ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 05 | May - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A REVIEW OF ENDOTHELIAL BIOMARKERS IN CRITICALLY ILL COVID-19 PATIENTS AND ROLE OF DEXAMETHASONE IN AMELIORATING THEM.

Clinical Research

Kamaljit Bhattacharyya Junior Resident , Department of Pathology, Burdwan Medical College & Hospital, West Bengal , India.

Sagnik Banerjee Junior Resident, Department Of Anaesthesiology , Nil Ratan Sircar Medical College & Hospital, West Bengal ,India.

Soma Ghosh* Associate Professor , Department of Pathology, Burdwan Medical College & Hospital, West Bengal , India. *Corresponding Author

ABSTRACT

Coronavirus disease caused by the virus SARS-nCOV2 first detected in 2019 in Wuhan, China and then spread throughout the world creating a havoc and severe burden on the available health care resources worldwide. Multiple studies have been done to find out the exact pathogenesis of this disease. However, few studies have focussed on the aspect of endothelial injury as marker of pulmonary damage in covid 19 patients .This study aims to review the already existing articles on the importance of endothelial biomarkers like VCAM, ICAM , P- selectin, Ang-2 and others as hallmark of pulmonary endothelial injury in critically ill COVID-19patients and to draw a meaningful conclusion. Further, it also aims to find the role of Dexamethasone in reducing the inflammation and endothelial injury in such patients.

KEYWORDS

COVID 19, Endothelial biomarkers, Covid ICU patients,Pulmonary Injury, Dexamethasone

BACKGROUND:

Covid 19 caused by severe acute respiratory syndrome coronavirus 2(SARS-nCov 2) first detected in 2019 has led to almost 5.5 million deaths among 308 million total cases worldwide with a total of 9.2 billion administered vaccine doses as of January 2022. [1]Of these a vast number of patients needed admission in intensive care unit and mechanical ventilation.[1] In some studies, it has been found that endotheliopathy is associated with the lung injury found in Covid 19 and the level of endothelial biomarkers like Ang-2, P- selectin , E-selectin etc can be used to predict mortality and survival in these patients.[2] Endothelial biomarkers have also been foundto be elevated in patients with non-covid acute respiratory distress syndrome (ARDS) but not to the extent seen in covid ARDS.[2,3] The objective of this study was to review all such existing literature and come to a consensus regarding the use of endothelial biomarkers in predicting the mortality in critically ill COVID 19 patients. Dexamethasone has been widely used in treating acute inflammation in ARDS but its role in prevention of endothelial lung injury is not much known. [4] This study also aims to highlight on this aspect of use of Dexamethasone.

Pathogenesis:

The alveolar capillary membrane is formed of two separate barriers, the microvascular endothelium and the alveolar epithelium.[5] The integrity of this barrier is compromised by either endothelial or epithelial injury or more commonly both in case of ARDS. So, endothelial markers are significant in both covid and non covid ARDS.[5,6] There are several markers to identify endothelial damage[6] .The initial rolling interaction of leucocyte is mediated by a family of proteins called selectins. [6]

There are three types of selectin expressed on leucocytes (L selectin),on endothelium (E selectin), on platelets and endothelium (p - selectin).[6,7] There are several adhesion molecules that cause transmigration of leucocytes like ICAM, VCAM. [7]Ang -2 is and endothelial growth factor which causes polymorphonuclear cell infiltration and vascular leakage. Ang-1 maintains vessel integrity and prevent leakage. Ang 2 identifies breaching of vascular barrier[7,8]

Cytokine storm is an uncontrolled systemic hyperinflammation caused by cytokine excess, it can cause multiorgan failure and death .[9]Cytokines like IL-1,IL-6,IL-8,IL-10,TNF α , Interferon γ are involved in this storm. Rapid deterioration andmortality risk in covid 19 cases could be related to cytokinestorm.

Studies conducted show patients admitted in ICUwith higher level of IL-2,IL-7,IL-10,granulocyte colony stimulating factor , interferon inducible protein IP-10,monocyte chemoattractant protein MCP-1,macrophage inflammatory protein 1 alpha, and TNF α compared to non ICU patients.[8,9]

Dexamethasone, a very potent and highly selective glucocorticoid was first approved for use in 1961. Despite causing pituitary adrenal depression and being long acting (t1/2>36 hrs), it doesn't cause much fluid retention or hypertension. It has good anti-inflammatory and immunosuppressive actions being twenty five times more active than hydrocortisone and has been widely used in treatment of severe covid 19 mainly due to its actions on the cytokinestorm.[8,9] Many mechanisms of its action have been found including negative regulation of COX-2 , negative regulation of genes for cytokines in endothelial cells and macrophages thereby leading to reduced production of cytokines likeIL-1,IL-2,IL-3,TNF alpha, reduced production of ICAM and ELAM in endothelial cells with reduced production of acutephase reactants.[8,9,10]

All these mechanisms have been found tobe effective in treating diffuse alveolar and endothelail damage.[8,9,10]Nagele P et al found in their study that vascular endothelial cells canbe infected by SARS-CoV2. There was evidence of widespread endothelial injury with associated inflammation in advanced cases ofCOVID-19. [11]Prior evidence has established the crucial role of endothelial cells in maintaining and regulating vascular homeostasis with blood coagulation. Aggravation of endothelial dysfunction in COVID-19 may therefore impair organ perfusion and thus cause a procoagulatory state resulting in both macrovascular and microvascular thrombotic events. [9,10,11]

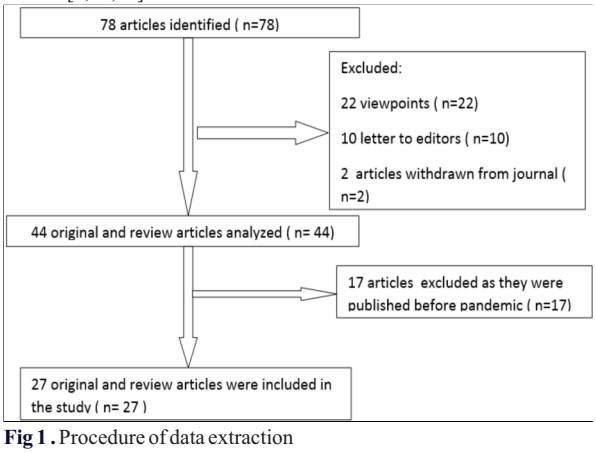

Fig 1 . Procedure of data extraction

Methodology:

We searched " Google Scholar" , "PubMed" and " Cochrane Library" from June 2020 to January 2022 with keywords " Covid 19" ,"Endothelial Biomarkers", "Covid ICU patients" and " Dexamethasone" .Fig 1.

All the articles relevant to the study were taken up and analysed as per Inclusion and Exclusion criteria.

DISCUSSION:

A retrospective study by Guervilly et al was conducted on 99 covid positive patients in Aix-Marseille university where circulating endothelial cell (CEC) level in ICU admitted patients was significantly higher than in non ICU patients along with elevated levels of IP-10, sVCAM-1, IL-6, E-selectin. The level of(CEC) positively correlated with duration of hospital stay ofthe patients. Increased level of (CEC)also found associated with increased level of IP-10,VCAM-1showing evidence of endothelial injury in such covid 19 patients. [12] A prospective study was conducted by Spadaro et al which included Covid 19 dedicated ICUs and non covid ICU of Ferrara university hospital. They found statistical higher plasma levels of Ang-2 and ICAM-1in non-survivors compared to survivors at time of inclusion in Covid 19 related ARDS. But the levelsof P selectin ,E selectin ,RAGE did not differ. So,Ang- 2 and ICAM-1 considered the predictors of mortality. Inclassical ARDS, RAGE and P-selectin level was higher compared to covid related ARDS . Level of Ang-2, ICAM-1, E-selectin were higher in case of Covid related ARDS than classical ARDS.[13]

An observational study was conducted by Vassiliou et al on 38 patients. They found higher values of P selectin, E selectin, Ang-2 and ICAM in the ICU non-survivors than survivors in critically ill covid 19 patients. Apart from vWF, level of these molecularmarkers can act as mortality indicator. Ang, ICAM , E selectin also showed to be of good prognostic value to possibly identify thepatients who may die subsequently in ICU. Even, patients admitted in ICU showed higher levels of Ang 2,vwf, than non ICU patients.[14]

The study by Iraklis etal suggested that increased Ang-2 level in ARDS patients was both associated with increased mortality and organ failure besides lung.They also found plasma level of Ang-2 holding predictive value against number of days of unassisted ventilation.

More precisely with greater values thepatients presented with more days of organ failure besides ARDS. [15]

Study by Wong et al found that SARS patients showed marked elevation of Th1 cytokine interferon (IFN)-γ, inflammatory cytokines like interleukin IL-1, IL-6 and IL-12for at least 2 weeks after disease onset and significant elevation of neutrophil chemokine IL-8, monocytechemoattractant protein-1 (MCP-1), and Th1 chemokine,IFN-γ-inducible protein-10 (IP-10).Corticosteroid reduced significantly IL-8, MCP-1 and IP-10 concentrations from five to eight days after treatment in their study population.[16]

Study by Kim et al provided an overview of cytokinestorm in COVID-19 and treatments currently being usedto address it .Further they discussed the potential therapeutic role of extracorporeal cytokine removal totreat the cytokine storm associated with COVID-19. [17] Study by Mendez et al in 2020 in Valencia found that a significant number of Covid 19 patients showed a sustained increase in endothelial markers. [18]

Further it was noted that proADM and proendothelin levels were significantly elevated in ICU admitted covid patients and the elevated levels correlated with poor mortality. [18]

Mancuso et al found that viable circulating endothelial progenitors (CEPs) were significantly increased in Covid 19 patients and a positive correlation was found between the copies of SARS-CoV-2 RNA in the cellular fraction and apoptotic CEPs per millilitre in severe COVID-19 patients .They concluded that CD146+ CEC and CEP can be used as biomarkers of endothelial damage in COVID-19 patients. [19] The pulmonary endothelium is increasingly being seen as important in both the progression and resolution of ARDS and can be used as a therapeutic target. Pulmonary edema from increased endothelial permeability is hallmark of acute lung injury [19]

In 2020, a study by Kim et al in South Korea showed that Dexamethasone usage in mechanically in tubated Covid 19 patients was associatedwith decrease in C- Reactive protein and improved radiological score as well as marginally with increased sp02/Fi02ratio. Further it was found that dexamethasone usage led to significant reduction in concentration of ICAM 1, Ang-2 and sRAGE. They concluded that Dexamethasone reduced endothelial injury in severe covid 19 without delay of viral clearance. [20] The RECOVERY (Randomized Evaluation of COVID-19 Therapy trial)conducted in 2020 found that Dexamethasone 6 mg once per day for 10 days reduced deaths by one-third in ventilated patients and by one fifth in other patients, receiving oxygen therapy.[21]

Lee et al demonstrated that early corticosteroid therapy (within seven days of illness) in SARS was associated with a higher subsequent plasma viral load and therefore should be used judiciously.[22]

Furthermore SARS CoV RNA was detected in plasma within day four of onset of fever, peaking in the first followed by rapid decline in the second week in previously healthy adult patients.[22]

Villar et al found that in patients suffering from moderate to severe ARDS receiving lung protective mechanical ventilation ,intravenous dexamethasone (20mg OD on Day 1-5 and 10 mg OD on Day 6-7) usage resulted in higher number of ventilator free days [95% CI 2.57 to7.03, $p<0.0001$) with no significant additional adverse effects. They concluded that early administration of Dexamethasone could reduce duration of mechanicalventilation and overall mortality in patients in established moderate to severe ARDS. [23] Mehta et al reviewed published guidelines with recommendations and observed that among the currently available agents, low dose corticosteroid and heparin can be beneficial in management of cytokinestorm and that further consensus is needed in use ofhigh dose Vitamin C and Tocilizumab [24]

Tian et al performed a systematic review and observed pre existing cardiometabolic disease and increased acute inflammation with end organ damage(cardiac, renal ,liver, haematological) at admission were associated with increased COVID 19 mortality risk. They also highlighted the importance of endothelial dysfunction and the role of endothelial markers inCOVID 19 pneumonia. [25] Study by Bahl et al in 2021 found that there was a mortality benefit in initiating corticosteroids in patients with more than seven days of onset of symptoms. Even, corticosteroid reduced risk of death in intubated covid patients .Further it was found that patients receiving first dose of corticosteroids after 72 h of hospital stay had a lower risk of death compared to patients with first dose at earlier time intervals and time from symptom onset more than sevendays should trigger initiation of corticosteroids. [26]

Lee et al in their study found that patients who received dexamethasone within 24hours of hypoxemia suffered from less severity of the disease in comparison to those who received after 24hrs . [27]

CONCLUSION:

Endothelial biomarkers are raised in critically ill Covid 19 patients in excess than what can be found in other ARDS patients. So they can be used as prognostic marker. Further studies need to be conducted in quantifying them and to find out how they can be actually useful in predicting mortality insuch patients. Though Dexamethasone has been foundto reduce these biomarkers, there is need for more elaborate studies to find the appropriate time to start it incorrelation with elevated biomarkers and the actual dosage needed to reduce them.

Conflict Of Interest Declared: None

Source Of Support: Nil

REFERENCES

[1] World Health Organisation : WHO Coronavirus (COVID-19) Dashboard; global situation.https://covid 19.who.int/
[2] Parashar A. COVID-19: Current understanding of its pathophysiology,clinical presentation, and treatment. Post Graduate Medical Journal.2020; 0:1–9.
[3] F. Millar, C. Summers, M. Griffiths, M. Toshner, and A. Proudfoot."The pulmonary endothelium in acute respiratory distress syndrome:insights and therapeutic opportunities," Thorax,2016; 71(5): 462–473.
[4] Zhao JP, Hu Y, Du RH, et al. Expert consensus on the use ofcorticosteroid in patients with 2019-nCoV pneumonia. Zhonghua Jie HeHe Hu Xi Za Zhi 2020;43:183-184. (In Chinese.) .
[5] Kumar,Abbas, Fausto ,Aster. Robbins and Cotran Pathologic Basis of Disease, Ninth Edition.South Asia Edition. Elsevier Publishers : 671-674.
[6] Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al .Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among Covid-19 patients: a systemic review and meta-analysis. Research.(2020)
[7] N. A. Maniatis and S. E. Orfanos. "The endothelium in acute lung injury/acute respiratory distress syndrome". Current Opinion in Critical Care,2008; 14(1) : 22–30.
[8] Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020 Mar28;395(10229):1054-1062.

[9] Mehta Y,Dixit SB, Zirpe KG, Ansari AS.Cytokine Storm in Novel Coronavirus Disease (COVID-19) : Expert management considerations. Indian J Crit Care Med 2020; 24: 429-434.
[10] Zhonghua Liu Xing Bing Xue Za Zhi. Novel Coronavirus Pneumonia Emergency ResponseEpidemiology, The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China 2020 ; 41:145-151.
[11] Nagele P,HaubnerB,Tanner C. : Endothelial dysfunction in COVID-19:current findings and therapeuticimplications. Atherosclerosis 2020;314:58–62.
[12] Guervilly C, Burtey S, Sabatier F, Cauchois R, Lano G, Abdili E, DavietF,Arnaud L, Brunet P, Hraiech S, Jourde-Chiche N, Koubi M, Lacroix R, PietriL, Berda Y, Robert T, Degioanni C, Velier M, Papazian L, Kaplanski G,Dignat-George F. Circulating Endothelial Cells as a Marker of EndothelialInjury in Severe COVID -19. J Infect Dis. 2020 Nov 9;222(11):1789-1793.
[13] Spadaro S, Fogagnolo A, Campo G, Zucchetti O, Verri M, Ottaviani I,Tunstall T, Grasso S, Scaramuzzo V, Murgolo F, Marangoni E, VieceliDallaSega F, Fortini F, Pavasini R, Rizzo P, Ferrari R, Papi A, Volta CA, ContoliM.Markers of endothelial and epithelial pulmonary injury in mechanicallyventilated COVID-19 ICU patients. Crit Care. 2021 Feb 19;25(1):74.
[14] Vassiliou AG, Keskinidou C, Jahaj E, Gallos P, Dimopoulou I,Kotanidou A, Orfanos SE. ICU Admission Levels of Endothelial Biomarkersas Predictors of Mortality in Critically Ill COVID-19 Patients. Cells. 2021 .Jan 19;10(1):186.
[15] Iraklis Tsangaris, ArgiriosTsantes, EleniVrigkou, PetrosKopterides,AimiliaPelekanou, Katerina Zerva, George Antonakos,DimitriosKonstantonis, IriniMavrou, Georgios Tsaknis,EvdoxiaKyriazopoulou, Maria Mouktaroudi, StylianiKokori, Stylianos E.Orfanos, Evangelos J. Giamarellos-Bourboulis,ApostolosArmaganidis. "Angiopoietin-2 Levels as Predictors of Outcomein Mechanically Ventilated Patients with Acute Respiratory DistressSyndrome". Disease Markers, 2017, ArticleID 6758721.
[16] Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokinesand chemokines in severe acute respiratory syndrome. Clin Exp Immunol2004;136:95-103.
[17] Kim JS, Lee JY, Yang JW, Lee KH, Effenberger M, Szpirt W, KronbichlerA, Shin JI. Immunopathogenesis and treatment of cytokine storm inCOVID-19. Theranostics. 2021 Jan 1; 11(1):316-329.
[18] Méndez R, González-Jiménez P, Latorre A, Piqueras M, Bouzas L,Yépez K, Ferrando A, Zaldívar-Olmeda E, Moscardó A, Alonso R, Reyes S,Menéndez R. Acute and sustained increase in endothelial biomarkers inCOVID-19. Thorax. 2021 Oct 4:thoraxjnl-2020-216797.
[19] Mancuso P, Gidaro A, Gregato G, Raveane A, Cremonesi P, Quarna J,Caccia S, Gusso L, Rusconi S, Giacomelli A, Cogliati C, Bertolini F.Circulating endothelial progenitors are increased in COVID-19 patientsand correlate with SARS-CoV-2 RNA in severe cases. J ThrombHaemost.2020 Oct;18(10):2744-2750.
[20] Kim W-Y, Kweon OJ, Cha MJ, Baek MS, Choi S-H (2021) Dexamethasonemay improve severe COVID-19 via ameliorating endothelial injury andinflammation: A preliminary pilot study. PLoS ONE 16(7): e0254167.
[21] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, StaplinN,Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T,Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K,Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ.Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med.2021 Feb 25;384(8):693-704.
[22] Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroidtreatment on plasma SARS-associated Coronavirus RNA concentrationsin adult patients. J Clin Virol2004;31:304-309.
[23] Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for theacute respiratory distress syndrome: a multicentre, randomisedcontrolled trial. Lancet Respir Med 2020;8:267-276.
[24] Mehta Y, Dixit SB, Zirpe KG, Ansari AS. Cytokine Storm in NovelCoronavirus Disease (COVID-19): Expert Management Considerations.Indian J Crit Care Med 2020; 24: 429-434.
[25] Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al Predictorsof mortality in hospitalized COVID-19 patients: a systematic review andmeta-analysis. J Med Virol. (2020) 92:1875–83.
[26] Bahl, A., Johnson, S. & Chen, NW. Timing ofcorticosteroids impacts mortality in hospitalizedCOVID-19 patients. Intern Emerg Med 16, 1593–1603 (2021).
[27] Lee H.W.ParkJ.LeeJ.K.ParkT.Y.HeoE.Y.The effect of the timing ofdexamethasone administration in patients with COVID-19pneumonia.Tuberc Respir. Dis. (Seoul). 2021;84(3):217-225.