HLA Ligand Binding in Cytokine Storm Stage with Convalescent Plasma Therapy: A Cytotoxic Activity Switching-off

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Abstract— *The potential of Convalescent Plasma Therapy (CPT) as the last effort for immunocompromised COVID-19 patients are not controversial anymore, but the mechanism which supports the anti-ligand-binding and memory cell should be broadly known. While p53 mutation associated CD4 has not been ready, memory cells could not know the lymphocyte induced up-regulation in cytokine storm stage, made lymphopenia. Keyword setting of lymphopenia mechanism-COVID-19, searching in Science Direct and other search engines, is used in this Systematic Review PRISMA design.*

Immunocompromised patients including obese and old age is included, also Lymphocytopenia – ARDS, Diabetes Type 1. Cardiac arrest, cardiac arrhythmia, hypertension alone was excluded. References (15) that supported lymphocytopenia mechanism-COVID-19 are selected. About 15 million and 4,593 participants of COVID-19 patients with only 1½ Systematic Review due to the mechanism of lymphocytopenia and off reaction with CPT are recorded.

Lymphocytopenia cause by cytokine storm in week-2 COVID-19, while in low CD4 (Th) in this cytokine storm COVID-19, could be stronger and faster in week-1st in the second infection on person with diabetes. CPT serum, is the only way to switch-off cytotoxic activity, and increase the lymphocyte again.

Conclusions

CPT switch-off cytotoxic activity on Human Leucocyte Antigen (HLA) binding ligand in immunocompromised patients.

Keywords— Cytotoxic activity; HLA ligand binding; Lymphocytopenia; Lymphopenia; COVID-19; critical ARDS.

I. INTRODUCTION

Severe respiratory distress and/or hypoxemia or life-threatening (shock, multi-organ failure, or requiring mechanical ventilation), cause of DIC (lymphocytopenia), become the cause of mortality in cytokine storm stage COVID-19 pandemic.

Whereas the rate of viral PCR results turned from positive to negative with Convalescence Plasma Therapy (CPT) are reported, but the using of it, is hindered by complex therapy antiviral, chloroquine, antibiotic, and vaccination hope. In the population, the diagnostic with a rapid test based on IgG and IgM has colonized the ceremony of red zone COVID-19 area, whereas swab-PCR which chasing mass of people as market share and market segment till to each remote corner which is in a green zone even so.

Utmost CPT has not yet reached significant statistics proven although its 1,4 Odd Ratio between added CPT and control standard therapy only.[1] Diabetes and old-aged become the causa of 5,42% COVID-19 pandemic mortality.[2] Effective without the invasive mechanical ventilator and reduce the mortality in COVID-19 has been reported.[3] Mutation of p53 in low and middle neighborhood social economic status (nSES) associated to DM,[4] Hypoxia-DIC-Lymphocytopenia due to cytokine storm has become the mechanism of 2% mortality rate of week-2 COVID-19, low CD4 (helper T lymphocyte) in this

cytokine storm period which become an earlier week-1st period in the second infection (faster and stronger reaction).[5] On the other hand while the ligand could be lock by antibody marked by IgG or IgM in Convalescent Plasma Transfusion (CPT), the only way in Old age/ DM COVID-19 management. Hypooxide DIC as the cause of most 2% mortality rate in the COVID-19 pandemic, are ligand base in Diabetic patients.

II. METHOD

Using keyword of lymphopenia mechanism-COVID-19 searching in Science Direct and other search engines, highly preferred Systematic Review and Meta-analysis design. Lymphocytopenia - ARDS and Diabetes (Type 1 DM is included), besides other immunocompromised patients incl. obese. Cardiac arrests, cardiac arrhythmia, hypertension alone were excluded. PRISMA design is used to get and select the references with support the existence of the lymphopenia mechanism in COVID-19.

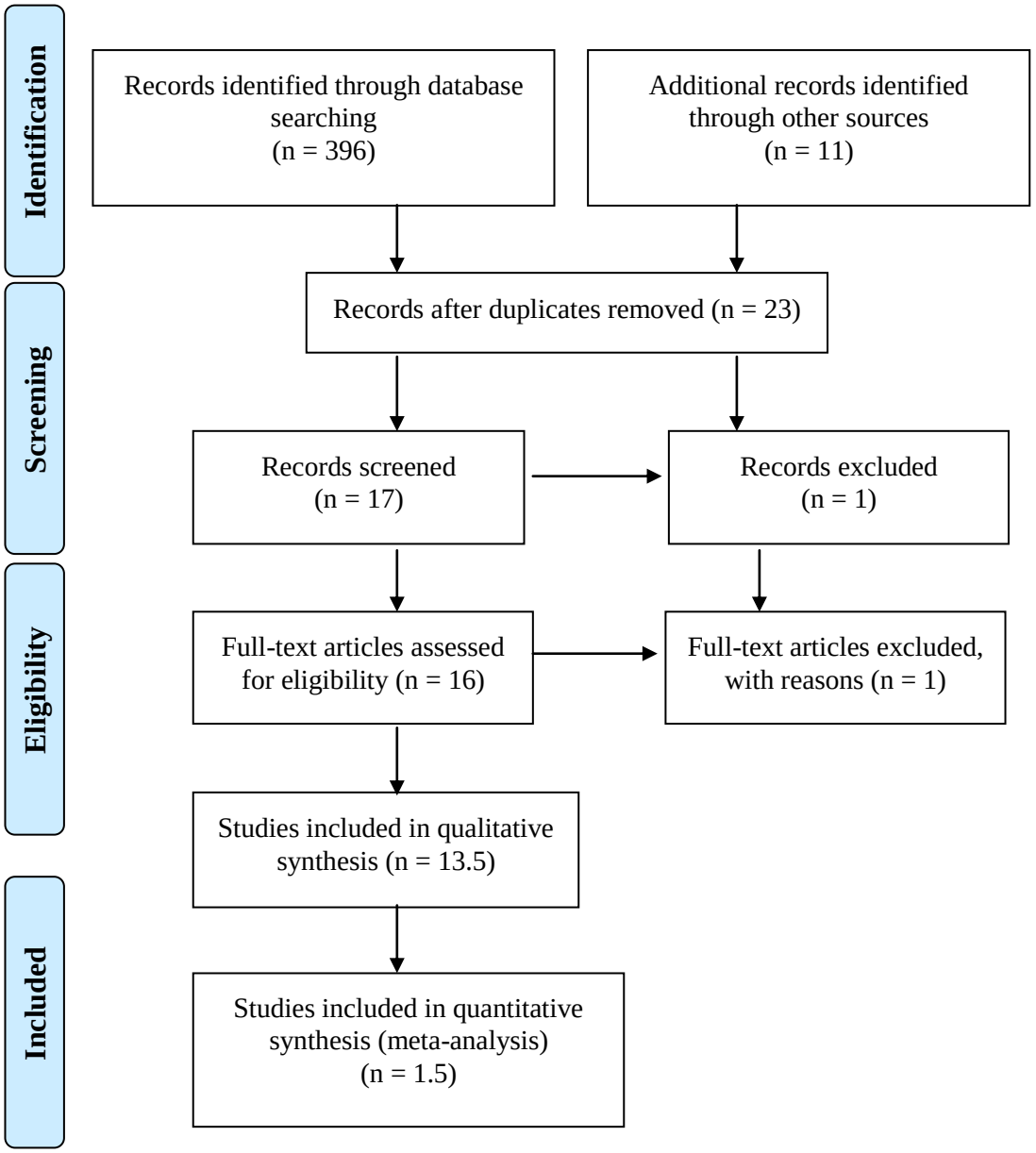

FIGURE 1: Flowchart how to select 15 references that support the lymphopenia mechanism in COFID-19

III. RESULT

This study of The Systematic Review (SR) included only 1 SR, 1 Observational with Systematic Evaluation, the other is 2 cross-sectional Report, 2 hypotheses, 6 Retrospective (case-control), 3 reviews.

TABLE 1
FIFTH-TEEN REFERENCES LYMPHOPENIA IN COVID-19 WHICH DESCRIBE PROGNOSIS

Ref. No.	Study year Ref	Design	Population	Lymphopenia	CPT and others
[6]	Velavan 2020 *IJID* 95(x):304-7	Cross-sectional	ICU pts. 191 COVID-19 pts	D-Dimer Lymphopenia	Mild vs. severe vs. fatal
[7]	Bani-Sadr 2020 *Int J Antimicrob Agents* 106077	Cross-sectional Before, after	257 COVID-19 pts. 27 March 2020	Lymphopenia < 1G/L	Corticosteroid (vs CPT)
[8]	Gupta A 2020 *Med Hypotheses 143(June): 110122*	Hypothesis	Early clinical course	Lymphopenia IL-6 >> TNF-a >>	receptor antagonist Prostaglandin signaling
[9]	Zhao Q 2020 *IJID* 96(x): 131-5	SR and MA	2282 with and without severe	Lymphocyte count-severity	<1.5x109/L: severe
[10]	Yang J 2020 *New Microbe New Infect* 35(xx): 100679	Observational Systematically Evaluate	Severe viral pneumonia 670/2995 15.5 vs. 4.3%	Lymphopenia-severity and mortality	Corticosteroid Rx/ is highly controversial
[11]	Mozafari 2020 *Med Hypotheses* 143 (July): 110111	Hypothesis	Severe stage	Lymphopenia and cytokine storms	NF-KB pathway through var mechanism
[12]	Khan S 2020 Saudi Pharm J 28(8): 1004-8	Retrospective	122 RT-PCR* confirmed pts. asymptomatic or mild symptoms	5-7 days recovery in mild symptoms fever 76.22%)	Lianhuaqingwen with Arbitol hydrochloride
[13]	Toledo 2020 *ClinChimActa* 510(July): 170-176	Review	183 COVID-19 pts. 41 SARS-CoV-2 pts.	Hematological changes incl. Lymphopenia	Fatal respiratory disease
[14]	Zhang Y 2020*Thromb Res*193 (March):110-115	Review	1099 COVID-19 pts.	Lymphopenia then thrombocytopenia	Both as pts. Prognosis with COVID-19
[15]	Zhang J 2020 *Brain Behav Immun* 88(June): 50-8	Retrospective	135 Wuhan single-center hospitalized COVID-19 pts.	Lower absolute lymphocyte count NLR 3.17, slowrec. from lymphopenia	Good vs. poor Sleep quality of confirmed patients:
[16]	Dhama K 2020 *Travel Med Infect Dis* x(x):101830	Review	Almost 15 million of July 22, 2020	Lymphopenia, erythrocyte sedimentation rate, CRP, LDH, proinflammatory cytokine	Counter spread, effective vaccine, therapeutics/drugs
[17]	Sun D 2020 *Clin Chim Acta* 208 (Apr):122-9	Retrospective incl. 2 cohorts	45 pts severe 12 pts no-severe	PBICs: Lymphocyte, B, E decrease, Neutrophil increase	Disease-associated phases severe
[5]	Liu S-p 2020 *DRCP* 167(x): 108338	Retrospective	255 pts: 41 ICU	Lymphopenia Higher IL-6	ICU/death Diabetes>>
[18]	Finelli C 2020 *Adv Biol Regul* 77(July):100742	Retrospective	46 multicentre CPT in Italy	Lymphopenia	Prognostic evaluation
[19]	Lv Z 2020*Microbes Infect* 22(4-5):195-9	Retrospective	354 patients hospitalized in Wuhan	IL-6 >, IL-10 >, CRP> Leucocytosis Neutropil Lymphopenia	Pneumonia outbreak: Critical male vs. females, severe and mild

IV. DISCUSSION

Lymphopenia or lymphocytopenia occurs since early in the clinical course and becomes the severity of the predictor and prognosis of COVID-19 outcome.[8] The association and signaling to be lymphopenia will be discuss started with table 1. References that support the association of lymphopenia mechanism in COVID-19 revealed various pathways such as

corticosteroid,[7] prostaglandin,[8] NF-KB,11Mozafari Lianhuaqingwen,[12] CPT.[18] The successful outcome in using the stuff in stopping the pathways depends on the stage of severity: mild, severe, or critical. Lymphopenia and coagulation abnormalities are useful for prognostic evaluation of critical patients.

4.1 Mild COVID-19 and lymphopenia

The fast incubation and spreading worldwide of COVID-19 then become pandemic and have been associated with a profound impact in clinical practice and hematologic setting. First of all, given the immunosuppressant agent like corticosteroid that is normally administered to patients with cytokine storm, increased the risk of a more severe viral infection. It could be followed by lymphopenia degree.[6] IL-1 and IL-6 is also used in risk stratification to predict severe and fatal hospitalized patients,[6] which mild COVID-19 are self quarantined at home. Comorbid cases will be faster and stronger drop the lymphopenia.[5]

In the outpatient clinics, the mild stage is the major cases, with or without pneumonia, and could also already have lymphopenia used for controlling the severity. The collection of the blood of convalescence plasma therapy, in asymptomatic patients, depends on the rapid test and PCR-swab test, but never lymphopenia status to avoid the transmission of COVID-19.

Finally, other hematologic laboratory alterations have been identified in early and mild infection with relatively low Viral Load (VL), which is thrombocytopenia and coagulation abnormalities. It is also useful for the prognostic evaluation of infected patients. It is 95-98 % self-limited flu common cold. It depends on the ratio of the antibody vs. the VL.

4.2 Severe COVID-19 and HLA ligand binding

Lymphocyte absolute count $<1.5x10^9$/L is a severe stage of COVID-19.[9] Under the fact that inflammatory mediators are active in individuals with COVID-19, blocking the predominant pathway could be helpful: DPP4 inhibitor.[11] Many therapies in this stage are controversial and increased the lymphopenia, the hospitalized patients become in fatal risk: critical risk.

4.3 Critical stage with high N/L ratio in diabetes patients

Patients with KIR6.2Sur 1 mutation, such as in diabetes patients, become un-discharged/died group suffered from decreased counts of total T lymphocytes, CD4 + T lymphocytes, CD8 + T lymphocytes, as well as NK cells at 2 weeks after treatment.[17]

Neutrophil increased and lymphocyte decrease in aggravated phase.[19]

4.4 The mechanism of antibody monoclonal of COVID-19

Stop the IL-1 signaling, mitigate the IL-6 signaling and other signaling pathways become the principal of COVID-19 therapies. Hyperglycemia is a strong predictor of poor prognosis in COVID-19.[5] Antigen-presenting cells (APC) and transferred to the APC surface by exosome where it can be recognized by helper T lymphocytes. Usual 1st-week infection or free weakly bound peptide fragments are not recognized, and this is the principle of a subsequent immune response, free cytotoxic reaction, then a cytotoxic response in the second week.

Pleiotropic effect of IL-1 generated by macrophages,[20] is also known to stimulate proliferation of B and T lymphocytes whereas both produce lymphotoxin and make lymphocytopenia. On the other hand, IL-1 intensify Neutrophil Extracellular Traps (NETs) which protect against mild infection and microbes. Uncontrolled NETs production can cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), coagulopathy, multiple organ failure, and autoimmune disease,[20] which the ARDS till multi-organ failure highly reported in diabetes patients.[21,22,23,24,25,26,27] This 2nd-week sign is faster and in more powerful reaction in the second COVID-19 infection. Alveolar edema before hemorrhage and fibrin exudation in the alveolar spaces indicate the acute phases,[28] is also due to the KIR6.2Sur1 mutation in Diabetes patients.[29] The severity of the fibrosis depends on the onset and duration of the disease.[28]

CPT will be the only ligand rich that could bind the viral antigen act as ligand and will switching-off the cytotoxic activity when others could not be handle by normal standards of care.[18,30]

V. LIMITATION

Experience with the survivors of ARDS patients, other side effects of steroid therapy,[31] chloroquine,[32] anti-diabetes agent,[33,34]diabetes[35,36,37,38] and other comorbid have not been evaluated extensively in COVID-19. Well-controlled vs. poorly-controlled DM have also risk different in stage of lymphopenia.[38] Well-controlled before and after CPT in the recipient and donor without HLA memory should also be recorded, as with other critical illness, COVID-19 has also been shown to

worsen multi-organ function, particularly in those with pre-existing metabolic syndrome,[31] and uncontrolled diabetes,[38] Whereas corticosteroid replacement is expected,[39] chloroquine is controversies and antiviral therapies if considered, antibody binding affinity,[40] IL-6 inhibitors,[41] lymphopenia is a simple and practical way during the course and as target therapy.[9]

VI. CONCLUSION

Convalescence Plasma Therapy Switch-off cytotoxic activity upon HLA ligand binding is the basic mechanism associated mortality in 2ndweek and 1st-week the second infection of COVID-19 with DM and immunocompromised patients.

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CONFLICT OF INTEREST

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AUTHORSHIP CONTRIBUTION

Both authors participated in research design, conducted experiments, performed data analysis/ included, and excluded references in the PRISMA design flowchart. Both wrote or contributed to the writing of the manuscript.

REFERENCES

[1] Li L, Hu Y, Tong M, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19 A Randomized Clinical Trial. JAMA doi.10.1001/jama.2020.10044.

[2] Liu J, Zheng X, Huang Y, Shan H, Huang J. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol 2020;74–6.https://doi.org/10.1016/j.jaci.2020.05.021.

[3] Liu C, Wu C, Zheng X, Zeng F, Liu J, Wang P, et al. Clinical features and multidisciplinary treatment outcome of COVID-19 pneumonia: A report of three cases. J Formos Med Assoc 2020;(xxxx):4–11. https://doi.org/10.1016/j.jfma.2020.04.008.

[4] Mutalib PS. Aflatoxin B1 Exposure Induced Obesity/Breast Cancer Based in Neighborhood Socioeconomic Status. International Journal of Environmental & Agriculture Research (IJOEAR) 2018;4(10):54-60.

[5] Liu S, Zhang Q, Wang W, Zhang M, Liu C, Xiao X, et al. Hyperglycemia is a strong predictor of poor prognosis in COVID-19. Diabetes Res Clin Pract 2020;167:108338. https://doi.org/10.1016/j.diabres.2020.108338.

[6] Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis. 2020;95:304–7. https://doi.org/10.1016/j.ijid.2020.04.061.

[7] Bani-Sadr F, Hentzien M, Pascard M, Andreoletti L, Kanagaratnam L, Pii DJ, et al. Corticosteroid therapy for patients with CoVID-19 pneumonia: a before-after study. Int J Antimicrob Agents. 2020. https://doi.org/10.1016/j.ijantimicag.2020.106077).

[8] Gupta A, Chander Chiang K. Prostaglandin D2 as a mediator of lymphopenia and a therapeutic target in COVID-19 disease. Med Hypotheses. 2020;143(June):110122. http://doi.org/10.1016/j.mehy.2020.110122.

[9] Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Deng Y, et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. Int J Infect Dis 2020;96:131–5. https://doi.org/10.1016/j.ijid.2020.04.086.

[10] Yang J, Yang L, Luo R, Xu J. Corticosteroid administration for viral pneumonia : COVID-19 and beyond. New Microbe New Infect. 2020;35(xxxx):100679. https://doi.org/10.1016/j.cmi.2020.06.020.

[11] Mozafari N, Azadi S, Mehdi-Alamdarlou S, Ashrafi H, Azadi A. Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. Med Hypotheses. 2020;143(July).http://doi.org/10.1016/j.mehy.2020.110111.

[12] Khan S, Ali A, Shi H, Siddique R, Nabi G, Hu J, et al. COVID-19 : Clinical aspects and therapeutics responses. Saudi Pharm J 2020;28(8):1004–8.

[13] Letícia de Oliveira Toledo S, Sousa Nogueira L, das Graças Carvalho M, Romana Alves Rios D, de Barros Pinheiro M. COVID-19: Review and hematologic impact. Clin Chim Acta 2020;510(July):170–6. https://doi.org/10.1016/j.cca.2020.07.016

[14] Zhang Y, Zeng X, Jiao Y, Li Z, Liu Q, Yang M, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. Thromb Res 2020;193(March):110–5. https://doi.org/10.1016/j.thromres.2020.06.008.

[15] Zhang J, Xu D, Xie B, Zhang Y, Huang H, Liu H, et al. Poor-sleep is associated with slow recovery from lymphopenia and an increased need for ICU care in hospitalized patients with COVID-19: A retrospective cohort study. Brain Behav Immun 2020;88(June):50–8. https://doi.org/10.1016/j.bbi.2020.05.075.

[16] Dhama K, Patel SK, Sharun K, Pathak M, Tiwari R, Yatoo MI, et al. SARS-CoV-2 jumping the species barrier: zoonotic lessons from SARS, MERS and recent advances to combat this pandemic virus. Travel Med Infect Dis 2020;x(x):101830. https://doi.org/10.1016/j.tmaid.2020.101830.

[17] Sun D wei, Zhang D, Tian R hui, Li Y, Wang Y shi, Cao J, et al. The underlying changes and predicting role of peripheral blood inflammatory cells in severe COVID-19 patients: A sentinel? Clin Chim Acta 2020;508(April):122–9. https://doi.org/10.1016/j.cca.2020.05.027.

[18] Finelli C, Parisi S. The clinical impact of COVID-19 epidemic in the hematologic setting. Adv Biol Regul 2020;77(July):100742. https://doi.org/10.1016/j.jbior.2020.100742.

[19] Lv Z, Cheng S, Le J, Huang J, Feng L, Zhang B, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Microbes Infect 2020;22(4–5):195–9. https://doi.org/10.1016/j.micinf.2020.05.007.

[20] Yaqinuddin A, Kashir J. Novel therapeutic targets for SARS-CoV-2-induced acute lung injury: Targeting a potential IL-1β/neutrophil extracellular traps feedback loop. Med Hypotheses 2020;143(May):109906. https://doi.org/10.1016/j.mehy.2020.109906.

[21] Hussain A, Bhowmik B, Cristina N. COVID-19 and diabetes : Knowledge in progress. Diabetes Res Clin Pract 2020;162:108142. https://doi.org/10.1016/j.diabres.2020.108142.

[22] Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: Findings from the CORONADO study and other recent reports. Diabetes Metab 2020; https://doi.org/10.1016/j.diabet.2020.05.008.

[23] Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation , hypercoagulability , and prognosis of COVID-19 patients. Diabetes Res Clin Pract 2020;164:108214. https://doi.org/10.1016/j.diabres.2020.108214.

[24] Shah K, Tiwaskar M, Chawla P, Kale M, Deshmane R. Diabetes & Metabolic Syndrome : Clinical Research & Reviews Hypoglycemia at the time of Covid-19 pandemic. Diabetes Metab Syndr Clin Res Rev 2020;14(5):1143–6. https://doi.org/10.1016/j.dsx.2020.07.003.

[25] Piarulli F, Lapolla A. Letter to the Editor COVID 19 and low-glucose levels : Is there a link ? Diabetes Res Clin Pract [Internet]. 2020;(xxxx):108283.https://doi.org/10.1016/j.diabres.2020.108283

[26] Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes: Lessons learned for our future (an experience to be used). Diabetes Res Clin Pract 2020;162:108137. http://www.sciencedirect.com/science/article/pii/S0168822720303879.

[27] Sagnelli et all. COVID-19 and low-glucose levels: Is there a link? J Infect. 2020;xxx(xxxx):18–20. http://doi.org/10.1016/j.jinf.2020.05.043.

[28] Renu K, Prasanna PL, Valsala Gopalakrishnan A. Coronaviruses pathogenesis, comorbidities and multi-organ damage – A review. Life Sci 2020;255(April):117839.https://doi.org/10.1016/j.lfs.2020.117839.

[29] McClenaghan C, Woo KV, Nichols CG. Pulmonary Hypertension and ATP-Sensitive Potassium Channels: Paradigms and Paradoxes. Hypertension. 2019;74(1):14–22.

[30] Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020;55(5):1-13.

[31] Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective. Diabetes Metab Syndr Clin Res Rev 2020;14(5):971–8. https://doi.org/10.1016/j.dsx.2020.06.054.

[32] Bajpai J, Pradhan A, Singh A. ScienceDirect Review article Hydroxychloroquine and COVID-19 e A narrative review. Indian J Tuberc 2020;(xxxx).https://doi.org/10.1016/j.ijtb.2020.06.004.

[33] Kumar A, Khunti K. Assessment of risk , severity , mortality , glycemic control and antidiabetic agents in patients with diabetes and COVID-19 : A narrative review. Diabetes Res Clin Pract 2020;165:108266. https://doi.org/10.1016/j.diabres.2020.108266.

[34] Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: A possible role beyond diabetes. Diabetes Res Clin Pract 2020;164:108183.https://doi.org/10.1016/j.diabres.2020.108183.

[35] Dariya B, Purnachandra G. Cytokine and Growth Factor Reviews Understanding novel COVID-19 : Its impact on organ failure and risk assessment for diabetic and cancer patients. Cytokine Growth Factor Rev 2020;53(May):43–52. https://doi.org/10.1016/j.cytogfr.2020.05.001.

[36] Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. J Diabetes Complications 2020;(xxxx):107637. http://www.ncbi.nlm.nih.gov/pubmed/32456846.

[37] Hussain A, Bhowmik B, Cristina N. COVID-19 and diabetes : Knowledge in progress. Diabetes Res Clin Pract 2020;162:108142. https://doi.org/10.1016/j.diabres.2020.108142.

[38] Raoufi M, Khalili S, Mansouri M, Mahdavi A, Khalili N. Well-controlled vs poorly-controlled diabetes in patients with COVID-19 : Are there any differences in outcomes and imaging findings ? Diabetes Res Clin Pract 2020;166:108286. https://doi.org/10.1016/j.diabres.2020.108286.

[39] Yang J-W, Yang L, Luo R-G, Xu J-F. Corticosteroid administration for viral pneumonia: COVID-19 and beyond. Clin Microbiol Infect. 2020;(xxxx).http://doi.org/10.1016/j.cmi.2020.06.020.

[40] Yang D, Frego L, Lasaro M, Truncali K, Kroe-Barrett R, Singh S. Efficient Qualitative and Quantitative Determination of Antigen-induced Immune Responses. J Biol Chem 2016 Jul 29;291(31):16361–74.

[41] Song Y. TITLE PAGE COVID-19 Treatment : Close to a Cure ? – A Rapid Review of Pharmacotherapies for the Novel Coronavirus Department of Pharmacy Services. Int J Antimicrob Agents 2020;(March):1–25. https://doi.org/10.1016/j.ijantimicag.2020.106080.