



31.

Bölüm

COVID-19 ENFEKSİYONUNA BAĞLI GELİŞEN PULMONER KOMPLİKASYONLAR VE YÖNETİMİ

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COVID-19 enfeksiyonuna bağlı pulmoner komplikasyonlar;

1. Erken dönem: Pnömoni, Sepsis, Akut Respiratuar Distres Sendromu (ARDS), Koagülasyon bozuklukları-Venöz Tromboemboli, Bakteriyel Süperenfeksiyon, Aspergillus ve Mukormikoz
2. Uzun dönem komplikasyonlar: Pulmoner Fibrozis

COVID-19'un 2019 Mart ayında panemi ilan edilmesinden bu yana 2021 Ağustos ayı itibarıyla dünyada 214,469 bin, Türkiye'de 6,293 bin doğrulanmış vaka bildirilmiştir (1).

Damlacık yoluyla bulaşmaktadır. Öksürme, hapşırma ile saçılan damlacıkların ağız, burun veya göz mukozasına götürmesi ile de bulaşabilmektedir.

Temastan sonra COVID-19 için inkübasyon süresinin 2-14 gün civarındadır ve vakanın pek çoğunda temastan 4 ile 5 gün sonrasemptomlar ortaya çıkar.

Spesifik bir klinik bulgu yoktur, daha çok viral enfeksiyon seyrine benzer gidiş gösterir. İnkübasyon süresi sonunda hafif ya da şiddetli semptomlar ortaya çıkar (2,3). En sık belirtiler öksürük (%46-82), ateş (%77-82), bulantı, yorgunluk, kas ağrısı, koku kaybıdır.Boğaz ağrısı, baş ağrısı ve burun akıntısı da bildirilmiştir. (4).

Çoğunlukla hafif-orta derecede hastalık (%55) şeklinde seyreder. Vakaların %30'unda 5. gün civarında hastalığın pprogresyonuyla beraber nefes darlığı ortaya çıkar(5,6). Şiddetli vakalarda ikinci haftada genel durumda bozulma tipiktir. Bu hastalarda genellikle birinci haftada ileri derecede hipoksemi, karaciğer fonksiyon testlerinde bozulma ve bilateral pnömoni ortaya çıkar (%75)(7).Hastanade yatan hastaların çoğu standart bakımla iyileşirken %20'sinde şiddetli solunum yetmezliğine ilerler(6).

Akciğerler COVID-19'un ilk yerleştiği organdır (8,9), virüs Anjiyotensin convertin enzim 2 (ACE 2) reseptörlerine bağlanarak hücreye girer. Enfekte birey tarafından ortama salınan damlacıkların boyutu 1–10 µm çapındadır ve bu boyut kolaylıkla alt akciğere inebilir.Ayrıca akciğer dokusu diğer dokulara göre daha fazla ACE 2 eksprese etmektedir. Virüs epitelyal hücreleri enfekte ettiğinde immün yanıt oluşturan interferonlar üretilir (10). Dentritik hücreler, makrofajlar, ve nötrofillerin alana toplanmasıyla immün yanıt başlar ve kontrolsüz enflamatuar yanıt ortaya çıkabilir (9).

Klinik olarak akciğer enfeksiyonu 4 ağırlık derecesine göre sınıflandırılır (11):

1. Hafif düzeyde klinik özellikler gösteren tip:
Klinik semptomlar hafiftir ve hiçbir belirti yoktur, radyolojik olarak pnömoni bulguları mevcut değildir.

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parametreleri ile hastaların takip edilmesi önerilmektedir (143).

Fibrozise gidişi azaltmak için(144):Fibrozis oluşması için risk faktörlerinden uzak durma, replikasyonun azaltılması, inflamasyonun azaltılması, antifibrotik tedavi önerilmektedir

Mekanik ventilasyon uygulanan hastalarda düşük Tidal volüm ve basınç uygulamak en önemli koruyucu önlemlerdir.

Uygulanan antiviral tedavilerin fibrozisi engelleyici etkisinin olup olmadığı bilinmemektedir.

Antiinflamatuvar tedavi de kortikosteritler üzerinde çok durulmuştur. Akut faz reaktanları, komplemanlar ve sitokinlerin sentezini engeller. Taburcu olduktan 1 ay sonra DLCO'da %31.6, FVC'de %9.6 düzelme olduğu tespit edilmiştir (145).

Bununla birlikte altta yatan kardiyovasküler hastalığı olan bireylerde kortikosteroidlerin hangi dozda ve ne kadar süre ile verileceği net değildir.

Antisitokin ilaçlardan İL1 blokörü (Anakinra) ve İL6 blokörü (Tocilizumab) ağır pnömonili hastalarda sekelleri önlemeyebilir fakat bu konuda ilave çalışmalar gerekmektedir(146).

İdiopatik Pulmoner fibrozis(IPF) ve COVID-19 enfeksiyonunda ortaya çıkan akciğer fibrozisinde IPF'de onay alan iki ilaç Pirfenidon ve Nintedanip COVID-19 enfeksiyonunda ortaya çıkan fibrozis için yoğun araştırmalar mevcuttur, fakat şu an onay alınmış herhangi bir antifibrotik ajan mevcut değildir. Bu iki ilaca ilaveten Tetrandin, Fuzheng Huayau, Anluohuaksian, İnsan Amnion Sıvısı, Mezenkimal Kök hücre ve Hiperbarik oksijen tedavisi de COVID-19 enfeksiyonuna bağlı ortaya çıkan fibrozis tedavisinde araştırmaları devam eden ajanlardır. Bu ilaçlardan Tetrandin Faz 4, Pirfenidon faz 3 aşamasındadır. (147).

COVID-19 sonrası fibrozisin araştırıldığı bir çalışmada taburculuk sonrası solunum

semptomları devam eden hastalarda taburculuk sonrası birinci, üçüncü ve altıncı aylarda SFT ve HRCT ile kontrollerin yapılması planlanmış olup çalışma devam etmektedir (NTC04416100). Başka çalışmada ise taburculuk sırasında, 3 ay ve bir yıl sonra çekilecek toraks tomografisi ile akciğer fibrozisi görülme sıklığı araştırılmaktadır (NTC04483752).

Sonuç olarak (148) ;

1. Pnömonisi olmayan ya da taburcu olurken pnömonisi gerileyen hastalarda takibe gerek yoktur.
2. Hafif-orta ağırlıklı olgular taburculuktan 12 hafta sonra kontrol edilmeli, nefes darlığı devam ediyorsa İnterstisyel akciğer hastalığı, Pulmoner emboli açısından tetkik edilmelidir.
3. Yoğun bakımda takip edilen hastalar 4-6 hafta sonra kontrol edilmeli, 12. haftada akciğer grafisi çekilmeli, semptomları devam ediyorsa İnterstisyel akciğer hastalığı, Pulmoner emboli açısından takip edilmelidir, HRCT (tromboemboli düşünülüyorsa Kontrastlı Toraks BT), Ekokardiyografi, Solunum fonksiyon testi, 6 dk yürüme testi ile değerlendirilmelidir.

KAYNAKLAR

1. WHO Coronavirüs (COVID-19) Dashboard [Internet]. [a.yer 29 Ağustos 2021]. Erişim adresi: <https://COVID19.who.int>
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, vd. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirüs-Infected Pneumonia. N Engl J Med [Internet]. 29 Ocak 2020 [a.yer 15 Ağustos 2021]; Erişim adresi: <https://www.nejm.org/doi/10.1056/NEJMoa2001316>
3. The Incubation Period of Coronavirüs Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application | Annals of Internal Medicine [Internet]. [a.yer 15 Ağustos 2021]. Erişim adresi: <https://www.acpjournals.org/doi/10.7326/M20-0504>
4. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirüs 2 Infection: A Cross-sectional Study | Clinical Infectious Diseases | Oxford Academic [Internet]. [a.yer 15 Ağustos 2021]. Erişim adresi: <https://academic.oup>

- com/cid/article/71/15/889/5811989
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, vd. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 17 Mart 2020;323(11):1061-9.
 6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, vd. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. Şubat 2020;395(10223):497-506.
 7. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, vd. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 01 Nisan 2020;20(4):425-34.
 8. Spagnolo P, Balestro E, Aliberti S, Coconcelli E, Biondini D, Casa GD, vd. Pulmonary fibrosis secondary to COVID-19: a call to arms? *Lancet Respir Med*. Ağustos 2020;8(8):750-2.
 9. Hou YJ, Okuda K, Edwards CE, Martinez DR, Asakura T, Dinnon KH, vd. SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. *Cell*. Temmuz 2020;182(2):429-446.e14.
 10. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J*. Nisan 2020;55(4):2000607.
 11. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). *Chin Med J (Engl)*. 05 Mayıs 2020;133(9):1087-95.
 12. Bakanlığın TS. COVID-19 Salgın Yönetimi ve Çalışma Rehberi Bilimsel Danışma Kurulu Çalışması 1 Ekim 2020. Retrieved; 2020.
 13. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. *Front Med*. 02 Nisan 2020;1-10.
 14. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, vd. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 30 Nisan 2020;382(18):1708-20.
 15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, vd. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet Lond Engl*. 15 Şubat 2020;395(10223):507-13.
 16. Gottlieb M, Sansom S, Frankenberger C, Ward E, Hota B. Clinical Course and Factors Associated With Hospitalization and Critical Illness Among COVID-19 Patients in Chicago, Illinois. *Acad Emerg Med Off J Soc Acad Emerg Med*. Ekim 2020;27(10):963-73.
 17. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, vd. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 22 Mayıs 2020;369:m1966.
 18. Reilev M, Kristensen KB, Pottegård A, Lund LC, Halas J, Ernst MT, vd. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *Int J Epidemiol*. 01 Ekim 2020;49(5):1468-81.
 19. Sente Fonseca SN, de Queiroz Sousa A, Wolkoff AG, Moreira MS, Pinto BC, Valente Takeda CF, vd. Risk of hospitalization for COVID-19 outpatients treated with various drug regimens in Brazil: Comparative analysis. *Travel Med Infect Dis*. Aralık 2020;38:101906.
 20. Bassetti M, Giacobbe DR, Bruzzi P, Barisione E, Centanni S, Castaldo N, vd. Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP). *Infect Dis Ther*. 30 Temmuz 2021;
 21. Shah BA, Ahmed W, Dhobi GN, Shah NN, Khursheed SQ, Haq I. Validity of pneumonia severity index and CURB-65 severity scoring systems in community acquired pneumonia in an Indian setting. *Indian J Chest Dis Allied Sci*. Mart 2010;52(1):9-17.
 22. Satici C, Demirkol MA, Sargin Altunok E, Gursoy B, Alkan M, Kamat S, vd. Performance of pneumonia severity index and CURB-65 in predicting 30-day mortality in patients with COVID-19. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. Eylül 2020;98:84-9.
 23. Iijima Y, Okamoto T, Shirai T, Mitsumura T, Sakakibara R, Honda T, vd. MuLBSTA score is a useful tool for predicting COVID-19 disease behavior. *J Infect Chemother Off J Jpn Soc Chemother*. Şubat 2021;27(2):284-90.
 24. Charles PGP, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, vd. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 01 Ağustos 2008;47(3):375-84.
 25. Myrstad M, Ihle-Hansen H, Tveita AA, Andersen EL, Nygård S, Tveit A, vd. National Early Warning Score 2 (NEWS2) on admission predicts severe disease and in-hospital mortality from COVID-19 - a prospective cohort study. *Scand J Trauma Resusc Emerg Med*. 13 Temmuz 2020;28(1):66.
 26. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, vd. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. *Front Microbiol*. 2019;10:2752.
 27. Grifoni E, Valoriani A, Cei F, Vannucchi V, Moroni F, Pelagatti L, vd. The CALL Score for Predicting Outcomes in Patients With COVID-19. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 23 Ocak 2021;72(1):182-3.
 28. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. :354.
 29. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [a.yer 01 Eylül 2021]. Erişim adresi: <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>
 30. Hotchkiss RS, Opal SM. Activating Immunity to Fight a Foe - A New Path. *N Engl J Med*. 26 Mart 2020;382(13):1270-2.
 31. Behrens EM, Koretzky GA. Review: Cytokine Storm Syndrome: Looking Toward the Precision Medicine Era. *Arthritis Rheumatol Hoboken NJ*. Haziran 2017;69(6):1135-43.

32. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. *Clin Immunol Orlando Fla*. Haziran 2020;215:108448.
33. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, vd. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. Mayıs 2020;55:102763.
34. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, vd. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet Lond Engl*. 28 Mart 2020;395(10229):1054-62.
35. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. Haziran 2020;46(6):1294-7.
36. Rochwerg B, Agarwal A, Siemieniuk RA, Agoritsas T, Lamontagne F, Askie L, vd. A living WHO guideline on drugs for COVID-19. *BMJ*. 04 Eylül 2020;370:m3379.
37. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, vd. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*. 06 Ekim 2020;324(13):1330-41.
38. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, vd. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. *Ann Intern Med*. 20 Ekim 2020;173(8):623-31.
39. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, vd. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Lond Engl*. 16 Mayıs 2020;395(10236):1569-78.
40. Naesens L, Guddat LW, Keough DT, van Kuilenburg ABP, Meijer J, Vande Voorde J, vd. Role of human hypoxanthine guanine phosphoribosyltransferase in activation of the antiviral agent T-705 (favipiravir). *Mol Pharmacol*. Ekim 2013;84(4):615-29.
41. Sissoko D, Laouenan C, Folkesson E, M'Lebing A-B, Beavogui A-H, Baize S, vd. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. *PLoS Med*. Mart 2016;13(3):e1001967.
42. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, vd. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial [Internet]. *Infectious Diseases (except HIV/AIDS)*; 2020 Mar [a.yer 22 Ağustos 2021]. Erişim adresi: <http://medrxiv.org/lookup/doi/10.1101/2020.03.17.20037432>
43. Brown L-AK, Freemantle N, Breuer J, Dehbi H-M, Chowdhury K, Jones G, vd. Early antiviral treatment in outpatients with COVID-19 (FLARE): a structured summary of a study protocol for a randomised controlled trial. *Trials*. 08 Mart 2021;22(1):193.
44. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, vd. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *J Infect*. Temmuz 2020;81(1):e21-3.
45. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. Temmuz 2020;26(7):917-21.
46. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, vd. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19. *N Engl J Med*. 07 Mayıs 2020;382(19):1787-99.
47. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, vd. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 27 Nisan 2020;ciaa478.
48. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, vd. Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19. *N Engl J Med*. 14 Temmuz 2021;
49. Pause in distribution of bamlanivimab-etesevimab [İnternet]. Pause in distribution of bamlanivimab-etesevimab. [a.yer 22 Ağustos 2021]. Erişim adresi: <https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/bamlanivimab-etesevimab-distribution-pause.aspx>
50. CZARSKA-THORLEY D. EMA issues advice on use of regdanvimab for treating COVID-19 [Internet]. *European Medicines Agency*. 2021 [a.yer 22 Ağustos 2021]. Erişim adresi: <https://www.ema.europa.eu/en/news/ema-issues-advice-use-regdanvimab-treating-COVID-19>
51. Eom JS, Ison M, Streinu-Cercel A, Săndulescu O, Preotescu L-L, Kim Y-S, vd. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection [Internet]. *In Review*; 2021 Mar [a.yer 22 Ağustos 2021]. Erişim adresi: <https://www.researchsquare.com/article/rs-296518/v1>
52. FACT SHEET FOR HEALTHCARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BARICITINIB. :13.
53. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, vd. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. Temmuz 2020;146(1):137-146.e3.
54. COVID-19 therapeutic alert – Interleukin-6 inhibitors (tocilizumab or sarilumab) for hospitalised patients with COVID-19 pneumonia (adults). :16.
55. Pinzon RT, Wijaya VO, Buana RB. Interleukin-6 (IL-6) inhibitors as therapeutic agents for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Infect Public Health*. 01 Ağustos 2021;14(8):1001-9.
56. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, vd. Effect of Tocilizumab vs

- Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med.* 01 Ocak 2021;181(1):32-40.
57. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, vd. Efficacy of Tocilizumab in Patients Hospitalized with COVID-19. *N Engl J Med.* 10 Aralık 2020;383(24):2333-44.
 58. Pontali E, Volpi S, Antonucci G, Castellaneta M, Buzzi D, Tricerri F, vd. Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease. *J Allergy Clin Immunol.* Temmuz 2020;146(1):213-5.
 59. Putman M, Chock YPE, Tam H, Kim AHJ, Sattui SE, Berenbaum F, vd. Antirheumatic Disease Therapies for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. *Arthritis Rheumatol Hoboken NJ.* Ocak 2021;73(1):36-47.
 60. Balasubramanian S, Nagendran TM, Ramachandran B, Ramanan AV. Hyper-inflammatory Syndrome in a Child With COVID-19 Treated Successfully With Intravenous Immunoglobulin and Tocilizumab. *Indian Pediatr.* 15 Temmuz 2020;57(7):681-3.
 61. Monteagudo LA, Boothby A, Gertner E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. *ACR Open Rheumatol.* Mayıs 2020;2(5):276-82.
 62. Ucciferri C, Auricchio A, Di Nicola M, Potere N, Abbate A, Cipollone F, vd. Canakinumab in a subgroup of patients with COVID-19. *Lancet Rheumatol.* Ağustos 2020;2(8):e457-ee458.
 63. Group RC, Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, vd. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial [Internet]. 2021 Haz [a.yer 22 Ağustos 2021] s. 2021.06.15.21258542. Erişim adresi: <https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1>
 64. Casadevall A, Pirofski L-A. The convalescent sera option for containing COVID-19. *J Clin Invest.* 01 Nisan 2020;130(4):1545-8.
 65. Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, vd. The Effect of Convalescent Plasma Therapy on Mortality Among Patients With COVID-19: Systematic Review and Meta-analysis. *Mayo Clin Proc.* Mayıs 2021;96(5):1262-75.
 66. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, vd. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *BioRxiv Prepr Serv Biol.* 01 Mart 2021;2021.01.18.427166.
 67. Cele S, Gazy I, Jackson L, Hwa S-H, Tegally H, Lustig G, vd. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma [Internet]. 2021 Oca [a.yer 22 Ağustos 2021] s. 2021.01.26.21250224. Erişim adresi: <https://www.medrxiv.org/content/10.1101/2021.01.26.21250224v1>
 68. Metcalfe SM. Mesenchymal stem cells and management of COVID-19 pneumonia. *Med Drug Discov.* 01 Mart 2020;5:100019.
 69. Wang J, Shi P, Chen D, Wang S, Wang P, Feng X, vd. Research status of the safety and efficacy of mesenchymal stem cells in the treatment of COVID-19-related pneumonia: A systematic review and meta-analysis. *Stem Cells Dev.* 20 Ağustos 2021;
 70. Lamb K, Piper D. Southmedic OxyMask(TM) compared with the Hudson RCI(*) Non-Rebreather Mask(TM): Safety and performance comparison. *Can J Respir Ther CJRT Rev Can Ther Respir RCTR.* 2016;52(1):13-5.
 71. Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. *BMJ.* 19 Eylül 1998;317(7161):798-801.
 72. Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. *Respir Care.* Mayıs 2005;50(5):604-9.
 73. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, vd. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med.* Haziran 2020;46(6):1099-102.
 74. Winck JC, Ambrosino N. COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems. *Pulmonology.* Ağustos 2020;26(4):213-20.
 75. Saxena P, Mani RK. Noninvasive ventilation success: Combining knowledge and experience. *Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med.* Ağustos 2014;18(8):492-3.
 76. Frat J-P, Brugiere B, Ragot S, Chatellier D, Veinstein A, Goudet V, vd. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. *Respir Care.* Şubat 2015;60(2):170-8.
 77. Duan J, Chen B, Liu X, Shu W, Zhao W, Li J, vd. Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: A multicenter observational study. *Am J Emerg Med.* Ağustos 2021;46:276-81.
 78. Phua J, Kong K, Lee KH, Shen L, Lim TK. Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure. *Intensive Care Med.* Nisan 2005;31(4):533-9.
 79. Serafim RB, Póvoa P, Souza-Dantas V, Kalil AC, Salluh JIF. Clinical course and outcomes of critically ill patients with COVID-19 infection: a systematic review. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis.* Ocak 2021;27(1):47-54.
 80. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) | SpringerLink [Internet]. [a.yer 30 Ağustos 2021]. Erişim adresi: <https://link.springer.com/article/10.1007%2Fs00134-020-06022-5>
 81. Cinel I, Kasapoglu US, Gul F, Dellinger RP. The initial resuscitation of septic shock. *J Crit Care.* Haziran 2020;57:108-17.
 82. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, vd. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax.* Kasım 2020;75(11):1009-16.

83. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, vd. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 20 Haziran 2012;307(23):2526-33.
84. Fanelli V, Vlachou A, Ghannadian S, Simonetti U, Slutsky AS, Zhang H. Acute respiratory distress syndrome: new definition, current and future therapeutic options. *J Thorac Dis*. Haziran 2013;5(3):326-34.
85. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, vd. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. Haziran 2020;46(6):1099-102.
86. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. *Am J Respir Crit Care Med*. 15 Şubat 2017;195(4):438-42.
87. Hager DN, Krishnan JA, Hayden DL, Brower RG, ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med*. 15 Kasım 2005;172(10):1241-5.
88. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med*. Mayıs 2020;8(5):433-4.
89. Nin N, Muriel A, Peñuelas O, Brochard L, Lorente JA, Ferguson ND, vd. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med*. Şubat 2017;43(2):200-8.
90. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care*. Aralık 2020;24(1):154, s13054-020-02880-z.
91. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, vd. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 01 Temmuz 2020;180(7):934-43.
92. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, vd. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-6.
93. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta Int J Clin Chem*. Temmuz 2020;506:145-8.
94. Qu R, Ling Y, Zhang Y-H-Z, Wei L-Y, Chen X, Li X-M, vd. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J Med Virol*. Eylül 2020;92(9):1533-41.
95. Zhang J, Zhou L, Yang Y, Peng W, Wang W, Chen X. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med*. Mart 2020;8(3):e11-2.
96. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost JTH*. Mayıs 2020;18(5):1094-9.
97. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect*. Aralık 2020;9(1):727-32.
98. Nishimura H, Yamaya M. A Synthetic Serine Protease Inhibitor, Nafamostat Mesilate, Is a Drug Potentially Applicable to the Treatment of Ebola Virus Disease. *Tohoku J Exp Med*. Eylül 2015;237(1):45-50.
99. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 04 Haziran 2020;135(23):2033-40.
100. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, vd. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost JTH*. Ağustos 2020;18(8):1859-65.
101. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D a. MPJ, Kant KM, vd. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. Temmuz 2020;191:145-7.
102. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, vd. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. Temmuz 2020;191:9-14.
103. Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, vd. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 13 Kasım 2017;65(11):1806-12.
104. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, vd. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 30 Temmuz 2015;373(5):415-27.
105. 106. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect*. Ağustos 2020;81(2):266-75.
106. 107. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, vd. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 03 Aralık 2020;71(9):2459-68.
107. 108. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, vd. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 28 Temmuz 2020;ciaa1065.
108. 109. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, vd. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 29 Ağustos 2020;ciaa1298.
109. 110. Schauvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, vd. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort

- study. *Lancet Respir Med*. Ekim 2018;6(10):782-92.
110. 111. Lang M, Som A, Mendoza DP, Flores EJ, Li MD, Shepard J-AO, vd. Detection of Unsuspected Coronavirus Disease 2019 Cases by Computed Tomography and Retrospective Implementation of the Radiological Society of North America/Society of Thoracic Radiology/American College of Radiology Consensus Guidelines. *J Thorac Imaging*. 01 Kasım 2020;35(6):346-53.
 111. 112. Rutsaert L, Steinfors N, Van Hunsel T, Bomans P, Naesens R, Mertes H, vd. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care*. 01 Haziran 2020;10(1):71.
 112. 113. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, vd. COVID-19 associated pulmonary aspergillosis. *Mycoses*. 2020;63(6):528-34.
 113. 114. Armstrong-James D, Koh M, Ostermann M, Cockwell P. Optimal management of acute kidney injury in critically ill patients with invasive fungal infections being treated with liposomal amphotericin B. *BMJ Case Rep*. 12 Mayıs 2020;13(5):e233072.
 114. 115. Heinz WJ, Buchheidt D, Ullmann AJ. Clinical evidence for caspofungin monotherapy in the first-line and salvage therapy of invasive *Aspergillus* infections. *Mycoses*. Ağustos 2016;59(8):480-93.
 115. 116. Kofla G, Ruhnke M. Pharmacology and metabolism of anidulafungin, caspofungin and micafungin in the treatment of invasive candidosis: review of the literature. *Eur J Med Res*. 28 Nisan 2011;16(4):159-66.
 116. 117. Mizutari K, Nishimoto K, Ono T. Cutaneous mucormycosis. *J Dermatol*. Mart 1999;26(3):174-7.
 117. 118. Yun MW, Lui CC, Chen WJ. Facial paralysis secondary to tympanic mucormycosis: case report. *Am J Otol*. Mayıs 1994;15(3):413-4.
 118. 119. Saydam L, Erpek G, Kizilay A. Calcified Mucor fungus ball of sphenoid sinus: an unusual presentation of sinoorbital mucormycosis. *Ann Otol Rhinol Laryngol*. Ekim 1997;106(10 Pt 1):875-7.
 119. 120. Black fungus: Here is a list of states with highest number of mucormycosis cases [Internet]. *Hindustan Times*. 2021 [a.yer 27 Ağustos 2021]. Erişim adresi: <https://www.hindustantimes.com/india-news/black-fungus-states-with-highest-number-of-mucormycosis-cases-101621559394002.html>
 120. 121. John TM, Jacob CN, Kontoyiannis DP. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. *J Fungi*. Nisan 2021;7(4):298.
 121. 122. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, vd. Coronavirus Disease (COVID-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. *Mycopathologia*. Mayıs 2021;186(2):289-98.
 122. 123. Khatri A, Chang K-M, Berlinrut I, Wallach F. Mucormycosis after Coronavirus disease 2019 infection in a heart transplant recipient - Case report and review of literature. *J Mycol Med*. Haziran 2021;31(2):101125.
 123. 124. Hanley B, Naresh KN, Roufousse C, Nicholson AG, Weir J, Cooke GS, vd. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe*. Ekim 2020;1(6):e245-53.
 124. 125. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol*. Ağustos 1994;39(1):3-22.
 125. 126. Agrawal R, Yeldandi A, Savas H, Parekh ND, Lombardi PJ, Hart EM. Pulmonary Mucormycosis: Risk Factors, Radiologic Findings, and Pathologic Correlation. *RadioGraphics*. Mayıs 2020;40(3):656-66.
 126. 127. Cornely OA, Arıkan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, vd. ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. Nisan 2014;20:5-26.
 127. 128. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis Off Publ Infect Dis Soc Am*. Haziran 2000;30(6):851-6.
 128. 129. Patterson TF, Thompson GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, vd. Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 15 Ağustos 2016;63(4):433-42.
 129. 130. Chretien M-L, Legouge C, Pagès P-B, Lafon I, Ferrant E, Plocque A, vd. Emergency and elective pulmonary surgical resection in haematological patients with invasive fungal infections: a report of 50 cases in a single centre. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. Eylül 2016;22(9):782-7.
 130. 131. Coffey MJ, Fantone J, Stirling MC, Lynch JP. Pseudoaneurysm of pulmonary artery in mucormycosis. *Radiographic characteristics and management*. *Am Rev Respir Dis*. Haziran 1992;145(6):1487-90.
 131. 132. Mahase E. COVID-19: What do we know about "long COVID"? *BMJ*. 14 Temmuz 2020;370:m2815.
 132. 133. Rubin R. As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts. *JAMA*. 13 Ekim 2020;324(14):1381-3.
 133. 134. Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 11 Ağustos 2020;324(6):603-5.
 134. 135. Tenforde MW. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020. *MMWR Morb Mortal Wkly Rep* [Internet]. 2020 [a.yer 31 Ağustos 2021];69. Erişim adresi: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm>
 135. 136. New research identifies those most at risk from "long COVID" [Internet]. [a.yer 31 Ağustos 2021]. Erişim adresi: <https://www.kcl.ac.uk/news/study-identifies-those-most-risk-long-COVID>
 136. 137. Vinod N. Pulmonary Involvement in COVID-19 and 'Long COVID': The Morbidity, Complications

- and Sequelae. *J Pulmonol Respir Res.* 15 Haziran 2021;5(1):034-48.
137. 138. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol.* Ağustos 2020;30(8):4381-9.
138. 139. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine Growth Factor Rev.* Haziran 2020;53:66-70.
139. 140. Hamada N, Kuwano K, Yamada M, Hagimoto N, Hiasa K, Egashira K, vd. Anti-vascular endothelial growth factor gene therapy attenuates lung injury and fibrosis in mice. *J Immunol Baltim Md* 1950. 15 Temmuz 2005;175(2):1224-31.
140. 141. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. *Korean J Radiol.* Haziran 2020;21(6):746-55.
141. 142. Liu D, Zhang W, Pan F, Li L, Yang L, Zheng D, vd. The pulmonary sequelae in discharged patients with COVID-19: a short-term observational study. *Respir Res.* 24 Mayıs 2020;21(1):125.
142. 143. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. *Lancet Respir Med.* Eylül 2020;8(9):839-42.
143. 144. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. *Pulm Med.* 2020;2020:6175964.
144. 145. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, vd. Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment. *Ann Am Thorac Soc.* Mayıs 2021;18(5):799-806.
145. 146. Buckley LF, Wohlford GF, Ting C, Alahmed A, Van Tassell BW, Abbate A, vd. Role for Anti-Cytokine Therapies in Severe Coronavirus Disease 2019. *Crit Care Explor.* Ağustos 2020;2(8):e0178.
146. 147. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med.* Ağustos 2020;8(8):807-15.
147. 148. COVID-19: information for the respiratory community | British Thoracic Society | Better lung health for all [İnternet]. [a.yer 24 Ağustos 2021]. Erişim adresi: <https://www.brit-thoracic.org.uk/COVID-19/COVID-19-information-for-the-respiratory-community/>