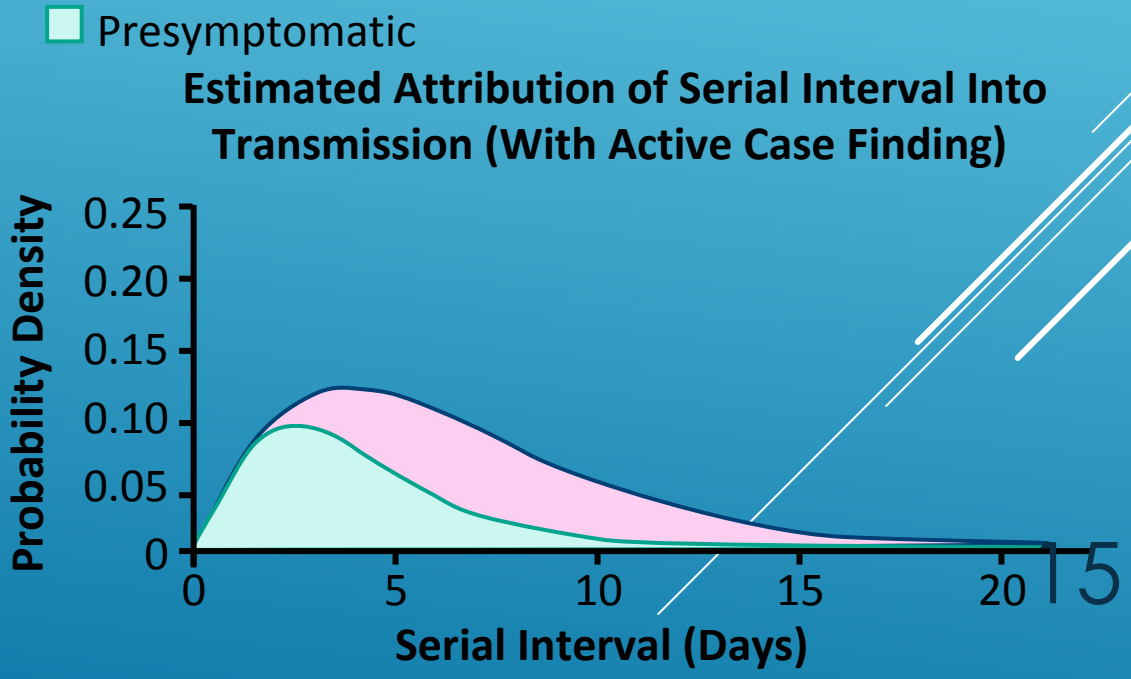


1. Li. NEJM. 2020;382:1199. 2. Lauer. Ann Intern Med. 2020;172:577.

PRESEMTOMATİKTEN SEMPTOMATİK DÖNEME GEÇİŞ

- Presemtomatik dönemde virusun bulaşı; aktif olmayan olgularda %12-28
- Aktif olgularda presemptomatik dönemde bulaş %35-60





Liu. Wellcome Open Res. 2020;5:58

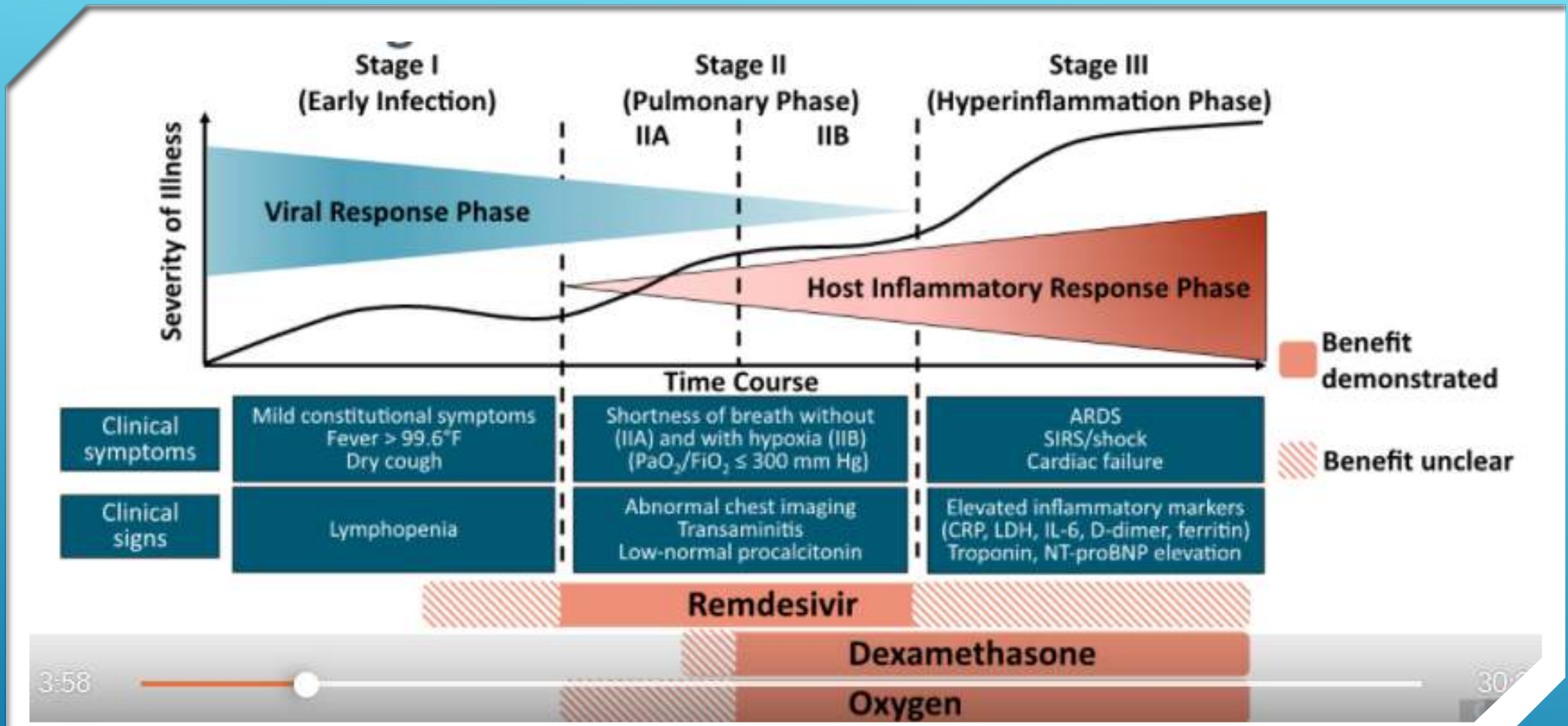

Stage I
(Early Infection)
Stage II
(Pulmonary Phase)
IIA
IIB
Stage III
(Hyperinflammation Phase)
Severity of Illness
Viral Response Phase
Host Inflammatory Response Phase
Time Course
Benefit demonstrated
Benefit unclear
Clinical symptoms
Mild constitutional symptoms
Fever > 99.6°F
Dry cough
Shortness of breath without (IIA) and with hypoxia (IIB) (PaO_2/FiO_2 ≤ 300 mm Hg)
ARDS
SIRS/shock
Cardiac failure
Clinical signs
Lymphopenia
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation
Remdesivir
Dexamethasone
Oxygen
3:58

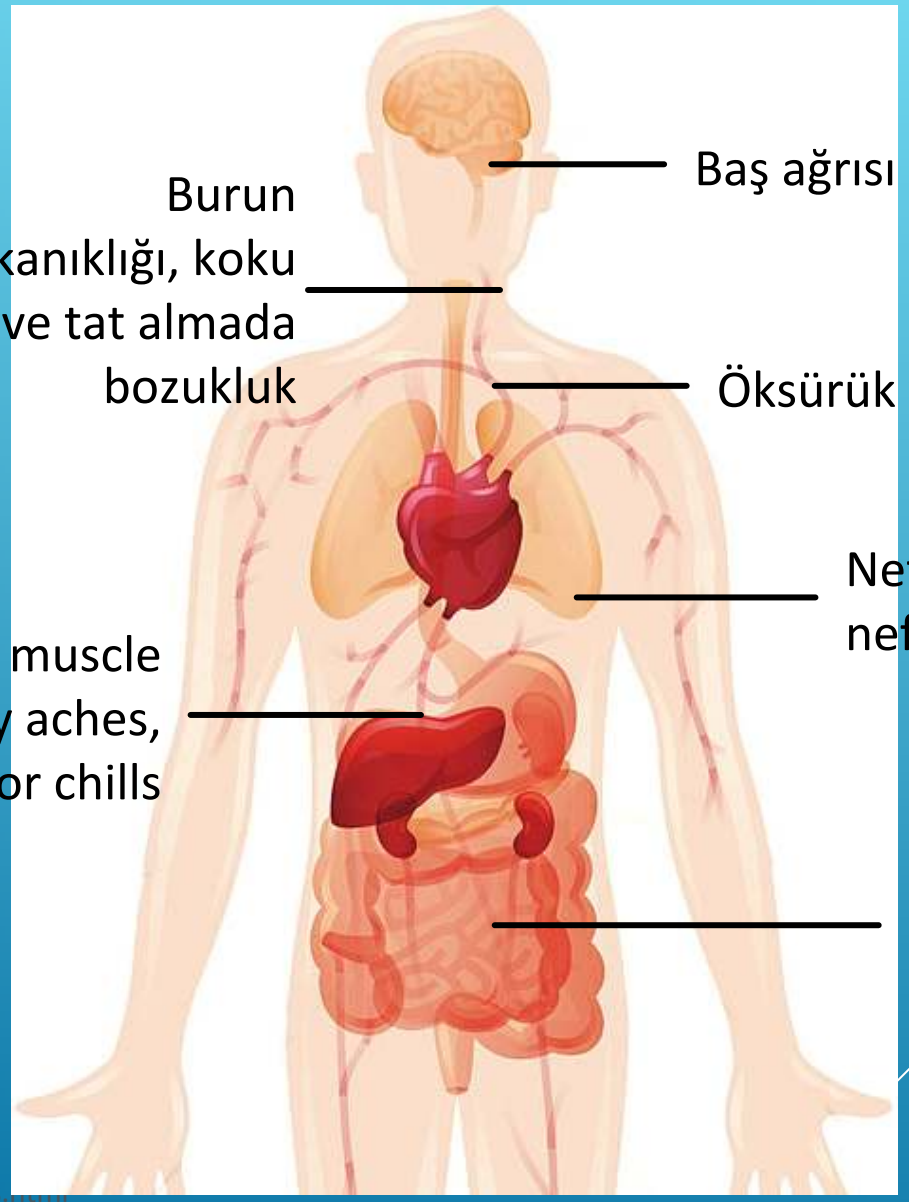
Table 1 Clinical spectrum of COVID-19 disease[1 36–41]

Severity of disease	Presentation
Asymptomatic	▶ No clinical symptoms ▶ Positive nasal swab test ▶ Normal chest X-ray
Mild illness	▶ Fever, sore throat, dry cough, malaise and body aches or ▶ Nausea, vomiting, abdominal pain, loose stools
Moderate illness	▶ Symptoms of pneumonia (persistent fever and cough) without hypoxemia ▶ Significant lesions on high-resolution CT chest
Severe illness	▶ Pneumonia with hypoxemia ($SpO_2 < 92\%$)
Critical state	▶ Acute respiratory distress syndrome, along with shock, coagulation defects, encephalopathy, heart failure and acute kidney injury

Parasher A. *Postgrad Med J* 2020;**0**:1–9. doi:10.1136/postgradmedj-2020-138577

COVİD-19 DA GÖRÜLEN PRİMER SEMPTOMLAR

"MARUZ KALDIKTAN SONRAKİ **2-14 gün**

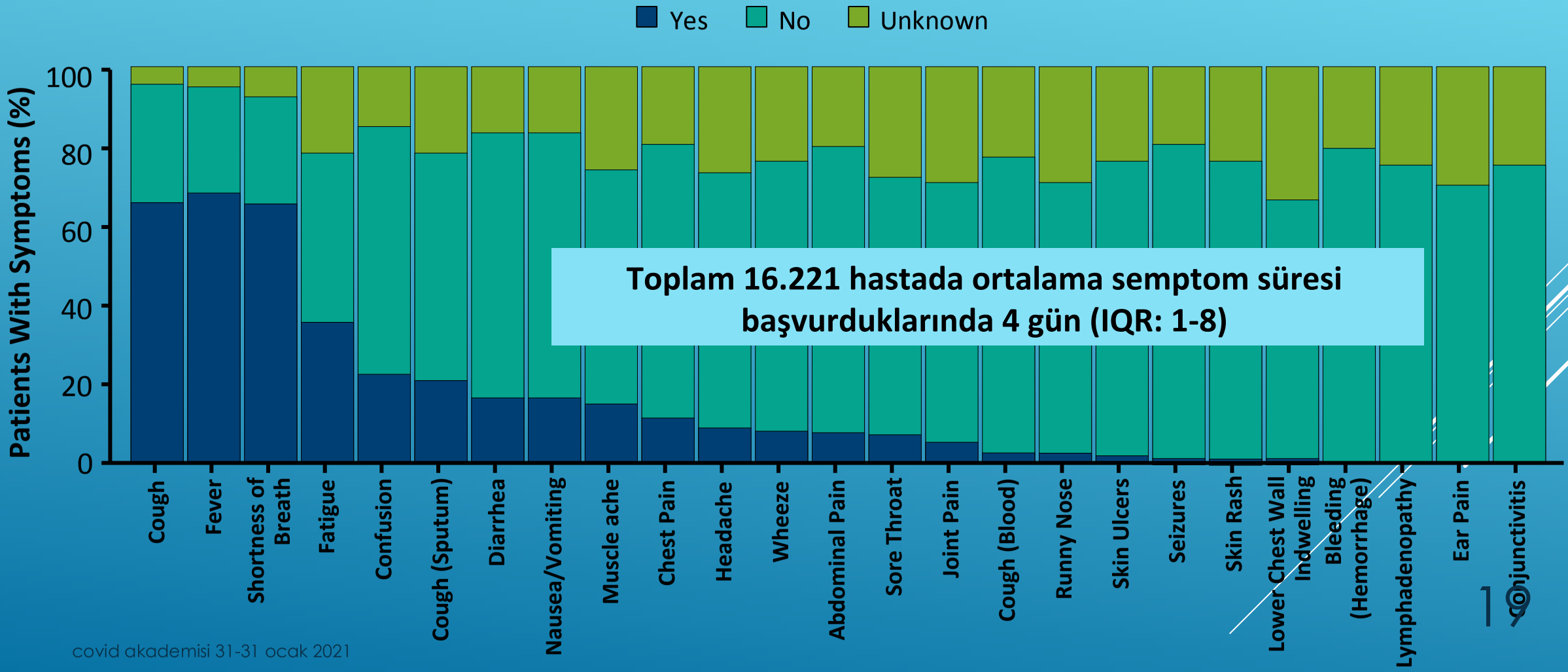


covid akademisi 31-31 ocak 2021

Li. J Med Virol. 2020;92:577.

https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

COVID-19–POSITIVE HASTANEYE YATANLARDA GÖRÜLEN SEMPTOMLAR(Uk)



Toplam 16.221 hastada ortalama semptom süresi başvurduklarında 4 gün (IQR: 1-8)

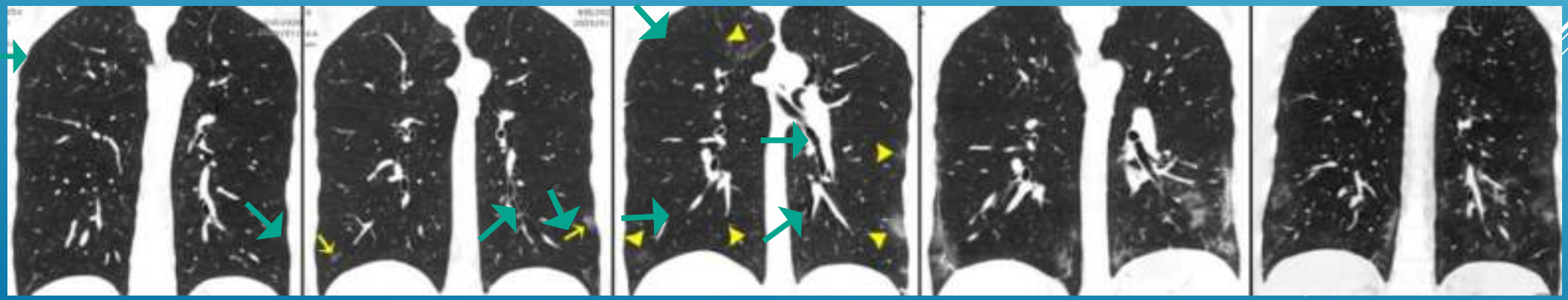
Docherty. BMJ. 2020;369:m1985.

Akciğer tomografisinde görülen değişiklikler

- En sık görülen bilateral periferal buzlu cam görünümü-konsolidasyon
- Semptomların başlamasından 6-11 gün içinde[1-3]
- 1014 olguda akciğer CT %97 sensitivite, %25 spesifite[4]
  - **Başlangıçta PCR + olguların %60-93 oranında akciğer CT pozitif olabilir.**

Ground-glass opacities

29-Yr-Old Man Presenting With Fever for 6 Days[4]



1. Bernheim. Radiology. 2020;295:685. 2. Pan. Radiology. 2020;295:715. 3. Wang. Radiology. 2020;296:E55. 4. Ai. Radiology. 2020;296:E32.

Slide credit: clinicaloptions.com

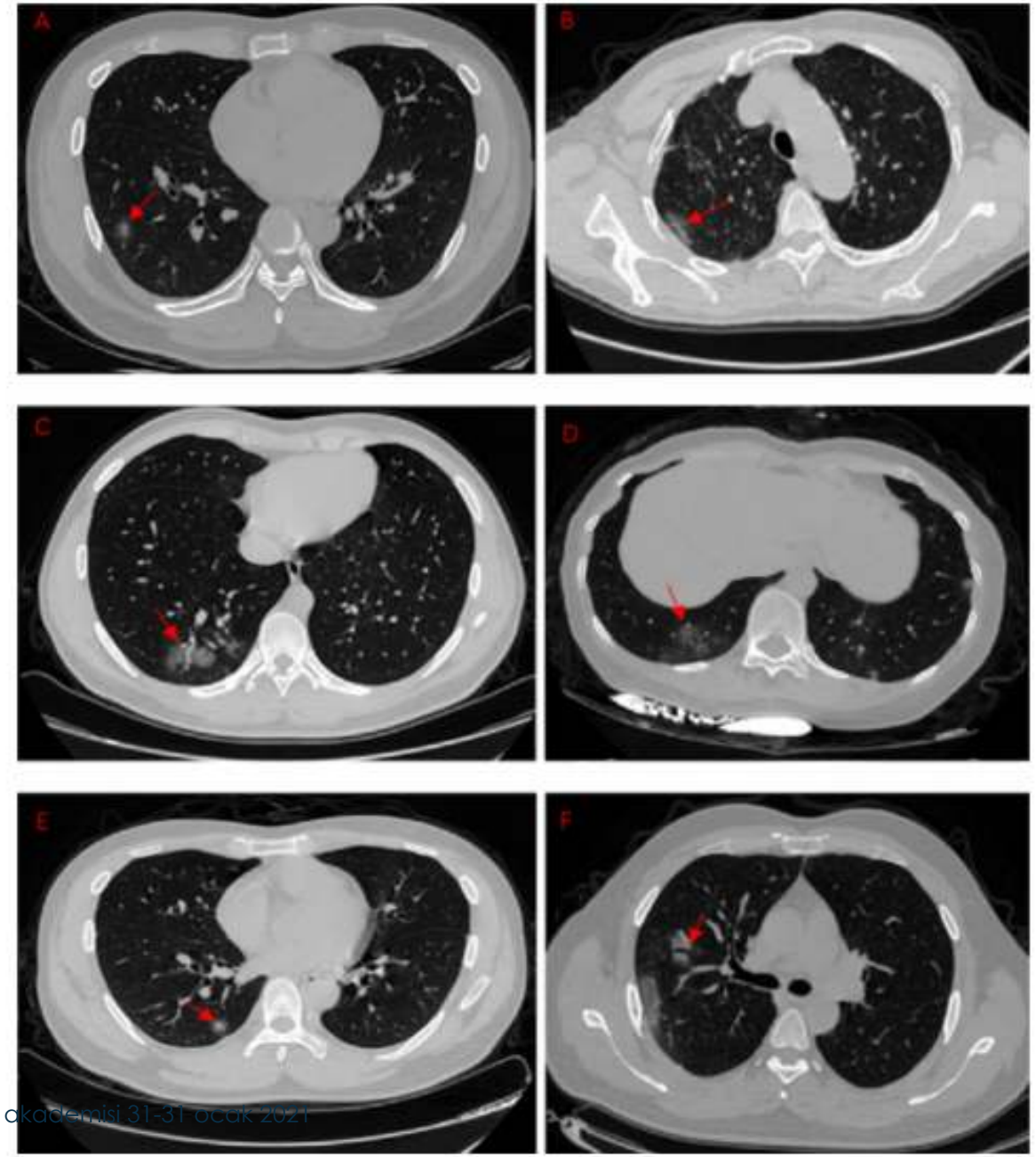


Fig. 1. The different GGO manifestations in COVID-19 pneumonia patient.
A: single, pure GGO. B: Pleural parallel sign. C: Vascular thickening sign. D: Fine reticulation. E: Halo sign. F: Air bronchogram.

58 asemptomatik hasta
Akc CT de:

- **buzlu cam,**
- **plevraya parelel,**
- **Vasküler kalınlaşma**
- **İnce retiküler**
- **Halo belirtisi**
- **Hava bronkogramı**

J Am Acad Dermatol
Volume 83, Number 4

31 ÜLKEDEN YAPILAN 171 hastada DERMATOLOJİK TUTULUM

Severity of COVID-19*

Pernio

- Feet (84%) and hands (32%)
- Pain/burning (71%) and pruritus (36%)
- After other COVID-19 symptoms (49%)
- Fever (35%), cough (35%);19% asymptomatic
- 16% hospitalized

Vesicular/ Urticarial/ Macular Erythema/ Morbilliform

- Trunk and extremities
- Pruritus in 61-74%
- Typically after other COVID-19 symptoms (19%)
- Fever (65-74%), cough (52-66%), sore throat (39-50%), shortness of breath (28-45%)
- 22-45% hospitalized across groups

Retiform purpura

- Extremities and buttocks
- Often asymptomatic (73%)
- After other COVID -19 symptoms (91%)
- Fever (64%), cough (73%), and shortness of breath (73%)
- 100% hospitalized
- 82% with ARDS

*Severity calculated based on percentage of patients hospitalized for COVID-19

Investigation	Remarks
Basic blood work	▶ Decreased WBC count as well as lymphopenia ▶ Increased levels of AST and ALT, LDH and CRP ▶ Increased D-dimer ▶ Increased PT/INR
Molecular testing via RT-PCR	▶ Techniques employed are RT-PCR and rRT-PCR which amplify viral genetic material obtained via nasal swab ▶ Poor sensitivity ▶ Repeat testing required for verification of viral clearance
Chest X-ray	▶ No significant findings early in the disease ▶ Bilateral patchy opacities in advanced disease
HRCT chest	▶ Multifocal bilateral 'ground or ground-glass' areas associated with consolidation areas with patchy distribution ▶ 'Reverse halo' sign ▶ Cavitation, calcification and lymphadenopathy ▶ High sensitivity for COVID-19 diagnosis
Serology/antibody testing	▶ Further research still required for a proper/sensitive antibody test

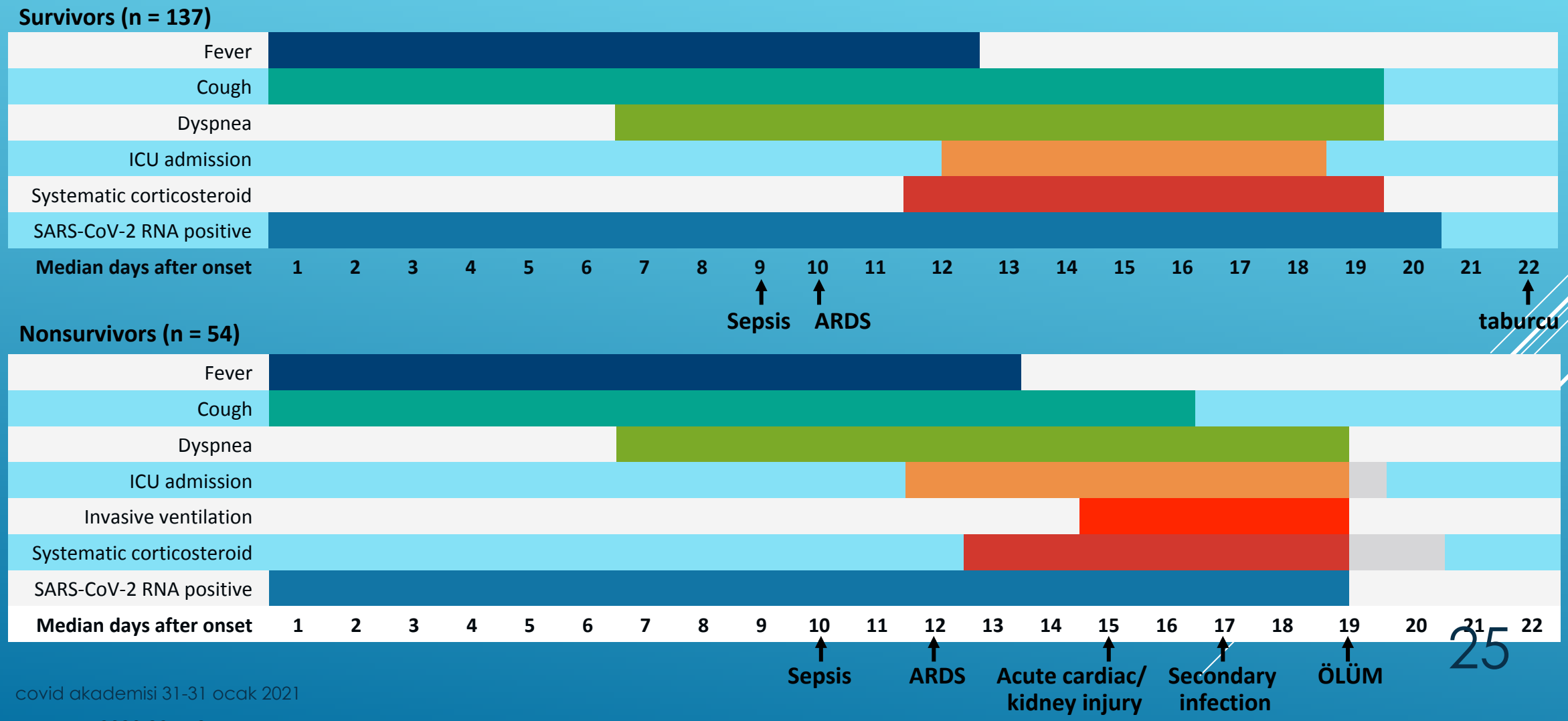
KLİNİK İZLEMDE AKCİĞER TOMOGRAFİSİ VE KAN BİYOKİMYASI

Radiographic or Lab Finding	All Patients (N = 1099)	Nonsevere Disease (n = 926)	Severe Disease (n = 173)
Abnormalities on chest radiograph,* n/N (%)	162/274 (59.1)	116/214 (54.2)	46/60 (76.7)
Abnormalities on chest CT,* n/N (%)	840/975 (86.2)	682/808 (84.4)	158/167 (94.6)
Median white cell count per mm^3 (IQR)	4700 (3500-6000)	4900 (3800-6000)	3700 (3000-6200)
Median lymphocyte count per mm^3 (IQR)	1000 (700-1300)	1000 (800-1400)	800 (600-1000)
Median platelet count x 1000 per mm^3 (IQR)	168 (132-207)	172 (139-212)	137.5 (99-179.5)
C-reactive protein ≥ 10 mg/L, n/N (%)	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)
D-dimer ≥ 0.5 mg/L, n/N (%)	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)
Lactate dehydrogenase ≥ 250 U/L, n/N (%)	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)
AST > 40 U/L, n/N (%)	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)
ALT > 40 U/L, n/N (%)	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)

*Ground-glass opacity, local patchy shadowing, bilateral patchy shadowing, or interstitial abnormalities.

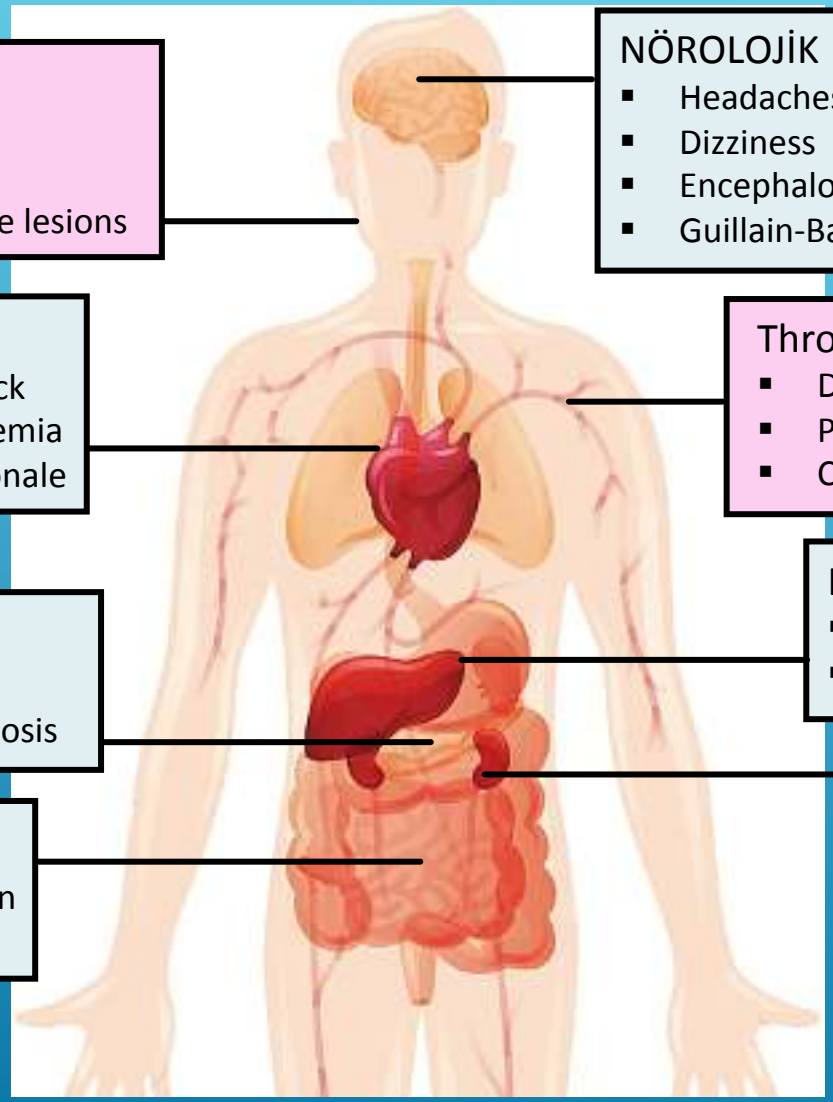
Guan. NEJM. 2020;382:1708.

ÇİNDE HASTANEYE YATAN VE YAŞAYAN/YAŞAMAYAN HASTALARDA KLİNİK BULGULAR



Zhou. Lancet. 2020;395:1054.

Akciğer dışı bulgular :geç veya kontrolde



CİLT
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

NÖROLOJİK
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

KALP
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

HEPATİK
- Elevated ALT/AST
- Elevated bilirubin

ENDOKRİN
- Hyperglycemia
- Diabetic ketoacidosis

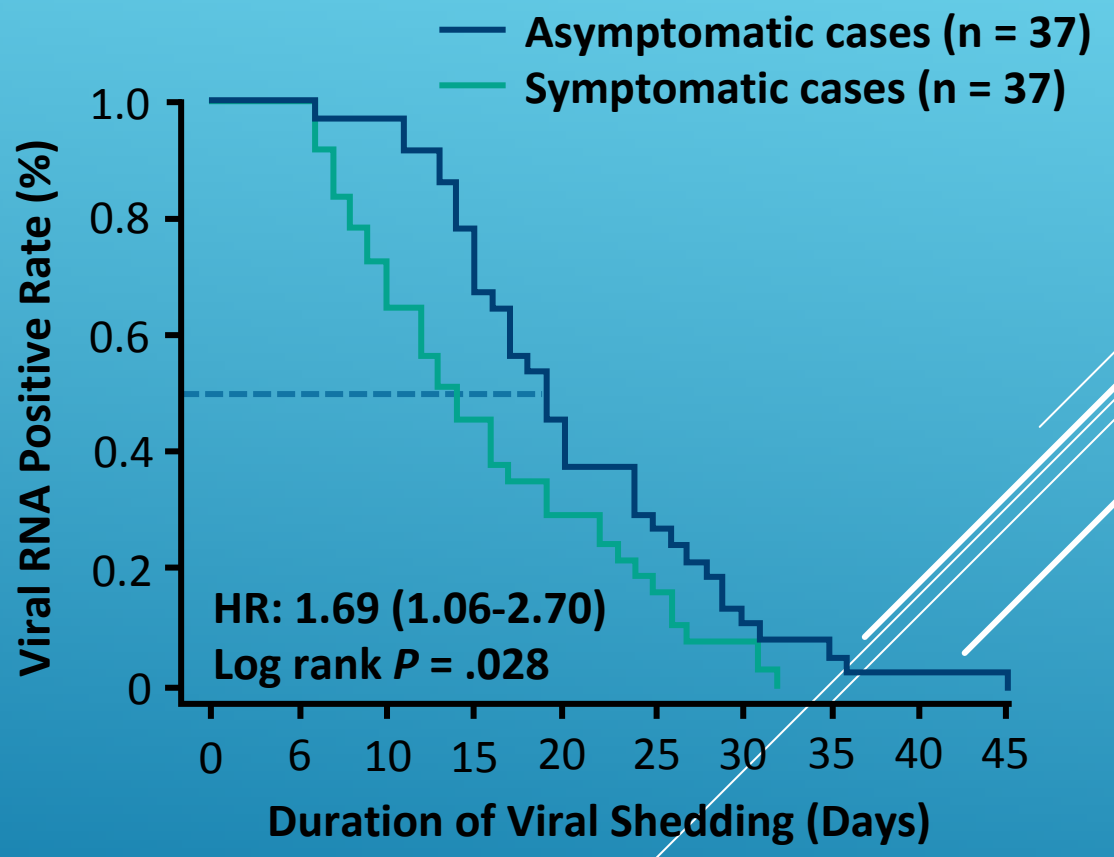
BÖBREK
- Acute kidney injury
- Proteinuria
- Hematuria

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Gupta. Nat Med. 2020;26:1017.

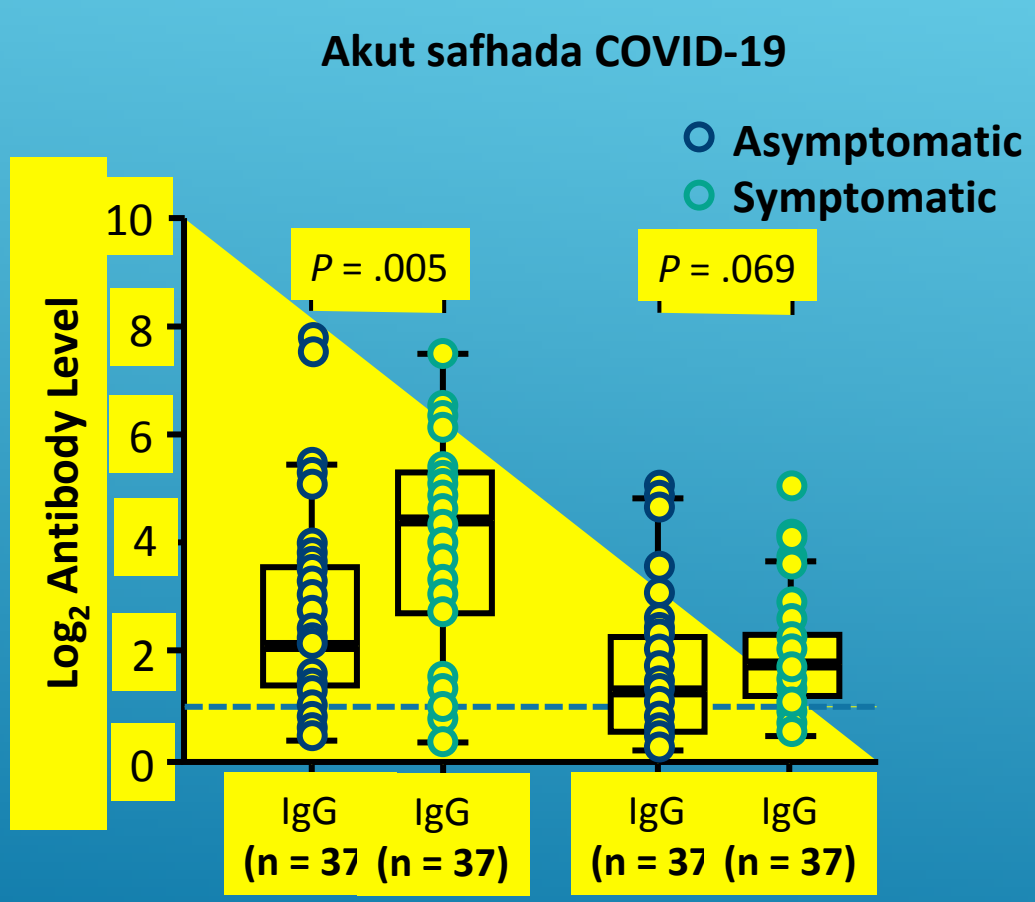
Covid-19 olgularında virolojik çoĞalma süreci

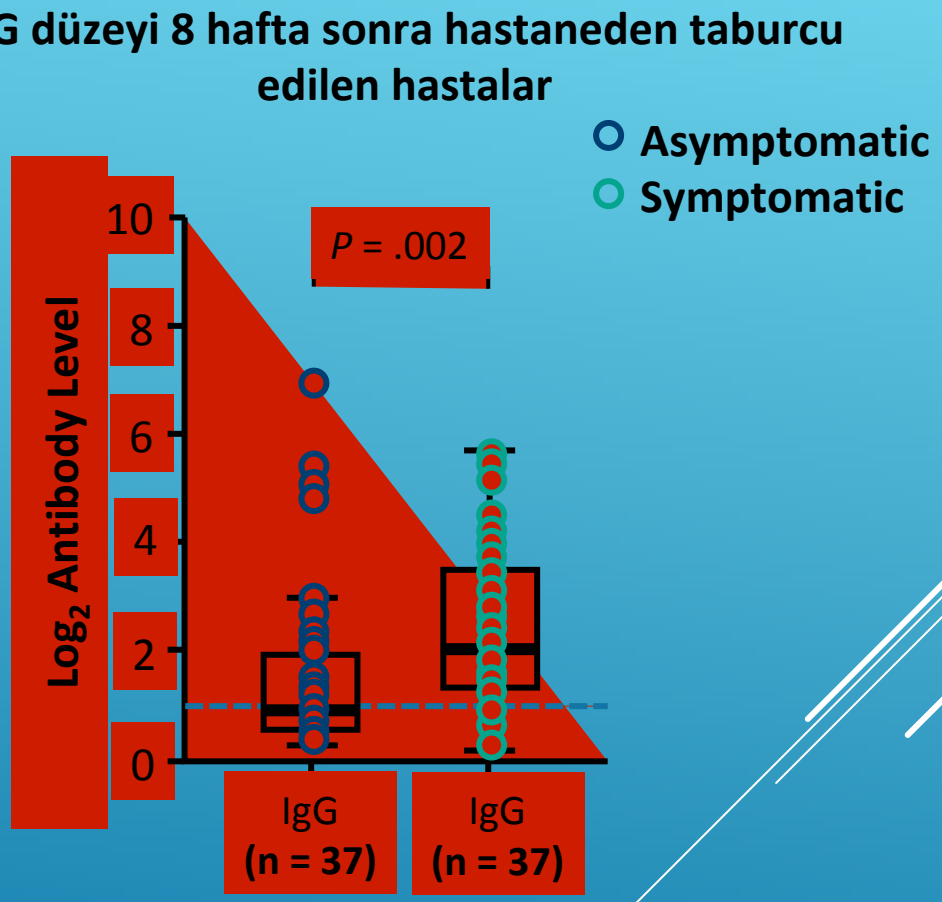
- 178 temas eden hasta Nisanda değerlendirilmiş-Wanzhou District, China, by April 10, 2020
- 37/178 (20%) ilk 14 günde asemptomatik ve sonra hastanede göz önüne alınmış
- 37 cins, yaş, hastanede kalış süreleri isolasyondan sonra değerlendirilmiş.
- **Asemptomatik olgular semptomatiklerden daha uzun süre virüsü bulunduruyorlar**
  - **Virusun çoğalması ve infeksiyonu tam bilinmiyor**



Long. Nat Med. 2020;26:1200.

Erken ve iyileŞme safhasında antikor cevabı : Asemptomatik ve Semptomatik olgularda

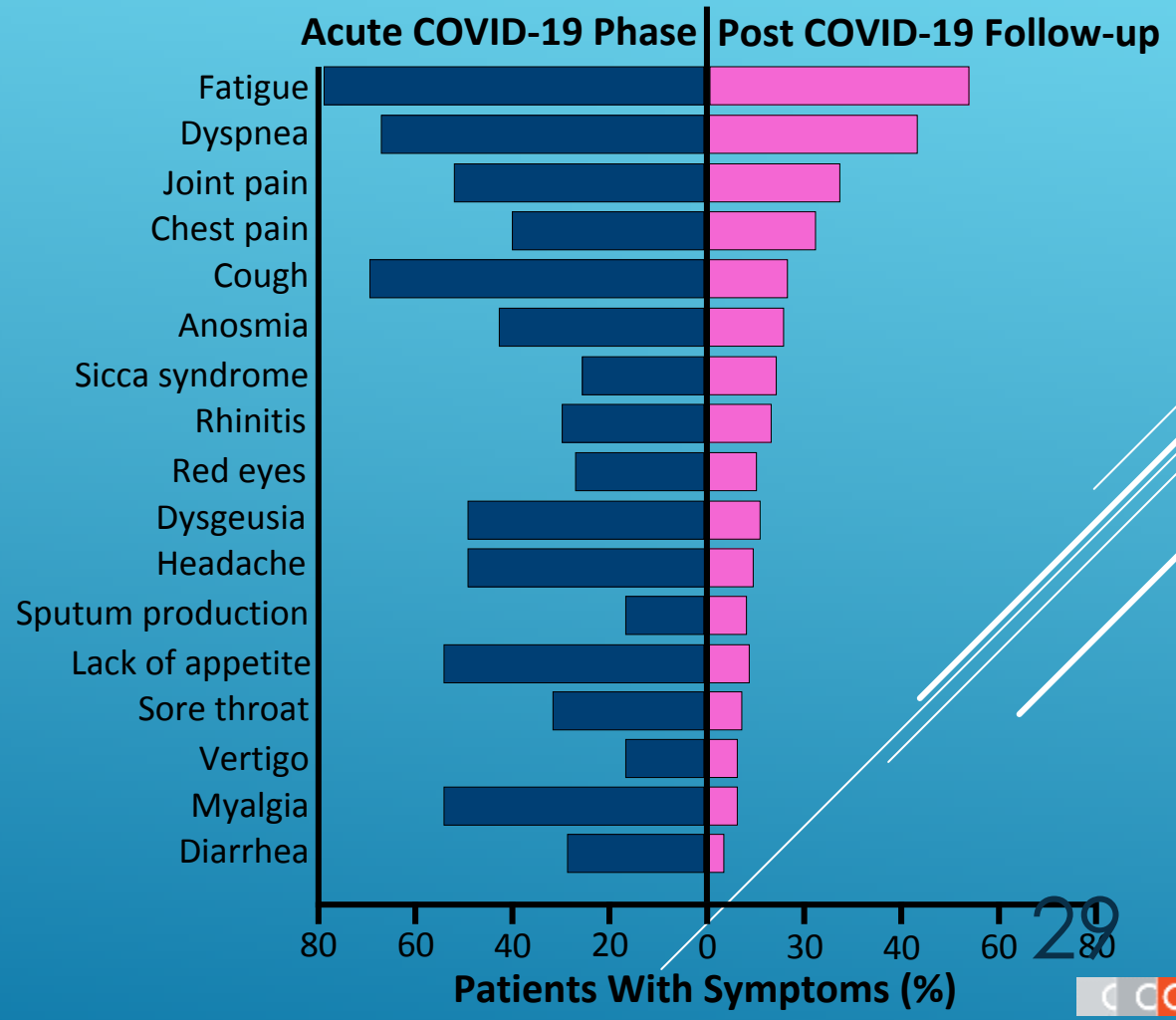




Long. Nat Med. 2020;26:1200.

COVID-19 Olgularında hastalıktan sonra devam eden semptomlar

- Ayaktan iyileşen 143 olgu
- Hastalıktan 60 gün sonra hayat kalitesi değerlendirilmiş:
- %32% bir iki semptom
- %55 >3 den fazla semptom
- %44 hiçbir semptom



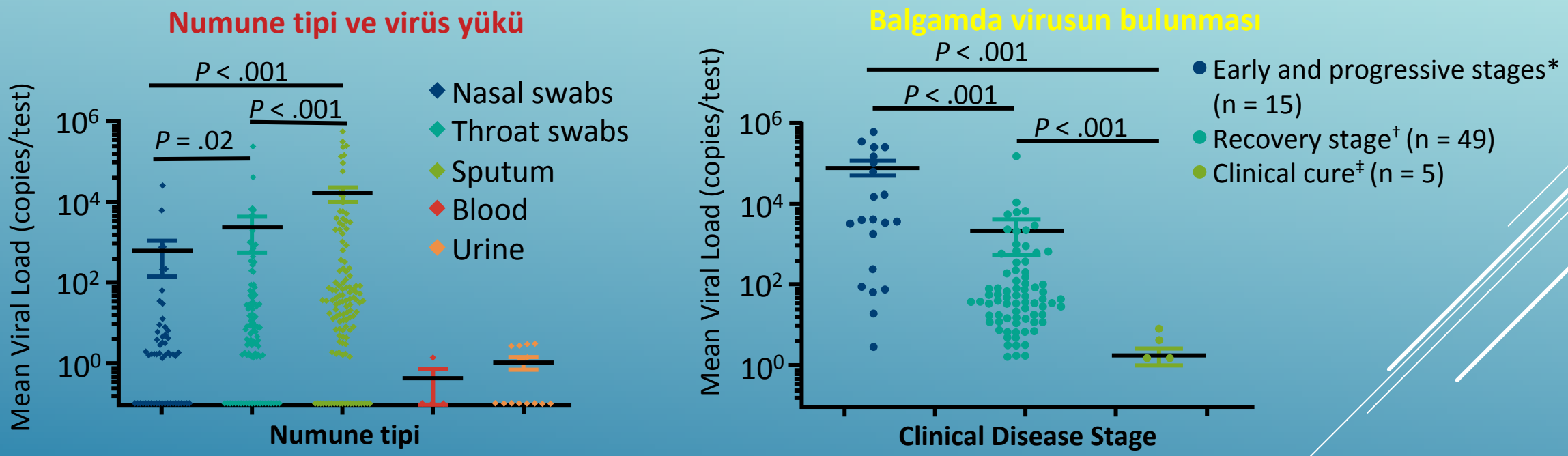
covid akademisi 31-31 ocak 2021

Carfi. JAMA. 2020;324:603.

Slide credit: clinicaloptions.com

Hastalığın devresine göre viral yükün bulunduğu numuneler

- Hastalardan elde edilen numunelerde PCR ile viral yük değerlendirlmesi sonucu Beijing laboratuvarlarında doğrulanmış COVID-19 (N = 76)

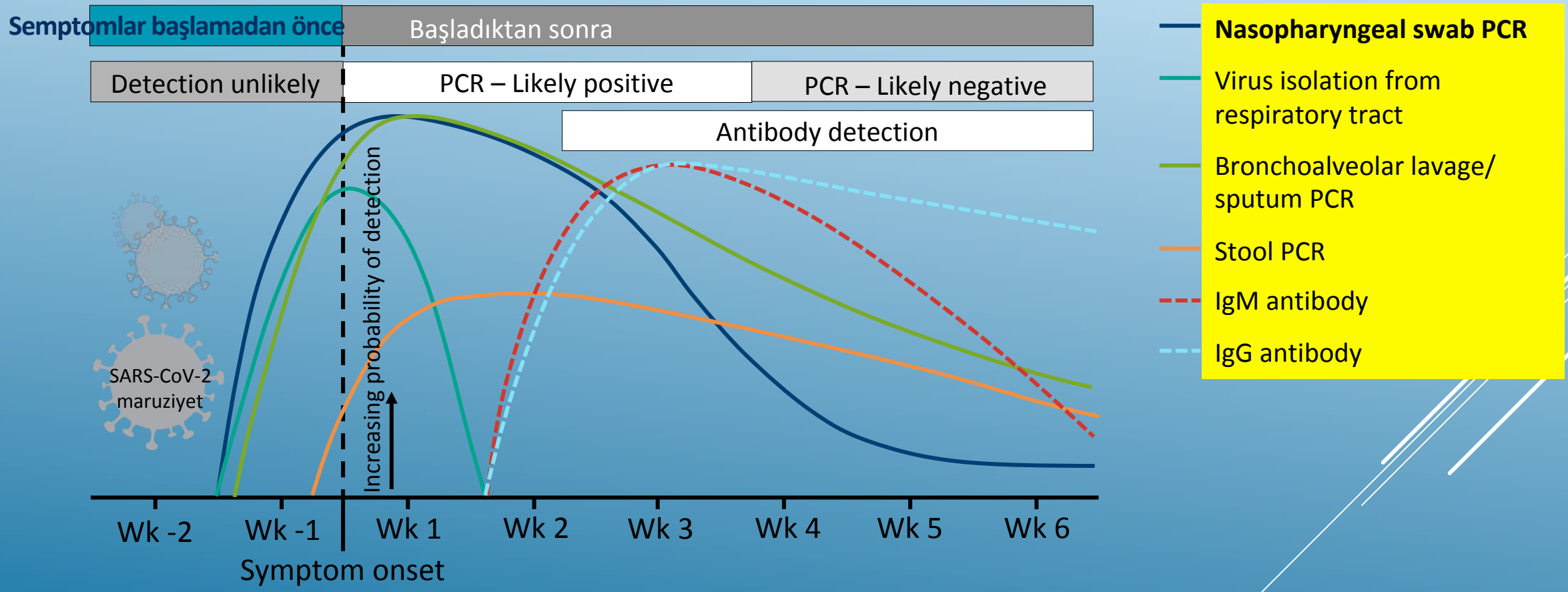


*Early stage: multifocal bilateral or isolated round ground-glass opacity with or without patchy consolidations and prominent peripherally subpleural distribution on chest CT. Progressive stage: Increasing number, range, or density of lung lesions on chest CT. †Recovery phase: lesions gradually absorbed. ‡Clinical cure: temperature recovery for > 3 days, improvement in respiratory symptoms, absorption of lung lesions, and 2 consecutive negative RT-PCR results from respiratory samples tested at least 1 day apart.

Yu. Clin Infect Dis. 2020;71:793.

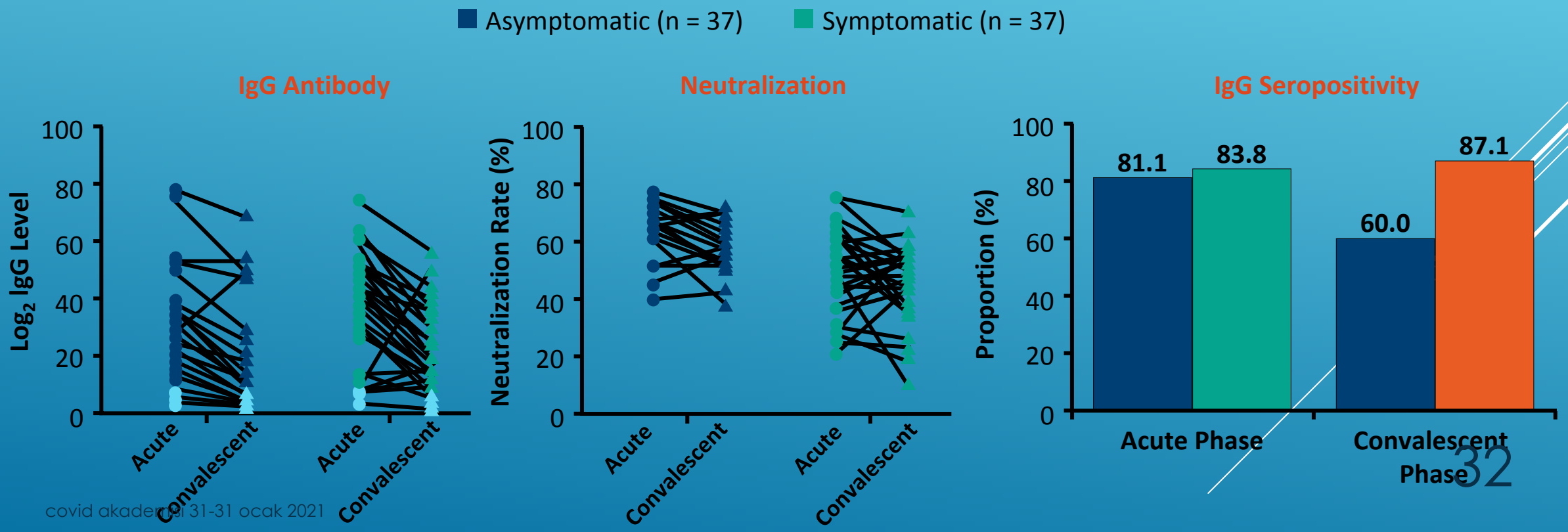
Slide credit: clinicaloptions.com

Tanıda haftalara göre kullanılan testler



Covid-19 olgularında semptomların yaptığı antikor cevabı

- Wuhan kentinde asemptomatik veya hafif(mild) covid-19 olgularında akut enfeksiyon veya erken iyileşme döneminde (8 haftalık izlem) antikor dinamizmi)



Long. Nat Med. 2020;26:1200.

WHO: Şüpheli olgu

1

Akut ateşli veya öksürük yada şu semptomlarının olması veya ≥ 3 fazla semptom genel halsizlik, başağrısı, myalji, boğaz ağrısı, ishal bulantı kusma mental değişiklişin arkasından bu ana semptomların görülmesi

Epidemiolojik kriterler olan semptomların başlangıç süresi 14 gün

Virusun bulaşacağı yüksek riskli alanda çalışmak*	Toplu taşıma alanlarında yolculuk etmek	Herhangi bir sağlık alanında çalışmak

veya

2

Ciddi akut solunum sistemi hastalarında (ateş ≥ 38°C ve öksürük 10 günden fazla sürüyorsa ve hastaneye yatma öyküsü varsa

veya

3

ASEMPTOMATİK olup epidemiyolojik kriterleri sağlamıyor ve SARS-CoV-2 Antigen pozitif
(NAAT required for confirmation)

***kapalı alanlarda, kamp, kamp benzeri kalabalığın olduğu yerlerde bulunanlar** .

covid akademisi 31-31 ocak 2021

WHO COVID-19 Case Definition. Updated December 16, 2020.
https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

Slide credit: clinicaloptions.com

WHO: Olabilir olgu

1

Akut ateş öksürük ve bunu takiben ≥ 3 semptomun olması: genel halsizlik, zayıflama, güçsüzlük,yorgunluk, baş ağrısımyalji, boğaz ağrısı, nezle, dispne,iştahsızlık,bulantı, kusma,ishal, mental durumda değişme

Pozitif olgu ile temas veya grupta bulunmak*

veya

2

COVID-19 radyolojik görüntülemeyi destekleyen akc CT bulgusu†

veya

3

Son zamanlarda tat ve koku almada kayıp ve izah edilemeyen diğer nedenler

veya

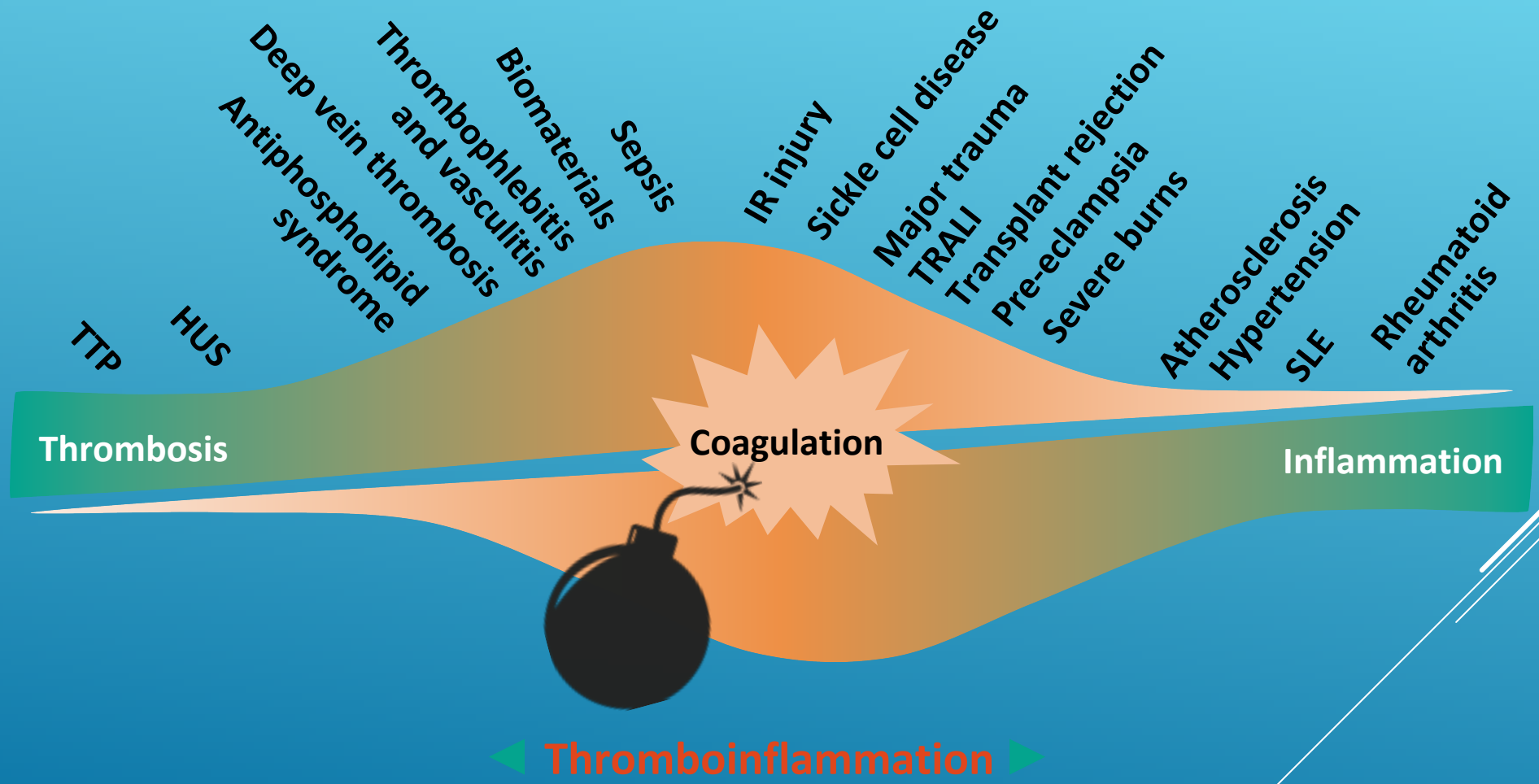
4

Solunum sıkıntısı ile ani ölümler ve nedeni açıklanamayan ARDS olguları ve ya COVİD 19 olgularının bulunduğu kalabalık ortamda bulunanlar*

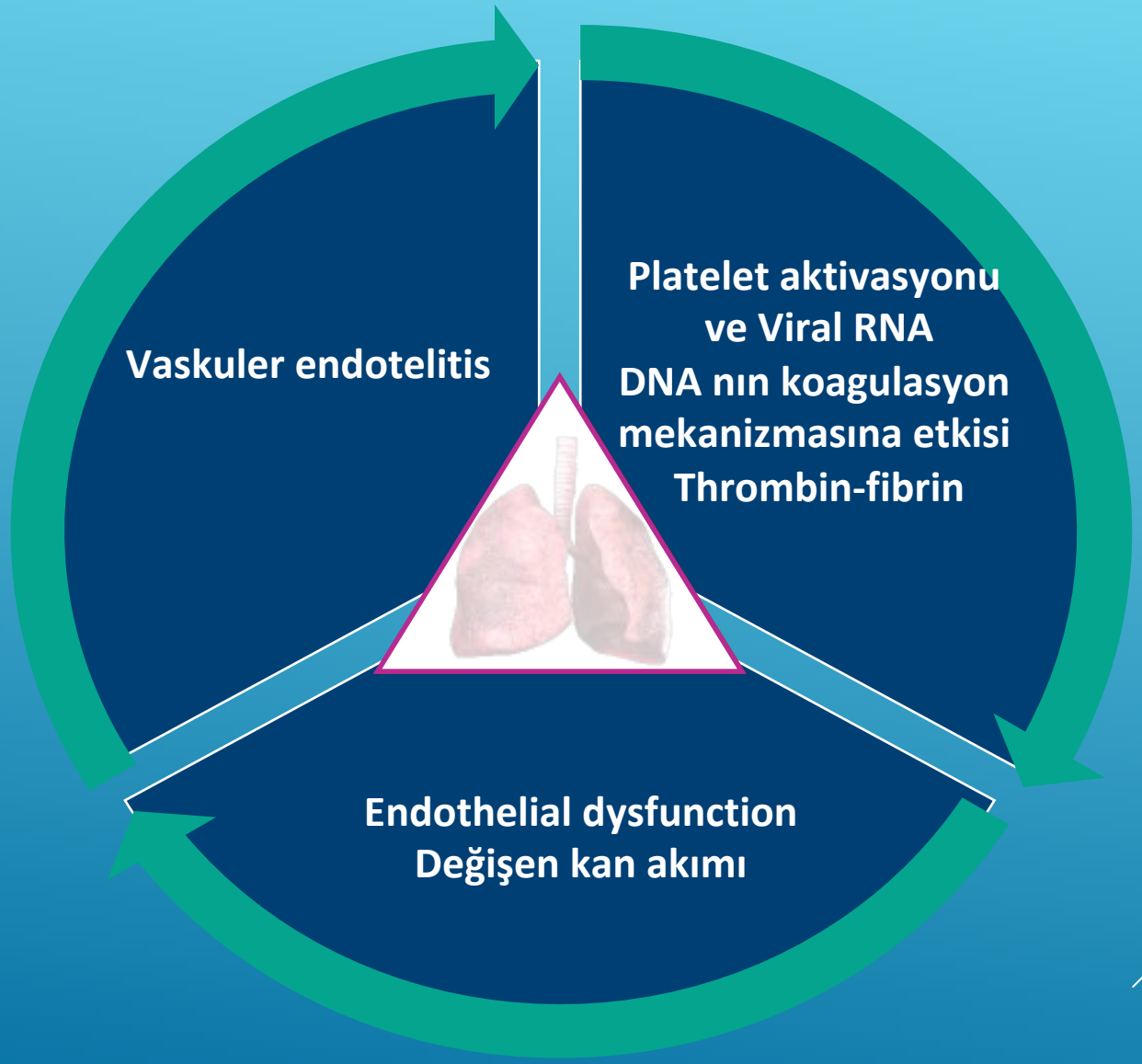
*En az bir kişide ≥ 1 NAAT-ile doğrulanmış veya ≥ 2 PCR pozitif kişinin olması.
†Tipik olarak bulanık opasite, periferal ve alt lopları tutan bilateral buzlu cam görünümü, plevral kalınlaşma, USG de konsolide alanlar.

covid akademisi 31-31 ocak 2021
WHO COVID-19 Case Definition. Updated December 16, 2020.
https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

COVID-19 Olgularında Koagulopati ve Tromboinflamasyon



VIRCHOW'S Üçlemesinin COVID-19 da uygulanması



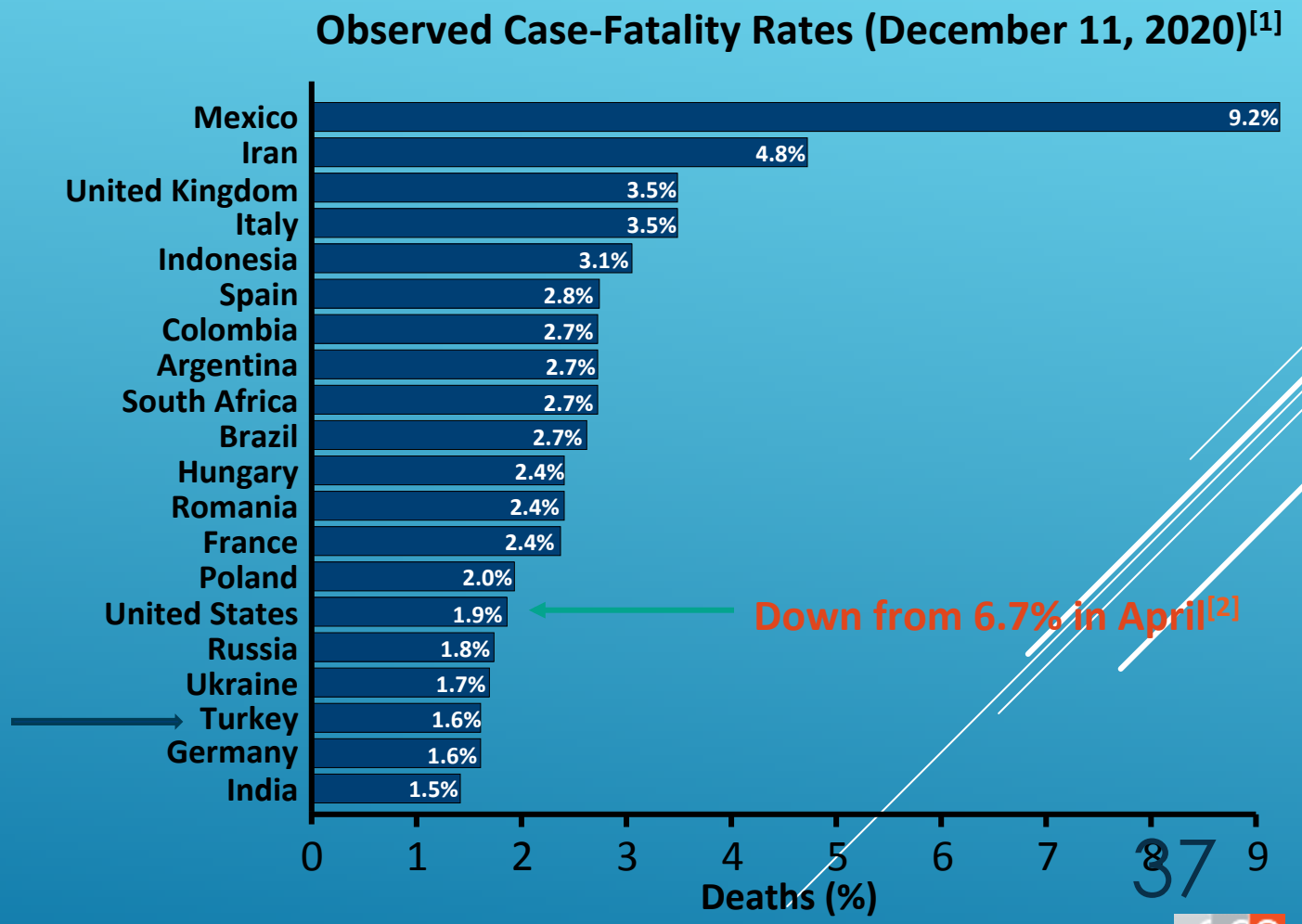
Becker. J Thromb Thrombolysis. 2020;15:1.

Slide credit: clinicaloptions.com

ÜLKELERE GÖRE ÖLÜM HIZI

New

- Yapılan test sayısı
- Demografik yapı
- Sağlık sistemi
- Bilinmeyen faktörler



TÜRKİYE %1.6

covid akademisi 31-31 ocak 2021

1. https://coronavirus.jhu.edu/data/mortality 2. https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

Slide credit: clinicaloptions.com

Daha çok alınacak yolumuz var

Teşekkür ederim