



Lymphopenia in COVID-19 Patients & Its Association with Uncontrolled Diabetes, Obesity and Elderly: A Perspective Review

Authors

Dr Jayesh G Kalbhande¹, Dr Vicky Kuldeep²

¹Consultant Surgeon, BARC Hospital

²DNB General Surgery, Senior Resident (PGRMO) BARC Hospital

Abstract

Recent and most new Pandemic is of COVID-19. This is the third time that coronavirus family has affected the human generation. COVID -19 has been found to have high morbidity with patients with co-morbidities and has been treated with supportive treatment. Low lymphocyte count and higher Neutrophil lymphocyte ratio is associated with poor prognosis in COVID 19. Old age, obesity and uncontrolled diabetes mellitus is associated with low lymphocyte count and high neutrophil lymphocyte ratio. Identification of high risk group and taking specific measures to reduce the risk factors in them may result in improving complications related to COVID 19.

Keywords: Lymphopenia in COVID-19, Mortality in COVID-19, Diabetes & COVID-19.

Introduction

A recent outbreak of pneumonia in cluster of patients in live animal food market Wuhan, China was discovered to be caused by novel coronavirus. The disease was named as Coronavirus Disease - 19 (COVID-19)⁽¹⁾. Chinese Officials first reported COVID-19 cases to WHO in December 2019. Initially the Chinese Centre of Disease Control and Prevention (CDC) named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was later labelled as COVID-19 by WHO in February 11,2020.⁽²⁾ Soon the disease spreads the pawns out of the country of its origin and involved most of the countries world over. On March 11, 2020 WHO declared COVID-19 as Pandemic.

COVID-19 clinically presents with fever, dry cough, muscle pain, diarrhoea, fatigue and it has been found that it can lead to sudden and rapid

deterioration in general condition resulting in respiratory failure and septic shock in severe cases. Effective immune response against viral infection is mediated by activation of cytotoxic T cells. Recent Study in China reported that 63% of COVID-19 cases were showing low circulating lymphocyte counts.⁽³⁾ Lymphocytes counts were drastically reduced in elderly and severely ill patients of COVID-19 as compared to younger ones with mild to moderate disease.⁽⁴⁾ Other Studies in China has replicated the same finding that Lymphopenia is predictor of poor prognosis COVID-19 patients.⁽⁵⁾

Methods

With the given knowledge of Lymphopenia as poor prognostic marker in COVID-19, we scrolled through internet for literature to support this. Literature was also searched for relationship of

uncontrolled DM, Obesity, age and effects of exercise on lymphocyte counts.

Review of Literature

Lymphopenia in COVID -19

Diao B et al did a retrospective observational cohort study to find the numbers and functionality of T Cell in COVID – 19 patients. It was found that more than 70% patients affected by COVID 19 had low CD4⁺, T cell Counts and CD8⁺ counts. In addition it showed that Total T cell Counts, CD4⁺ and CD8⁺ counts were significantly lower in ICU patients as compared to Non-ICU patients. On categorizing data in different age groups, Lowest T cells counts were found in patients with age more than 60 years. Overall this study suggested that elderly patients and severely ill patients had lower lymphocyte counts.⁽⁴⁾

Tan L. et al found that low lymphocyte count is a poor prognostic marker of COVID-19. Patients with severe disease had lower lymphocyte count of 15% on day 1. Whilst, who had moderate disease and were cured had lymphocyte count of about 27% on day 1 of the disease. Lower lymphocyte count on day 1 of disease may act as prognostic marker and may signify potentially serious outcome.⁽⁵⁾

Meijuan Zheng in their study found that total count of Natural killer and CD8⁺ T cells was significantly decreased in patients with COVID-19 patients. In addition to that, function of NK and CD8⁺ T cells got exhausted. Most importantly it was seen that patient who had recovered from the COVID-19 were found to have restored the near normal counts of NK and CD8⁺ T cells.⁽⁶⁾

Jingyuan Liu et al also found that, Patient with Neutrophil Lymphocyte Ratio (NLR) of more than 3.13 were associated with severe COVID-19 infection and often required ICU care.⁽⁷⁾

Relationship of Neutrophil-Lymphocyte Ratio (NLR) and Infection

Multiple studies in past relates Neutrophil-Lymphocyte ratio to septicemia and infectious

disease. Clark D et al did a systematic review and meta-analysis of Neutrophil-Lymphocyte ratio in infectious diseases. It suggested that there is likely to be an association between neutrophil lymphocyte ratio and outcome. In the Meta-Analysis, there were 10 studies reported the association of higher NLR with septicemia.⁽⁸⁾ A. Naess et al did a study on patients with fever and not having fever, which showed that Neutrophil-Lymphocyte ratio is a useful tool to diagnose patient with septicemia.⁽⁹⁾

Rajnish Kaushik et al in their study suggested that Neutrophil lymphocyte ration can be used for diagnosis of septicemia and also for prognosticating patients for poor outcome.⁽¹⁰⁾

Lymphopenia in Diabetes

A study on rats with purpose of examining the effect of uncontrolled diabetes & insulin treatment on lymphocyte metabolism. Alloxan was used to induce diabetes in rats. Since glucose and glutamate is essential for lymphocyte function, their metabolism were studied. They found that the levels of hexokinase, G6PDH and citrate synthase were reduced in uncontrolled Diabetics. Impairment of glucose and glutamate metabolism in the lymphocyte of diabetics affect the response against pathogens. The important fact here is that the changes in lymphocyte metabolism of glucose were significantly reversed by insulin treatment.⁽¹¹⁾

A study by Otton R et al on Alloxan-Induced diabetic rats showed that there is increased destruction in lymphocytes in Diabetes Mellitus. The expression of anti-apoptotic gene bcl-2 was reduced by 85%, on the contrary the activity of pro-apoptotic genes like bcl-xS (25%), c-myc (twofold) and p53 (38%) was increased in lymphocytes from uncontrolled diabetics compared with healthy controls. The addition of insulin to lymphocyte markedly reduced the DNA fragmentation.⁽¹²⁾

In an observational study by Devamsh et al on patients with type 2 diabetes mellitus, It was found that Absolute neutrophil count and

Neutrophil lymphocyte ratio was significantly raised in patients with HbA1c more than 9 as compared to those who are having HbA1c less than 9.⁽¹³⁾

Lymphopenia in Old age & Obesity

A Randomised controlled trial was done by Jian Li et al found a strong positive correlation between increasing Neutrophil lymphocyte ratio and advancing age. A relatively lower but positive correlation was established between Neutrophil lymphocyte ratio and Obesity. A higher neutrophil lymphocyte ratio in elderly and obese was suggestive of increased number of leucocytes or a decreased counts of lymphocyte.⁽¹⁴⁾

Lydia A Lynch et al studied relationship of lymphocyte with obesity. Samples were collected from 52 severely obese patients & 11 lean healthy controls. They further classified obese into metabolically healthy and unhealthy based upon Blood pressure, lipid profile and glycaemic control. In this study it was found that the number Natural Killer Cells (NK cells) and Cytotoxic T Lymphocytes (CTL) were significantly lower in obese group as compared to lean controls. The levels of NK cells and CTL were also higher in healthy obese as compared to unhealthy obese.⁽¹⁵⁾

In the study done by Chung-Yu Chen et al it was found that after taekwondo exercise training of 10 weeks period had better systemic inflammatory response. In this study it was found that exercise was associated with reduction in Neutrophil Lymphocyte Ratio.⁽¹⁶⁾

Discussion

COVID-19 started as an outbreak in Wuhan, China in Dec 19 has now evolved as Pandemic. China being first the nation to take control over COVID, has plenty to share and teach. The published articles consistently establishes relationship of lymphopenia with severity COVID 19 patients & depicts it as a poor prognostic marker. Lower the lymphocyte counts or higher is the neutrophil lymphocyte ratio and more severe is the corona virus disease.

We hypothesise that improving of initial lymphocyte count and decrease in neutrophil lymphocyte ratio may reduce the severity of infection of COVID 10 which can help in better outcome of COVID 19. The literature showed the association of uncontrolled Diabetes mellitus, obesity and old age with lower lymphocyte counts and high Neutrophil Lymphocyte ratio. Treatment of diabetes with Insulin and exercise was associated with higher lymphocytes and better immune response.

We propose screening of general population for Obesity, Uncontrolled diabetes and sedentary life style. Their diabetes can be strictly controlled with medication. Obesity can be reduced by Dietary measures and exercise. Institution of specific intervention in high risk population can help in reduction of complications related to COVID 19.

Conclusion

Low lymphocyte count and higher Neutrophil lymphocyte ratio is associated with poor prognosis in COVID 19. Old age, obesity and uncontrolled diabetes mellitus is associated with low lymphocyte count and high neutrophil lymphocyte ratio. Identification of high risk group and taking specific measures to reduce the risk factors in them may result in improving complications related to COVID 19.

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