

sistem imun dan dapat mengakibatkan kegagalan multiorgan. Pengukuran CRP pun harus dilakukan secara berkala agar pemantauan kondisi pasien lebih komprehensif dan jika perlu perawatan ICU segera (Zhang et al, 2020b).

Beberapa penelitian menunjukkan semakin tingginya kadar CRP, semakin beratnya inflamasi yang terjadi. Hal ini terkait dengan keberadaan CRP yang merupakan protein fase akut pada kondisi inflamasi, infeksi dan kerusakan jaringan (Zeng et al, 2020). Dan ada penelitian lain yang mengatakan terjadi peningkatan kadar CRP pada pasien dengan gejala berat dibanding gejala ringan dan pada *non survivor* lebih tinggi dibanding *survivor*. Hal ini menunjukkan semakin tinggi kadar CRP pasien maka semakin berat pula keadaannya yang mengindikasikan terjadinya inflamasi dan kegagalan multiorgan berat pada pasien (Ji et al, 2020).

Peningkatan CRP terjadi akibat adanya inflamasi berat sistemik sebagai respon akut. Peningkatan CRP berkaitan dengan perawatan ICU dan prognosis yang buruk (Bao et al, 2020).

Terdapat penelitian yang menyatakan meski terdapat peningkatan CRP pada pasien Covid-19 tetapi peningkatan CRP tidak berkorelasi dengan perawatan ICU (Zhang et al, 2020a).

CRP cenderung lebih sensitif dibandingkan marker laboratorium lain terhadap infeksi Covid-19 bergejala terhadap tidak bergejala, bergejala ringan terhadap bergejala berat, perawatan ICU terhadap tidak perawatan ICU, mortalitas dan kepulangan. CRP meningkat lebih tinggi sejalan dengan keparahan penyakit dan sangat berhubungan dengan prognosis (de Souza et al,

2020; Diriba et al, 2020; Ghayda et al, 2020; Henry et al, 2020; Huang et al, 2020; Izcovich et al, 2020; Ji et al, 2020; Kermali et al, 2020; Li et al, 2020; Liguoro et al, 2020; Ludvigsson, 2020; Sahu et al, 2020; Soraya & Ulhaq, 2020; Terpos et al, 2020; Zaigham & Anderson, 2020; Zhang et al, 2020a, Zhang et al, 2020b; Zeng et al, 2020).

Nilai CRP pada infeksi Covid-19 konsisten meningkat dengan variasi nilai sensitivitas dan spesifitas. Pada umumnya peningkatan  $>20$  mg/L memberikan gambaran keparahan gejala, prognosis buruk, dan mortalitas. Kerusakan jaringan akibat inflamasi pada infeksi Covid-19 yang berat dapat diprediksi dengan nilai CRP (Akbari et al., 2020; Elshazli et al., 2020; Ghahramani et al., 2020; Ghayda et al., 2020; Gidari et al., 2021; Huang et al., 2020; Ji et al., 2020; Kermali et al., 2020; Ou et al., 2020; Soraya & Ulhaq, 2020; Zaigham & Andersson, 2020; Zeng et al, 2020).

Nilai *risk ratio* dari CRP menunjukkan risiko prognosis buruk, penyakit berat dan perawatan ICU meningkat. Hal ini terkait semakin beratnya respon inflamasi yang terjadi maka akan semakin banyak organ target yang rusak (Henry et al., 2020; Huang et al., 2020; Terpos et al., 2020).

Nilai *odds ratio* pada peningkatan nilai CRP juga meningkat dengan signifikan dan bermakna. Sehingga, nilai CRP dapat menjadi prediktor terutama pada kasus berat dan prognosis buruk (Bao et al., 2020; Elshazli et al., 2020; Figliozzi et al., 2020; Izcovich et al., 2020; Yamada et al., 2020; Zhang et al., 2020).

Peningkatan CRP juga dipengaruhi oleh keadaan pasien saat masuk rumah sakit, utamanya superinfeksi bakteri, keadaan penyerta yang menjadi komorbid dan beratnya gejala (Ghayda et al, 2020).

## BAB 7

### KESIMPULAN DAN SARAN

#### A. Kesimpulan

Berdasarkan literature yang telah dianalisis, maka kesimpulan yang dapat ditarik adalah:

1. Infeksi Covid-19 lebih parah pada laki-laki, usia tua, dan adanya komorbid.
2. Gejala yang paling sering muncul pada pasien dengan infeksi Covid-19 adalah demam dan batuk, gejala gastrointestinal, sesak, malaise, myalgia, dan nyeri kepala.
3. Semakin tinggi kadar CRP, menunjukkan kondisi inflamasi yang semakin berat.
4. Pada gambaran *outcome* pada pasien dengan infeksi Covid-19 memberikan gambaran *discharge rate* lebih tinggi pada anak dibandingkan pada dewasa. Terdapat pula *case fatality rate* yang lebih tinggi pada dewasa dibandingkan anak, dan angka mortalitas ibu rendah.
5. Hubungan CRP dengan keparahan infeksi Covid-19 signifikan pada semua tolok ukur dan konsisten pada semua kondisi. Infeksi Covid-19 dengan gejala ringan memberikan gambaran hasil pemeriksaan CRP pada range 12,1 mg/L-41,78 mg/L, dan untuk gejala berat 43,8 mg/L-57,90 mg/L.

## B. Saran

Dengan adanya beberapa penelitian mengenai hubungan peningkatan kadar CRP terhadap tingkat keparahan pasien COVID-19 diharapkan agar tenaga medis dapat menjadikan kadar CRP sebagai salah satu biomarker untuk mengetahui tanda prognosis yang buruk, mencegah terjadinya tingkat keparahan lebih lanjut, komplikasi berat dan kematian pasien.

## DAFTAR PUSTAKA

- Akbari, H., Tabrizi, R., Lankarani, K. B., Aria, H., Vakili, S., Asadian, F., Noroozi, S., Keshavarz, P., & Faramarz, S. (2020). The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Life sciences*, 258, 118167. <https://doi.org/10.1016/j.lfs.2020.118167>
- Ali N. (2020). Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *Journal of medical virology*, 92(11), 2409–2411. <https://doi.org/10.1002/jmv.26097>
- Andrews, P., Cai, W., Rudd, J. A., & Sanger, G. J. (2021). COVID-19, nausea, and vomiting. *Journal of gastroenterology and hepatology*, 36(3), 646–656. <https://doi.org/10.1111/jgh.15261>
- Azer S. A. (2020). COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New microbes and new infections*, 37, 100738. <https://doi.org/10.1016/j.nmni.2020.100738>
- Baergen, R. N., & Heller, D. S. (2020). Placental Pathology in Covid-19 Positive Mothers: Preliminary Findings. *Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*, 23(3), 177–180. <https://doi.org/10.1177/1093526620925569>
- Bao, J., Li, C., Zhang, K., Kang, H., Chen, W., & Gu, B. (2020). Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. *Clinica chimica acta; international journal of clinical chemistry*, 509, 180–194. <https://doi.org/10.1016/j.cca.2020.06.009>
- Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- $\alpha$ . *Molecular psychiatry*, 21(5), 642–649. <https://doi.org/10.1038/mp.2015.67>

- Bchetnia, M., Girard, C., Duchaine, C., & Laprise, C. (2020). The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): A review of the current global status. *Journal of infection and public health*, 13(11), 1601–1610. <https://doi.org/10.1016/j.jiph.2020.07.011>
- Bellos, I., Pandita, A., & Panza, R. (2021). Maternal and perinatal outcomes in pregnant women infected by SARS-CoV-2: A meta-analysis. *European journal of obstetrics, gynecology, and reproductive biology*, 256, 194–204. <https://doi.org/10.1016/j.ejogrb.2020.11.038>
- Buonsenso, D., Sali, M., Pata, D., De Rose, C., Sanguinetti, M., Valentini, P., & Delogu, G. (2020). Children and COVID-19: Microbiological and immunological insights. *Pediatric pulmonology*, 55(10), 2547–2555. <https://doi.org/10.1002/ppul.24978>
- Campbell, K. H., Tornatore, J. M., Lawrence, K. E., Illuzzi, J. L., Sussman, L. S., Lipkind, H. S., & Pettker, C. M. (2020). Prevalence of SARS-CoV-2 Among Patients Admitted for Childbirth in Southern Connecticut. *JAMA*, 323(24), 2520–2522. <https://doi.org/10.1001/jama.2020.8904>
- Cao, Y., Liu, X., Xiong, L., & Cai, K. (2020). Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. *Journal of medical virology*, 92(9), 1449–1459. <https://doi.org/10.1002/jmv.25822>
- Cascella M, Rajnik M, Cuomo A, et al. (2021). *Features, Evaluation, and Treatment of Coronavirus (COVID-19)* [Updated 2021 Jan 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; - . Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554776/>
- Cecconi, M., Piovani, D., Brunetta, E., Aghemo, A., Greco, M., Ciccarelli, M., Angelini, C., Voza, A., Omodei, P., Vespa, E., Pugliese, N., Parigi, T. L., Folci, M., Danese, S., & Bonovas, S. (2020). Early Predictors of Clinical Deterioration in a Cohort of 239 Patients Hospitalized for Covid-19

- Infection in Lombardy, Italy. *Journal of clinical medicine*, 9(5), 1548.  
<https://doi.org/10.3390/jcm9051548>
- Chan, J. F., To, K. K., Tse, H., Jin, D. Y., & Yuen, K. Y. (2013). Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends in microbiology*, 21(10), 544–555.  
<https://doi.org/10.1016/j.tim.2013.05.005>
- Chen, W., Zheng, K. I., Liu, S., Yan, Z., Xu, C., & Qiao, Z. (2020). Plasma CRP level is positively associated with the severity of COVID-19. *Annals of clinical microbiology and antimicrobials*, 19(1), 18.  
<https://doi.org/10.1186/s12941-020-00362-2>
- Cheng, L., Li, H., Li, L., Liu, C., Yan, S., Chen, H., & Li, Y. (2020). Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Journal of clinical laboratory analysis*, 34(10), e23618.  
<https://doi.org/10.1002/jcla.23618>
- Ciceri, F., Beretta, L., Scandroglio, A. M., Colombo, S., Landoni, G., Ruggeri, A., Peccatori, J., D'Angelo, A., De Cobelli, F., Rovere-Querini, P., Tresoldi, M., Dagna, L., & Zangrillo, A. (2020). Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine*, 22(2), 95–97. Advance online publication.
- COVID-19 Treatment Guidelines Panel. (2020). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. *National Institutes of Health*. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed [2021 Jan].
- D'Amico, F., Baumgart, D. C., Danese, S., & Peyrin-Biroulet, L. (2020). Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, 18(8), 1663–1672. <https://doi.org/10.1016/j.cgh.2020.04.001>



- Darooghegi Mofrad, M., Milajerdi, A., Koohdani, F., Surkan, P. J., & Azadbakht, L. (2019). Garlic Supplementation Reduces Circulating C-reactive Protein, Tumor Necrosis Factor, and Interleukin-6 in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *The Journal of nutrition*, 149(4), 605–618. <https://doi.org/10.1093/jn/nxy310>
- de Souza, T. H., Nadal, J. A., Nogueira, R., Pereira, R. M., & Brandão, M. B. (2020). Clinical manifestations of children with COVID-19: A systematic review. *Pediatric pulmonology*, 55(8), 1892–1899. <https://doi.org/10.1002/ppul.24885>
- Dhama, K., Khan, S., Tiwari, R., Sircar, S., Bhat, S., Malik, Y. S., Singh, K. P., Chaicumpa, W., Bonilla-Aldana, D. K., & Rodriguez-Morales, A. J. (2020). Coronavirus Disease 2019-COVID-19. *Clinical microbiology reviews*, 33(4), e00028-20. <https://doi.org/10.1128/CMR.00028-20>
- Dick, A. G., Magill, N., White, T., Kokkinakis, M., & Norman-Taylor, F. (2019). C-reactive protein: what to expect after bony hip surgery for nonambulatory children and adolescents with cerebral palsy. *Journal of pediatric orthopedics. Part B*, 28(4), 309–313. <https://doi.org/10.1097/BPB.0000000000000634>
- Dhochak, N., Singhal, T., Kabra, S. K., & Lodha, R. (2020). Pathophysiology of COVID-19: Why Children Fare Better than Adults?. *Indian journal of pediatrics*, 87(7), 537–546. <https://doi.org/10.1007/s12098-020-03322-y>
- Ding, Q., Lu, P., Fan, Y., Xia, Y., & Liu, M. (2020). The clinical characteristics of pneumonia patients coinfecting with 2019 novel coronavirus and influenza virus in Wuhan, China. *Journal of medical virology*, 92(9), 1549–1555. <https://doi.org/10.1002/jmv.25781>
- Diriba, K., Awulachew, E., & Getu, E. (2020). The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. *European journal of medical research*, 25(1), 39. <https://doi.org/10.1186/s40001-020-00439-w>

- Diwakarla, S., Fothergill, L. J., Fakhry, J., Callaghan, B., & Furness, J. B. (2017). Heterogeneity of enterochromaffin cells within the gastrointestinal tract. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*, 29(6), 10.1111/nmo.13101. <https://doi.org/10.1111/nmo.13101>
- Eccles R. (2005). Understanding the symptoms of the common cold and influenza. *The Lancet. Infectious diseases*, 5(11), 718–725. [https://doi.org/10.1016/S1473-3099\(05\)70270-X](https://doi.org/10.1016/S1473-3099(05)70270-X)
- Elshazli, R. M., Toraih, E. A., Elgaml, A., El-Mowafy, M., El-Mesery, M., Amin, M. N., Hussein, M. H., Killackey, M. T., Fawzy, M. S., & Kandil, E. (2020). Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. *PloS one*, 15(8), e0238160. <https://doi.org/10.1371/journal.pone.0238160>
- Eschborn, S., & Weitkamp, J. H. (2019). Procalcitonin versus C-reactive protein: review of kinetics and performance for diagnosis of neonatal sepsis. *Journal of perinatology : official journal of the California Perinatal Association*, 39(7), 893–903. <https://doi.org/10.1038/s41372-019-0363-4>
- Fadila, M. F., & Wool, K. J. (2015). Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. *North American journal of medical sciences*, 7(3), 122–124. <https://doi.org/10.4103/1947-2714.153926>
- Farooqi, F., Dhawan, N., Morgan, R., Dinh, J., Nedd, K., & Yatzkan, G. (2020). Treatment of Severe COVID-19 with Tocilizumab Mitigates Cytokine Storm and Averts Mechanical Ventilation During Acute Respiratory Distress: A Case Report and Literature Review. *Tropical medicine and infectious disease*, 5(3), 112. <https://doi.org/10.3390/tropicalmed5030112>
- Figliozzi, S., Masci, P. G., Ahmadi, N., Tondi, L., Koutli, E., Aimo, A., Stamatelopoulos, K., Dimopoulos, M. A., Caforio, A., & Georgiopoulos, G. (2020). Predictors of adverse prognosis in COVID-19: A systematic review

and meta-analysis. *European journal of clinical investigation*, 50(10), e13362. <https://doi.org/10.1111/eci.13362>

Fu, L., Wang, B., Yuan, T., Chen, X., Ao, Y., Fitzpatrick, T., Li, P., Zhou, Y., Lin, Y. F., Duan, Q., Luo, G., Fan, S., Lu, Y., Feng, A., Zhan, Y., Liang, B., Cai, W., Zhang, L., Du, X., Li, L., ... Zou, H. (2020). Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *The Journal of infection*, 80(6), 656–665. <https://doi.org/10.1016/j.jinf.2020.03.041>

Galanopoulos, M., Gkeros, F., Doukatas, A., Karianakis, G., Pontas, C., Tsoukalas, N., Viazis, N., Liatsos, C., & Mantzaris, G. J. (2020). COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. *World journal of gastroenterology*, 26(31), 4579–4588. <https://doi.org/10.3748/wjg.v26.i31.4579>

Galdiero, M., & Napoli, C. (2020). COVID-19: Do not be phobic from fever. *Journal of infection and public health*, 13(7), 938. <https://doi.org/10.1016/j.jiph.2020.06.003>

Gallo Marin, B., Aghagoli, G., Lavine, K., Yang, L., Siff, E. J., Chiang, S. S., Salazar-Mather, T. P., Dumenco, L., Savaria, M. C., Aung, S. N., Flanigan, T., & Michelow, I. C. (2021). Predictors of COVID-19 severity: A literature review. *Reviews in medical virology*, 31(1), 1–10. <https://doi.org/10.1002/rmv.2146>

Gautret, P., Million, M., Jarrot, P. A., Camoin-Jau, L., Colson, P., Fenollar, F., Leone, M., La Scola, B., Devaux, C., Gaubert, J. Y., Mege, J. L., Vitte, J., Melenotte, C., Rolain, J. M., Parola, P., Lagier, J. C., Brouqui, P., & Raoult, D. (2020). Natural history of COVID-19 and therapeutic options. *Expert review of clinical immunology*, 16(12), 1159–1184. <https://doi.org/10.1080/1744666X.2021.1847640>

Ghahramani, S., Tabrizi, R., Lankarani, K. B., Kashani, S., Rezaei, S., Zeidi, N., Akbari, M., Heydari, S. T., Akbari, H., Nowrouzi-Sohrabi, P., & Ahmadizar, F. (2020). Laboratory features of severe vs. non-severe COVID-

- 19 patients in Asian populations: a systematic review and meta-analysis. *European journal of medical research*, 25(1), 30. <https://doi.org/10.1186/s40001-020-00432-3>
- Ghayda, R. A., Lee, J., Lee, J. Y., Kim, D. K., Lee, K. H., Hong, S. H., Han, Y. J., Kim, J. S., Yang, J. W., Kronbichler, A., Smith, L., Koyanagi, A., Jacob, L., & Shin, J. I. (2020). Correlations of Clinical and Laboratory Characteristics of COVID-19: A Systematic Review and Meta-Analysis. *International journal of environmental research and public health*, 17(14), 5026. <https://doi.org/10.3390/ijerph17145026>
- Giagulli, V. A., Guastamacchia, E., Magrone, T., Jirillo, E., Lisco, G., De Pergola, G., & Triggiani, V. (2021). Worse progression of COVID-19 in men: Is testosterone a key factor?. *Andrology*, 9(1), 53–64. <https://doi.org/10.1111/andr.12836>
- Gidari, A., Nofri, M., Saccarelli, L., Bastianelli, S., Sabbatini, S., Bozza, S., Camilloni, B., Fusco-Moffa, I., Monari, C., De Robertis, E., Mencacci, A., & Francisci, D. (2021). Is recurrence possible in coronavirus disease 2019 (COVID-19)? Case series and systematic review of literature. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*, 40(1), 1–12. <https://doi.org/10.1007/s10096-020-04057-6>
- Goldspink, D. A., Reimann, F., & Gribble, F. M. (2018). Models and Tools for Studying Enteroendocrine Cells. *Endocrinology*, 159(12), 3874–3884. <https://doi.org/10.1210/en.2018-00672>
- Hamming, I., Timens, W., Bulthuis, M. L., Lely, A. T., Navis, G., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of pathology*, 203(2), 631–637. <https://doi.org/10.1002/path.1570>
- Han, C., Duan, C., Zhang, S., Spiegel, B., Shi, H., Wang, W., Zhang, L., Lin, R., Liu, J., Ding, Z., & Hou, X. (2020). Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral

- RNA Testing, and Outcomes. *The American journal of gastroenterology*, *115*(6), 916–923.  
<https://doi.org/10.14309/ajg.0000000000000664>
- Han, J., Shi, L. X., Xie, Y., Zhang, Y. J., Huang, S. P., Li, J. G., Wang, H. R., & Shao, S. F. (2020). Analysis of factors affecting the prognosis of COVID-19 patients and viral shedding duration. *Epidemiology and infection*, *148*, e125.  
<https://doi.org/10.1017/S0950268820001399>
- Henry, B. M., Benoit, S. W., de Oliveira, M., Hsieh, W. C., Benoit, J., Ballout, R. A., Plebani, M., & Lippi, G. (2020). Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. *Clinical biochemistry*, *81*, 1–8.  
<https://doi.org/10.1016/j.clinbiochem.2020.05.012>
- Huang, I., Pranata, R., Lim, M. A., Oehadian, A., & Alisjahbana, B. (2020). C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Therapeutic advances in respiratory disease*, *14*, 1753466620937175.  
<https://doi.org/10.1177/1753466620937175>
- Huppert, L. A., Matthay, M. A., & Ware, L. B. (2019). Pathogenesis of Acute Respiratory Distress Syndrome. *Seminars in respiratory and critical care medicine*, *40*(1), 31–39. <https://doi.org/10.1055/s-0039-1683996>
- Izcovich, A., Ragusa, M. A., Tortosa, F., Lavena Marzio, M. A., Agnoletti, C., Bengolea, A., Ceirano, A., Espinosa, F., Saavedra, E., Sanguine, V., Tassara, A., Cid, C., Catalano, H. N., Agarwal, A., Foroutan, F., & Rada, G. (2020). Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PloS one*, *15*(11), e0241955.  
<https://doi.org/10.1371/journal.pone.0241955>
- Ji, P., Zhu, J., Zhong, Z., Li, H., Pang, J., Li, B., & Zhang, J. (2020). Association of elevated inflammatory markers and severe COVID-19: A meta-analysis. *Medicine*, *99*(47), e23315.  
<https://doi.org/10.1097/MD.00000000000023315>

- Jin, J. M., Bai, P., He, W., Wu, F., Liu, X. F., Han, D. M., Liu, S., & Yang, J. K. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Frontiers in public health*, 8, 152. <https://doi.org/10.3389/fpubh.2020.00152>
- Jutzeler, C. R., Bourguignon, L., Weis, C. V., Tong, B., Wong, C., Rieck, B., Pargger, H., Tschudin-Sutter, S., Egli, A., Borgwardt, K., & Walter, M. (2020). Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis. *Travel medicine and infectious disease*, 37, 101825. <https://doi.org/10.1016/j.tmaid.2020.101825>
- Kemenkes. (2020). *Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.01/MENKES/413/2020 039 tentang Pedoman Pencegahan dan Pengendalian Coronavirus Disease 2019 (Covid-19)*
- Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z., & Harky, A. (2020). The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life sciences*, 254, 117788. <https://doi.org/10.1016/j.lfs.2020.117788>
- Kushner, I., & Agrawal, A. (2007). CRP can play both pro-inflammatory and anti-inflammatory roles. *Molecular immunology*, 44(4), 670–671. <https://doi.org/10.1016/j.molimm.2006.02.001>
- Li, L. Q., Huang, T., Wang, Y. Q., Wang, Z. P., Liang, Y., Huang, T. B., Zhang, H. Y., Sun, W., & Wang, Y. (2020). COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of medical virology*, 92(6), 577–583. <https://doi.org/10.1002/jmv.25757>
- Li, M. Y., Li, L., Zhang, Y., & Wang, X. S. (2020). Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infectious diseases of poverty*, 9(1), 45. <https://doi.org/10.1186/s40249-020-00662-x>
- Liguoro, I., Pilotto, C., Bonanni, M., Ferrari, M. E., Pusiol, A., Nocerino, A., Vidal, E., & Cogo, P. (2020). SARS-COV-2 infection in children and

- newborns: a systematic review. *European journal of pediatrics*, 179(7), 1029–1046. <https://doi.org/10.1007/s00431-020-03684-7>
- Ludvigsson J. F. (2020). Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta paediatrica (Oslo, Norway : 1992)*, 109(6), 1088–1095. <https://doi.org/10.1111/apa.15270>
- Luo, X., Zhou, W., Yan, X., Guo, T., Wang, B., Xia, H., Ye, L., Xiong, J., Jiang, Z., Liu, Y., Zhang, B., & Yang, W. (2020). Prognostic Value of C-Reactive Protein in Patients With Coronavirus 2019. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 71(16), 2174–2179. <https://doi.org/10.1093/cid/ciaa641>
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA neurology*, 77(6), 683–690. <https://doi.org/10.1001/jamaneurol.2020.1127>
- Marchioni, E., & Minoli, L. (2010). Headache attributed to infections nosography and differential diagnosis. *Handbook of clinical neurology*, 97, 601–626. [https://doi.org/10.1016/S0072-9752\(10\)97052-8](https://doi.org/10.1016/S0072-9752(10)97052-8)
- Mehta, N. S., Mytton, O. T., Mullins, E., Fowler, T. A., Falconer, C. L., Murphy, O. B., Langenberg, C., Jayatunga, W., Eddy, D. H., & Nguyen-Van-Tam, J. S. (2020a). SARS-CoV-2 (COVID-19): What Do We Know About Children? A Systematic Review. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 71(9), 2469–2479. <https://doi.org/10.1093/cid/ciaa556>
- Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., & HLH Across Speciality Collaboration, UK (2020b). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*, 395(10229), 1033–1034. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)

- Mjaess, G., Karam, A., Aoun, F., Albisinni, S., & Roumeguère, T. (2020). COVID-19 and the male susceptibility: the role of ACE2, TMPRSS2 and the androgen receptor. *Progres en urologie : journal de l'Association française d'urologie et de la Societe française d'urologie*, 30(10), 484–487. <https://doi.org/10.1016/j.purol.2020.05.007>
- Mo, P., Xing, Y., Xiao, Y., Deng, L., Zhao, Q., Wang, H., Xiong, Y., Cheng, Z., Gao, S., Liang, K., Luo, M., Chen, T., Song, S., Ma, Z., Chen, X., Zheng, R., Cao, Q., Wang, F., & Zhang, Y. (2020). Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa270. Advance online publication. <https://doi.org/10.1093/cid/ciaa270>
- Mohamed, M. S., Moulin, T. C., & Schiöth, H. B. (2021). Sex differences in COVID-19: the role of androgens in disease severity and progression. *Endocrine*, 71(1), 3–8. <https://doi.org/10.1007/s12020-020-02536-6>
- Muyayalo, K. P., Huang, D. H., Zhao, S. J., Xie, T., Mor, G., & Liao, A. H. (2020). COVID-19 and Treg/Th17 imbalance: Potential relationship to pregnancy outcomes. *American journal of reproductive immunology (New York, N.Y. : 1989)*, 84(5), e13304. <https://doi.org/10.1111/aji.13304>
- Navas-Blanco, J. R., & Dudaryk, R. (2020). Management of Respiratory Distress Syndrome due to COVID-19 infection. *BMC anesthesiology*, 20(1), 177. <https://doi.org/10.1186/s12871-020-01095-7>
- Nehring SM, Goyal A, Bansal P, Patel BC. (2020). *C Reactive Protein*. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–
- Ou, M., Zhu, J., Ji, P., Li, H., Zhong, Z., Li, B., Pang, J., Zhang, J., & Zheng, X. (2020). Risk factors of severe cases with COVID-19: a meta-analysis. *Epidemiology and infection*, 148, e175. <https://doi.org/10.1017/S095026882000179X>



- Pan, L., Mu, M., Yang, P., Sun, Y., Wang, R., Yan, J., Li, P., Hu, B., Wang, J., Hu, C., Jin, Y., Niu, X., Ping, R., Du, Y., Li, T., Xu, G., Hu, Q., & Tu, L. (2020). Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *The American journal of gastroenterology*, *115*(5), 766–773. <https://doi.org/10.14309/ajg.0000000000000620>
- Parasher A. (2021). COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. *Postgraduate medical journal*, *97*(1147), 312–320. <https://doi.org/10.1136/postgradmedj-2020-138577>
- Pascarella, G., Strumia, A., Piliago, C., Bruno, F., Del Buono, R., Costa, F., Scarlata, S., & Agrò, F. E. (2020). COVID-19 diagnosis and management: a comprehensive review. *Journal of internal medicine*, *288*(2), 192–206. <https://doi.org/10.1111/joim.13091>
- Patel, K. P., Patel, P. A., Vunnam, R. R., Hewlett, A. T., Jain, R., Jing, R., & Vunnam, S. R. (2020). Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*, *128*, 104386. <https://doi.org/10.1016/j.jcv.2020.104386>
- Patel N. A. (2020). Pediatric COVID-19: Systematic review of the literature. *American journal of otolaryngology*, *41*(5), 102573. <https://doi.org/10.1016/j.amjoto.2020.102573>
- Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*, *286*(3), 327–334. <https://doi.org/10.1001/jama.286.3.327>
- Pedersen, S. F., & Ho, Y. C. (2020). SARS-CoV-2: a storm is raging. *The Journal of clinical investigation*, *130*(5), 2202–2205. <https://doi.org/10.1172/JCI137647>
- Pedomana Tatalaksana Covid-19. (2021). Edisi 3.

- Peluso, L., Abella, B. S., Ferrer, R., Kucher, N., Sunde, K., & Taccone, F. S. (2021). Fever management in COVID-19 patients. *Minerva anesthesiologica*, 87(1), 1–3. <https://doi.org/10.23736/S0375-9393.20.15195-2>
- Penfield, C. A., Brubaker, S. G., Limaye, M. A., Lighter, J., Ratner, A. J., Thomas, K. M., Meyer, J. A., & Roman, A. S. (2020). Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. *American journal of obstetrics & gynecology MFM*, 2(3), 100133. <https://doi.org/10.1016/j.ajogmf.2020.100133>
- Pepys, M. B. (2021). C-reactive protein predicts outcome in COVID-19: is it also a therapeutic target? *European Heart Journal*. <https://doi.org/10.1093/eurheartj/ehab169>
- Perico, L., Benigni, A., Casiraghi, F., Ng, L., Renia, L., & Remuzzi, G. (2021). Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nature reviews. Nephrology*, 17(1), 46–64. <https://doi.org/10.1038/s41581-020-00357-4>
- Poggiali, E., Zaino, D., Immovilli, P., Rovero, L., Losi, G., Dacrema, A., Nuccetelli, M., Vadacca, G. B., Guidetti, D., Vercelli, A., Magnacavallo, A., Bernardini, S., & Terracciano, C. (2020). Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. *Clinica chimica acta; international journal of clinical chemistry*, 509, 135–138. <https://doi.org/10.1016/j.cca.2020.06.012>
- Pollard, C. A., Morran, M. P., & Nestor-Kalinoski, A. L. (2020). The COVID-19 pandemic: a global health crisis. *Physiological genomics*, 52(11), 549–557. <https://doi.org/10.1152/physiolgenomics.00089.2020>
- Potere, N., Batticciotto, A., Vecchié, A., Porreca, E., Cappelli, A., Abbate, A., Dentali, F., & Bonaventura, A. (2021). The role of IL-6 and IL-6 blockade in COVID-19. *Expert review of clinical immunology*, 1–17. Advance online publication. <https://doi.org/10.1080/1744666X.2021.1919086>

- Rizzo, A. N., Aman, J., van Nieuw Amerongen, G. P., & Dudek, S. M. (2015). Targeting Abl kinases to regulate vascular leak during sepsis and acute respiratory distress syndrome. *Arteriosclerosis, thrombosis, and vascular biology*, 35(5), 1071–1079. <https://doi.org/10.1161/ATVBAHA.115.305085>
- Rod, J. E., Oviedo-Trespalacios, O., & Cortes-Ramirez, J. (2020). A brief-review of the risk factors for covid-19 severity. *Revista de saude publica*, 54, 60. <https://doi.org/10.11606/s1518-8787.2020054002481>
- Sahu, B. R., Kampa, R. K., Padhi, A., & Panda, A. K. (2020). C-reactive protein: A promising biomarker for poor prognosis in COVID-19 infection. *Clinica chimica acta; international journal of clinical chemistry*, 509, 91–94. <https://doi.org/10.1016/j.cca.2020.06.013>
- Shahid, Z., Kalayanamitra, R., McClafferty, B., Kepko, D., Ramgobin, D., Patel, R., Aggarwal, C. S., Vunnam, R., Sahu, N., Bhatt, D., Jones, K., Golamari, R., & Jain, R. (2020). COVID-19 and Older Adults: What We Know. *Journal of the American Geriatrics Society*, 68(5), 926–929. <https://doi.org/10.1111/jgs.16472>
- Shanes, E. D., Mithal, L. B., Otero, S., Azad, H. A., Miller, E. S., & Goldstein, J. A. (2020). Placental Pathology in COVID-19. *American journal of clinical pathology*, 154(1), 23–32. <https://doi.org/10.1093/ajcp/aqaa089>
- Sheriff, A., Kayser, S., Brunner, P., & Vogt, B. (2021). C-Reactive Protein Triggers Cell Death in Ischemic Cells. *Frontiers in immunology*, 12, 630430. <https://doi.org/10.3389/fimmu.2021.630430>
- Singh, S. P., Pritam, M., Pandey, B., & Yadav, T. P. (2021). Microstructure, pathophysiology, and potential therapeutics of COVID-19: A comprehensive review. *Journal of medical virology*, 93(1), 275–299. <https://doi.org/10.1002/jmv.26254>
- Slaats, J., Ten Oever, J., van de Veerdonk, F. L., & Netea, M. G. (2016). IL-1 $\beta$ /IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. *PLoS pathogens*, 12(12), e1005973. <https://doi.org/10.1371/journal.ppat.1005973>

- Soraya, G. V., & Ulhaq, Z. S. (2020). Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. *Medicina clinica*, 155(4), 143–151. <https://doi.org/10.1016/j.medcli.2020.05.017>
- Suwanwongse, K., & Shabarek, N. (2020). Rhabdomyolysis as a Presentation of 2019 Novel Coronavirus Disease. *Cureus*, 12(4), e7561. <https://doi.org/10.7759/cureus.7561>
- Takagi, H., Kuno, T., Yokoyama, Y., Ueyama, H., Matsushiro, T., Hari, Y., & Ando, T. (2021). Meta-regression of COVID-19 prevalence/fatality on socioeconomic characteristics of data from top 50 U.S. large cities. *Journal of medical virology*, 93(2), 595–598. <https://doi.org/10.1002/jmv.26335>
- Takahashi, T., Ellingson, M. K., Wong, P., Israelow, B., Lucas, C., Klein, J., Silva, J., Mao, T., Oh, J. E., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Liu, F., Meir, A., Sun, J., Wang, E. Y., Casanovas-Massana, A., Wyllie, A. L., Vogels, C., ... Iwasaki, A. (2020). Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature*, 588(7837), 315–320. <https://doi.org/10.1038/s41586-020-2700-3>
- Tan, C., Huang, Y., Shi, F., Tan, K., Ma, Q., Chen, Y., Jiang, X., & Li, X. (2020). C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *Journal of medical virology*, 92(7), 856–862. <https://doi.org/10.1002/jmv.25871>
- Tang, D., Comish, P., & Kang, R. (2020). The hallmarks of COVID-19 disease. *PLoS pathogens*, 16(5), e1008536. <https://doi.org/10.1371/journal.ppat.1008536>
- Terpos, E., Ntanasis-Stathopoulos, I., Elalamy, I., Kastritis, E., Sergentanis, T. N., Politou, M., Psaltopoulou, T., Gerotziafas, G., & Dimopoulos, M. A. (2020). Hematological findings and complications of COVID-19. *American journal of hematology*, 95(7), 834–847. <https://doi.org/10.1002/ajh.25829>
- Thompson, J. L., Nguyen, L. M., Noble, K. N., & Aronoff, D. M. (2020). COVID-19-related disease severity in pregnancy. *American journal of*

*reproductive immunology* (New York, N.Y. : 1989), 84(5), e13339.  
<https://doi.org/10.1111/aji.13339>

- Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., ... Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine*, 169(7), 467–473. <https://doi.org/10.7326/M18-0850>
- Volanakis J. E. (2001). Human C-reactive protein: expression, structure, and function. *Molecular immunology*, 38(2-3), 189–197. [https://doi.org/10.1016/s0161-5890\(01\)00042-6](https://doi.org/10.1016/s0161-5890(01)00042-6)
- Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, 323(11), 1061–1069. <https://doi.org/10.1001/jama.2020.1585>
- Wang, G., Wu, C., Zhang, Q., Wu, F., Yu, B., Lv, J., Li, Y., Li, T., Zhang, S., Wu, C., Wu, G., & Zhong, Y. (2020). C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. *Open forum infectious diseases*, 7(5), ofaa153. <https://doi.org/10.1093/ofid/ofaa153>
- Wang L. (2020). C-reactive protein levels in the early stage of COVID-19. *Medecine et maladies infectieuses*, 50(4), 332–334. <https://doi.org/10.1016/j.medmal.2020.03.007>
- Weng, L. M., Su, X., & Wang, X. Q. (2021). Pain Symptoms in Patients with Coronavirus Disease (COVID-19): A Literature Review. *Journal of pain research*, 14, 147–159. <https://doi.org/10.2147/JPR.S269206>
- Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*, 324(8), 782–793. <https://doi.org/10.1001/jama.2020.12839>

- Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., & Yang, C. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, behavior, and immunity*, *87*, 18–22. <https://doi.org/10.1016/j.bbi.2020.03.031>
- Xu, X. W., Wu, X. X., Jiang, X. G., Xu, K. J., Ying, L. J., Ma, C. L., Li, S. B., Wang, H. Y., Zhang, S., Gao, H. N., Sheng, J. F., Cai, H. L., Qiu, Y. Q., & Li, L. J. (2020a). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ (Clinical research ed.)*, *368*, m606. <https://doi.org/10.1136/bmj.m606>
- Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F. S. (2020b). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory medicine*, *8*(4), 420–422. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
- Yang, A. P., Liu, J. P., Tao, W. Q., & Li, H. M. (2020). The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *International immunopharmacology*, *84*, 106504. <https://doi.org/10.1016/j.intimp.2020.106504>
- Yasuhara, J., Kuno, T., Takagi, H., & Sumitomo, N. (2020). Clinical characteristics of COVID-19 in children: A systematic review. *Pediatric pulmonology*, *55*(10), 2565–2575. <https://doi.org/10.1002/ppul.24991>
- Ye, Q., Wang, B., Zhang, T., Xu, J., & Shang, S. (2020). The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *American journal of physiology. Gastrointestinal and liver physiology*, *319*(2), G245–G252. <https://doi.org/10.1152/ajpgi.00148.2020>
- Zaigham, M., & Andersson, O. (2020). Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta obstetrica et gynecologica Scandinavica*, *99*(7), 823–829. <https://doi.org/10.1111/aogs.13867>

- Zeng, F., Huang, Y., Guo, Y., Yin, M., Chen, X., Xiao, L., & Deng, G. (2020). Association of inflammatory markers with the severity of COVID-19: A meta-analysis. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*, *96*, 467–474. <https://doi.org/10.1016/j.ijid.2020.05.055>
- Zhang, J., Lee, K. S., Ang, L. W., Leo, Y. S., & Young, B. E. (2020a). Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected With COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *71*(16), 2199–2206. <https://doi.org/10.1093/cid/ciaa576>
- Zhang, Z. L., Hou, Y. L., Li, D. T., & Li, F. Z. (2020b). Laboratory findings of COVID-19: a systematic review and meta-analysis. *Scandinavian journal of clinical and laboratory investigation*, *80*(6), 441–447. <https://doi.org/10.1080/00365513.2020.1768587>
- Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)*, *395*(10229), 1054–1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
- Zhu, J., Ji, P., Pang, J., Zhong, Z., Li, H., He, C., Zhang, J., & Zhao, C. (2020). Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *Journal of medical virology*, *92*(10), 1902–1914. <https://doi.org/10.1002/jmv.25884>
- Zimmermann, P., & Curtis, N. (2020). Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Archives of disease in childhood*, archdischild-2020-320338. Advance online publication. <https://doi.org/10.1136/archdischild-2020-320338>