

## Modelling and analysis of complement system signalling pathways: Roles of C3, C5a and pro-inflammatory cytokines in SARS-CoV-2 infection

### Experimental observations

### References

C3 level has been reported high in mild, moderate, and severe conditions.	(Henry et al., 2021; Ma et al., 2021; Showers et al., 2021; B. Yan et al., 2021)
The concentration level of complement peptide C5a has been reported to be elevated.	(Alosaimi et al., 2021; Busch et al., 2020; Kurtovic & Beeson, 2021; Ma et al., 2021; Marina Noris et al., 2020; Prendecki et al., 2020; Ram Kumar Pandian et al., 2020; Showers et al., 2021)
Expression level of terminal complement complex MAC is high in ICU admitted patients compared to general wards admissions	(Alosaimi et al., 2021; De Nooijer et al., 2021; Ma et al., 2021; Marina Noris et al., 2020; Showers et al., 2021)
Concentration of CR1 largely decreased in severely affected Patients.	(Kisserli et al., 2021)
Concentration Level of PICyts highly expressed in the form of cytokine storm.	(Alosaimi et al., 2021; García, 2020; Merad & Martin, 2020)
Lymphocyte counted in the severe and critical patients reported significantly low.	(Showers et al., 2021; W. Yan et al., 2021)
Level of negative regulatory protein FI has been identified significantly low.	(Alosaimi et al., 2021)
Leucocytes such as Inflammatory Cells (ICs) neutrophils, and macrophages counted to be high.	(Busch et al., 2020; S. Mueller-Ortiz et al., 2017; Ram Kumar Pandian et al., 2020; Showers et al., 2021; W. Yan et al., 2021)
Lower lymphocytes have been reported in CBC reports of COVID-19 patients.	(Kazancioglu et al., 2020)
Concentration level of IFN $\alpha$ and IFN $\beta$ have been reported low. It has been known that C5a suppressed IFN $\beta$ production.	(Contoli et al., 2021; S. L. Mueller-Ortiz et al., 2017)
Type 1 interferon IFN $\alpha$ and IFN $\beta$ treatment against SARSCoV2 significantly has reduced the viral titers.	(Mantlo et al., 2020)
Expression level of DAF reported high in COVID-19.	(Lage et al., 2022)

**Table1.** For SARS-CoV-2 infection experimentally observed concentration levels of different entities.

Modelling and analysis of complement system signalling pathways: Roles of C3, C5a and pro-inflammatory cytokines in SARS-CoV-2 infection

## References

- Alosaimi, B., Mubarak, A., Hamed, M. E., Almutairi, A. Z., Alrashed, A. A., AlJuryyan, A., Enani, M., Alenzi, F. Q., & Alturaiki, W. (2021). Complement Anaphylatoxins and Inflammatory Cytokines as Prognostic Markers for COVID-19 Severity and In-Hospital Mortality. *Frontiers in Immunology*, *12*(July), 1–13. <https://doi.org/10.3389/fimmu.2021.668725>
- Busch, M. H., Timmermans, S. A. M. E. G., Nagy, M., Visser, M., Huckriede, J., Aendekerk, J. P., De Vries, F., Potjewijd, J., Jallah, B., Ysermans, R., Oude Lashof, A. M. L., Breedveld, P. H., Van De Poll, M. C. G., Van De Horst, I. C. C., Van Bussel, B. C. T., Theunissen, R. O. M. F. I. H., Spronk, H. M. H., Damoiseaux, J. G. M. C., Ten Cate, H., ... Van Paassen, P. (2020). Neutrophils and Contact Activation of Coagulation as Potential Drivers of COVID-19. *Circulation*, *142*(18), 1787–1790. <https://doi.org/10.1161/CIRCULATIONAHA.120.050656>
- Contoli, M., Papi, A., Tomassetti, L., Rizzo, P., Vieceli Dalla Sega, F., Fortini, F., Torsani, F., Morandi, L., Ronzoni, L., Zucchetti, O., Pavasini, R., Fogagnolo, A., Volta, C. A., Bartlett, N. W., Johnston, S. L., Spadaro, S., & Campo, G. (2021). Blood Interferon- $\alpha$  Levels and Severity, Outcomes, and Inflammatory Profiles in Hospitalized COVID-19 Patients. *Frontiers in Immunology*, *12*(March), 1–10. <https://doi.org/10.3389/fimmu.2021.648004>
- De Nooijer, A. H., Grondman, I., Janssen, N. A. F., Netea, M. G., Willems, L., Van De Veerdonk, F. L., Giamarellos-Bourboulis, E. J., Toonen, E. J. M., Joosten, L. A. B., Jaeger, M., Dijkstra, H., Lemmers, H., Van Emst, L., Schraa, K., Jacobs, C., Hijmans, A., Jansen, T., Weren, F., Fransman, L., ... Klop-Riehl, M. (2021). Complement Activation in the Disease Course of Coronavirus Disease 2019 and Its Effects on Clinical Outcomes. *Journal of Infectious Diseases*, *223*(2), 214–224. <https://doi.org/10.1093/infdis/jiaa646>
- García, L. F. (2020). Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Frontiers in Immunology*, *11*(June), 4–8. <https://doi.org/10.3389/fimmu.2020.01441>
- Henry, B. M., Szergyuk, I., de Oliveira, M. H. S., Lippi, G., Benoit, J. L., Vikse, J., & Benoit, S. W. (2021). Complement levels at admission as a reflection of coronavirus disease 2019 (COVID-19) severity state. *Journal of Medical Virology*, *93*(9), 5515–5522. <https://doi.org/10.1002/jmv.27077>
- Kazancioglu, S., Bastug, A., Ozbay, B. O., Kemirtlek, N., & Bodur, H. (2020). The Role of Hematological Parameters in Patients with Coronavirus Disease 2019 and Influenza Virus Infection. *Epidemiology and Infection*. <https://doi.org/10.1017/S095026882000271X>
- Kisserli, A., Schneider, N., Audonnet, S., Tabary, T., Goury, A., Cousson, J., Mahmoudi, R., Bani-Sadr, F., Kanagaratnam, L., Jolly,

Modelling and analysis of complement system signalling pathways: Roles of C3, C5a and pro-inflammatory cytokines in SARS-CoV-2 infection

- D., & Cohen, J. H. (2021). Acquired decrease of the C3b/C4b receptor (CR1, CD35) and increased C4d deposits on erythrocytes from ICU COVID-19 patients. *Immunobiology*, 226(3). <https://doi.org/10.1016/j.imbio.2021.152093>
- Kurtovic, L., & Beeson, J. G. (2021). Complement Factors in COVID-19 Therapeutics and Vaccines. *Trends in Immunology*, 42(2), 94–103. <https://doi.org/10.1016/j.it.2020.12.002>
- Lage, S. L., Rocco, J. M., Laidlaw, E., Rupert, A., Galindo, F., Kellogg, A., Kumar, P., Poon, R., Wortmann, G. W., Lisco, A., Manion, M., & Sereti, I. (2022). Activation of Complement Components on Circulating Blood Monocytes From COVID-19 Patients. *Frontiers in Immunology*, 13(February), 1–9. <https://doi.org/10.3389/fimmu.2022.815833>
- Ma, L., Sahu, S. K., Cano, M., Kuppaswamy, V., Bajwa, J., McPhatter, J., Pine, A., Meizlish, M. L., Goshua, G., Chang, C. H., Zhang, H., Price, C., Bahel, P., Rinder, H., Lei, T., Day, A., Reynolds, D., Wu, X., Schriefer, R., ... Kulkarni, H. S. (2021). Increased complement activation is a distinctive feature of severe SARS-CoV-2 infection. *Science Immunology*, 6(59), 1–17. <https://doi.org/10.1126/sciimmunol.abh2259>
- Mantlo, E., Bukreyeva, N., Maruyama, J., & Paessler, S. (2020). Antiviral activities of type I interferons to SARS-CoV-2 infection. *Antiviral Research*, 179. <https://doi.org/10.1016/j.antiviral.2020.104811>
- Marina Noris, Ariela Benigni, & Giuseppe Remuzzi. (2020). The case of complement activation in COVID-19 multiorgan impact. *Kidney International*, 98(2), 314–322. <https://doi.org/10.1016/j.kint.2020.05.013>
- Merad, M., & Martin, J. C. (2020). Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nature Reviews Immunology*, 20(6), 355–362. <https://doi.org/10.1038/s41577-020-0331-4>
- Mueller-Ortiz, S. L., Daniel G. Calame, N. S., Li, Y.-D., & Wetsel, R. A. (2017). The Complement Anaphylatoxins, C5a and C3a, Suppress Interferon-Beta Production in Response to *Listeria monocytogenes* by Inhibition of the Cyclic Dinucleotide-Activated Cytosolic Surveillance Pathway. *Immunol*, 198(8), 3237–3244. <https://doi.org/10.4049/jimmunol.1601420>
- Mueller-Ortiz, S., L., T., Calame, D. G., Shenoi, N., Li, Y.-D., & Wetsel, R. A. (2017). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical Rheumatology*, 198(8), 3237–3244. <https://doi.org/10.4049/jimmunol.1601420>
- Predecki, M., Clarke, C., Medjeral-Thomas, N., McAdoo, S. P., Sandhu, E., Peters, J. E., Thomas, D. C., Willicombe, M., Botto, M., & Pickering, M. C. (2020). Temporal changes in complement activation in haemodialysis patients with COVID-19 as a predictor of disease progression. *Clinical Kidney Journal*, 13(5), 889–896. <https://doi.org/10.1093/CKJ/SFAA192>

Modelling and analysis of complement system signalling pathways: Roles of C3, C5a and pro-inflammatory cytokines in SARS-CoV-2 infection

Ram Kumar Pandian, S., Arunachalam, S., Deepak, V., Kunjiappan, S., & Sundar, K. (2020). Targeting complement cascade: an alternative strategy for COVID-19. *3 Biotech*, *10*(11), 1–10. <https://doi.org/10.1007/s13205-020-02464-2>

Showers, C. R., Nuovo, G. J., Lakhanpal, A., Siegel, C. H., Aizer, J., Elreda, L., Halevi, A., Lai, A. R., Erkan, D., & Magro, C. M. (2021). A Covid-19 Patient with Complement-Mediated Coagulopathy and Severe Thrombosis. *Pathobiology*, *88*(1), 28–36. <https://doi.org/10.1159/000512503>

Yan, B., Freiwald, T., Chauss, D., Wang, L., West, E., Mirabelli, C., Zhang, C. J., Nichols, E. M., Malik, N., Gregory, R., Bantscheff, M., Ghidelli-Disse, S., Kolev, M., Frum, T., Spence, J. R., Sexton, J. Z., Alysandratos, K. D., Kotton, D. N., Pittaluga, S., ... Kazemian, M. (2021). SARS-CoV-2 drives JAK1/2-dependent local complement hyperactivation. *Science Immunology*, *6*(58), 1–19. <https://doi.org/10.1126/sciimmunol.abg0833>

Yan, W., Chen, D., Bigambo, F. M., Wei, H., Wang, X., & Xia, Y. (2021). Differences of blood cells, lymphocyte subsets and cytokines in COVID-19 patients with different clinical stages: a network meta-analysis. *BMC Infectious Diseases*, *21*(1), 1–9. <https://doi.org/10.1186/s12879-021-05847-9>