The role of Mild Thrombocytopenia in mild COVID-19 Infection: A Systematic Review

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Abstract—

Introduction: *The COVID-19 pandemic has caused the deaths of more than 9,122,116 people, mostly elderly and/or comorbid such as diabetes and immunosuppressed state using cortisone. While the quarantine measure is necessary, and pancytopenia happens during the hospitalization, earlier thrombocytopenia is often being implemented to manage DHF patients.*

Problem: *Patients with comorbid have thrombocytopenia and have been managed as DHF patients. Meanwhile, the cost of the pandemic is not limited to medical-aspect, and the virus has led to psychological-aspect of patients not being hospitalized in special COVID-19 barracks.*

Aims: *To reveal that thrombocytopenia could be used for COVID-19 diagnosis and as early as possible being managed on COVID-19 treatment management.*

Method: *Systematic Review with PRISMA Design, using Science Direct search machine and Mendeley My Library, with keywords thrombocytopenia and mild COVID-19. Bayesian network and analysis to support in finding references that support the pathogenesis of thrombocytopenia in COVID-19 in the mild stage. Systematic Review and Meta-analysis design are preferable.*

Result: *Flowchart of 15 references, supported thrombocytopenia in mild and the severe COVID-19, while lower thrombocytopenia in critical stage. At least 22 case reports with this mild thrombocytopenia and thrombosis. With over 28,789,321 people infected globally, mild thrombocytopenia in immunocompromised COVID-19 patients could be helped and monitored not to be severe and critical stage as early as possible.*

Conclusion: *Mild thrombocytopenia is useful in fighting mortality in the COVID-19 pandemic for primary care physicians.*

Keywords— Mild Thrombocytopenia; mild COVID-19; comorbid; diabetes; pandemic; pregnant; cortisone, Peripheral blood inflammatory cells (PBICs).

I. INTRODUCTION

Since December 2019, new COVID-19 outbreaks have occurred and spread around the world. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).. This viral pandemic of COVID-19 led to the deaths of over 9,122,116 peoples, mostly elderly or comorbid as diabetes, and immunosuppressed state, using cortisone, and chloroquine treatment.[1] Corona virus disease 2019 (COVID-19) is a pandemic which started in China in late 2019 and has now spread across the globe in 2020.[2] The clinical characteristics of patients are still unclear. Most patients had fever as the first symptom for admission. Other symptoms included cough, fatigue, hoarseness and diarrhoea. Certain patients did not have fever at the time of consultation, and most were not accompanied by organ damage.[3,4] Currently there is limited knowledge on medical comorbidities and COVID-19.[5] Clinicians are fighting against this new disease and are focusing on various factors that may lead to better survival outcomes. The common symptoms of COVID-19 infection are fever, cough, myalgia and fatigue.[6]

There was analysis of patients with COVID-19 had described various clinical characteristics and their association with the severity of disease, lymphopenia and eosinopenia may serve as predictors of disease severity and disease progression in COVID-19 patients, and enhancing the cellular immunity may contribute to COVID-19 treatment. [7,8] While the quarantine measure is necessary and pancytopenia happen during the hospitalization, earlier thrombocytopenia is often implemented of being managed as DHF patients.[9, 10, 11]. COVID-19 is more a systemic condition than it is a respiratory disease in severe cases, which evidence has revealed thrombocytopenia complications and associated with disease severity and increased mortality.[12]

The underlying changes of peripheral blood inflammatory cells (PBICs)in COVID-19 patients are little known, the risk factor for the underlying changes of PBICs and their predicting role in severe COVID-19 patients remain uncertain. Lymphopenia and eosinopenia may serve as predictors of disease severity and disease progression in COVID-19 patients, and enhancing the cellular immunity may contribute to COVID-19 treatment.[13] Lessons learn that patient with comorbid have thrombocytopenia and managed as DHF patients. [14] The costs of the pandemic are not limited to medical aspect, as the virus has led to psychological aspect not being hospitalized in special COVID-19 barracks.[15,16] Aims of this study is to reveal that thrombocytopenia could be used for COVID-19 diagnosis and as early as possible being managed on COVID-19 treatment management . We conduct a systematic review to evaluate the impact of various morbidities on serious events in COVID -19.

II. METHOD

Systematic Review design by PRISMA using Science Direct and other search engines. Also Using My Library of Mendeley.

Keywords of COVID-19 and thrombocytopenia were chosen. Mild COVID-19 and mild thrombocytopenia are included, severe and critical stage were excluded. With a Bayesian network and analysis also mild lymphopenia is monitored. Systematic Review and Meta-analysis are preferred due to the PRISMA list.

III. RESULT

Fifth-teen references are included which are 5 case reports, 10 reviews and no one is Systematic Reviews or Meta-analysis. Yang,[3] Mahboob,[17] Hussain,[1] Shi,[18] Mangalmurti,[19] Finelli,[4] Toledo,[7] Rapkiewicz,[20] Renu,[21] Schonrich,[13] Zhang,[22] Gouez,[23] Nauka,[24] Song,[25] Yamanoglu,[26] are recorded supporting mild thrombocytopenia in mild COVID-19.

Research novelty:

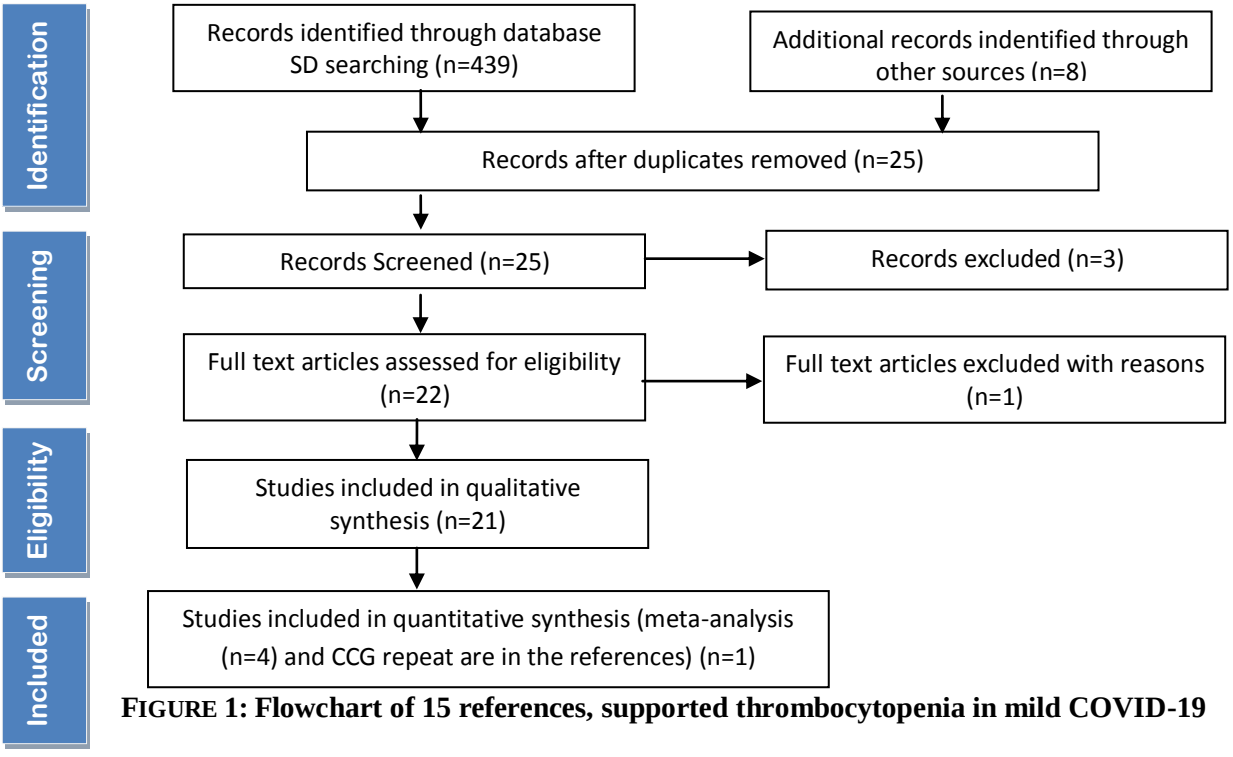

FIGURE 1: Flowchart of 15 references, supported thrombocytopenia in mild COVID-19

TABLE 1
FIFTEEN REFERENCES SUPPORTED THROMBOCYTOPENIA IN MILD COVID-19

Study, year	Design	Population	Thrombocytopenia	Mild/severe COVID-19
Yang, 2020	Review	Wuhan patients	Death	Socio-ecconomic
Mahboob, 2020	Case report	58-year-old woman	Large vessel stroke	Found to be COVID-19 positive
Hussain, 2020	Review	Diabetes, Old, Comorbid	Increased coagulation activity	Range Mild to ARDS
Shi, 2020	Review	COVID-19 patients	Coagulopathy Cytokine storm	Hypercoagulopathy
Mangalmurti, 2020	Basic concept	Cytokine storm	Lead to vascular damage	Worsening clinical outcome
Finelli 2020	Review	Given immunosuppressive with hematologic diseases	Thrombocytopenia, lymphopenia, coagulation abnormalities	Not postpone CPT
Toledo 2020	Review	SArS-Cov-2 infection patients	Hematological test Lymphopenia;	Excluded or confirm the Diagnosis
Rapkiewicz 2020	A case series	7 COVID-19 autopsies	Thrombi in the large pulmonary arteries in MOT	Thrombosis and predominant inflammation
Renu	Review	Comorbid in MOF	Venous thromboembolism	ARDS, ACE2,Cardiovascular, GI dysfunction, CKD, DM, liver, CNS, ocular, conjunctival
Schonrich, 2020	Review	ROS production	Immune system reacts insufficiently	Systemic tissue damage
Zhang 2020	Review	COViD-19 patients	Thrombocytopenia are not rare	Development of T remain to be elucidated
Gouez 2020	Case-report	3 COVID-19 patients on pregnant in China	Mild thrombocytopenia A third of non-pregnant	but to emergency in 1 pregnant case; 2 with PCR-Swab positive
Nauka 2020	Case-report	A 48 y non smoker male, suspect COVID-19	Trombocytopenia	Non critical patients DVP
Song 2020	Review	COVID-19 patients by frontline clinician	Cytokine release syndrome-Rx/ IL-6 inhibitors	Corticosteroid should be limited in comorbid patients
Yamanoglu 2020	Case report	7 series Asymptomatic to severe, result fatal in others	3 thrombocytopenia, and 2 during follow-up	Age and chronic diseases, source of transmission

MOF: Multi-organ function; ROS: Reactive Oxygen Species; NETs: Neutrophil Extracellular Traps; MOT: Multi-organ Tissue; CPT: Convalescence Plasma Therapy

IV. DISCUSSION

4.1 Devilishly radical NETs

Neutrophil extracellular traps (NETs)[13] leads to severe and critical COVID-19. The overwhelming production of reactive oxygen species (ROS) increases the NETs and T cells that are necessary to kill virus-infected cells. Vitamin C or NAC as an antioxidant will cut this vicious cycle.[13]

Coagulopathy on vascular thrombotic events (VTE) contributes to the risk of fatality[28]

Uncontrolled inflammation-mediated endothelial injury and dysregulation of renin-angiotensin system (RAS) are the potential mechanisms in severe and critical stage.[28]

These later fatal thrombotic events covered the thrombocytopenia in mild COVID-19 stage.

4.2 Multi-organ damage and comorbidities

Coronaviruses are associated with comorbidities.[21] Alveolar failure and severe respiratory malfunction are correlated with other damaging organ due to the risk of cardiovascular through ACE2, the dysfunction of gastrointestinal, the dysfunction of liver, the injury of lung, chronic kidney disease, diabetes mellitus, CNS risk, ocular risk, conjunctivitis, and conjunctival hyperemia and venous thromboembolism.[21] At the molecular level, immunopathology and coronaviruses provide information related to comorbidities that explain the coronaviruses replication (Viral Load) with multi-organ damage.[21]

Early diagnosis with thrombocytopenia in mild COVID-19 is useable in fighting multi-organ damage in comorbidities.

4.3 Covid-19 and Diabetes

It is important to understand the common properties of COVID-19 in relation to people with diabetes.[1] The "incubation period" is one of them in the diabetes patient with COVID-19. The general characteristic are from flu-like symptoms to distress syndrome of acute respiratory, failure of multiple organs, and death. Meanwhile, the significant predictor of the morbidity and mortality are comorbidities, diabetes, and elder people. The underlying mechanisms between diabetes and COVID-19 are chronic inflammation, coagulation activity that is increased, impairment of the immune response, potentially damaging pancreas caused by SARS-CoV-2.[1]

The use of chloroquine in diabetes subjects potentially trigger hypoglycemic event. Therefore, research in the future should consider this relationship in combination with its clinical management. [1] Fighting COVID-19 with diabetes at much early stage are the best way in winning the war against high mortality of these cases.

4.4 Cytokine Storm

The increasing of cytokinesis level in the circulation associated with all type of infections and immunity conditions are known as a cytokine storm. The function to protect by cytokines is an 'ideal' responses; a multi factorial which is being able to trigger responses to be pathological that lead to vascular damage, immunopathology, and worsening clinical outcomes.[19]Infection is higher in patients having diabetes mellitus (DM) compared to those who have not. The higher probability of infection is caused by defects in immunity and in humoral innate immunity. Many studies show that in cellular innate immunity the function of chemotaxis, phagocytosis, and killing of diabetic polymorphonuclear cells and diabetic monocytes/macrophages cells decreases than that of control. Control DM improve cellular function. Some bacterial infection becomes more virulent in the high-level glucose. The adherence among microorganisms is higher to diabetic compared to non-diabetic cells.[27]

4.5 Hematologic Setting

The impact COVID-19 pandemic is closely related to clinical practice in the hematologic setting. However, many therapies who administer immunosuppressive effect to patients with hematological diseases might encounter the increased risk of a more severe viral infection. Especially in marginal primary health care, the urgency and priority treatments of individual patient has to be reconsidered. Thrombocytopenia, lymphopenia, and coagulation abnormalities, being useful for the prognostic evaluation of infected patients, have been identified by hematologic laboratories.[4] Proven agents for the treatment of COVID-19 is still promising.[28]

A broad spectrum on the COVID-19 clinical progression have found individuals having asymptomatic after having a severe course while others end up in mortality. While the different clinical course in individuals is influenced by age and clinical diseases, genetic factors and the origin of transmission are considered as an important in the clinical course. The different structure of genetic is reported to be from the same source. Therefore, evaluation are conducted upon the similar but different clinical cases residing in the same nursing home and present to the hospital altogether. [26] As a result, since the significant challenge to be taken care of is performing treatment in intensive care units (ICU), it is essential to recognize early the severe form of triaging of patients supporting by laboratory markers.[29]

Several laboratory parameters severity stage are low lymphocyte count, D-dimers, cardiac troponin, CRP, ferritin, and IL-6. All of which are used in danger delamination to prognosticate hospitalized patients whether or not having severe and fatal COVID-19. Prognosis will be wrong when partly or whole of these parameters are altered.[29] There are also an association of thrombocytopenia and those other laboratory markers, especially thrombocyte and clinical course. Thrombocytopenia in the mild and severe stage of COVID-19 could be a sentinel lab marker especially in the mild diabetic patients (also elder and comorbidities).

On the follow-up experience with the mild Covid-19 diabetic patients, other side effects of steroid therapy, immunosuppressant stuff, evaluated extensively in the COVID-19 pandemic. COVID-19 has also been shown to have mild lower thrombocytopenia in pregnant women.[23]

When patients with critical COVID-19 and corticosteroid replacement are expected to be beneficial in this situation, in mild Covid-19, thrombocytopenia could also use for an indicator between the digging of 'say no to steroid in the population'.

V. LIMITATION

At this study and outcome level, incomplete retrieval of identify research does not identified thrombocyte counting for the early diagnosis in the mild case.[5]

Reporting bias on coagulopathy or thrombocytopenia caused by the coagulopathy such as vascular thrombotic events,[17,18] has covered the potential use of thrombocytopenia for the triage aim and for the patient with diabetes, old age and immunocompromised cases, which is easy got worse in wrong diagnosis and management, especially in the second infection of SAR-Cov-2 which is the immunoreaction is stronger and faster.

Reporting bias of this study is 1) corticosteroid give lymphocytopenia and when it stops, the lymphocyte increase again;[30,31,32] 2) people who are receiving active chemotherapy;[33] 3) the imaging of CT can be sorted into four phases: early phase, progressive phase, severe phase, and dissipative phase is demonstrated,[34] another stage, that is mild, severe and critical,[29,35] then mild, moderate, severe, critical.[36]

Early diagnosis and appropriate medication are able to decrease the mortality rate.[35] One of the risk factors causing severe/critical outcomes is diabetes. [35] At initial diagnosis, the absolute number of lymphocytes could not predict the progression risk from severe to critical condition,[35] but not thrombocytopenia which is not rare in COVID-19 patients.[22]

Zheng finds that in the first time of diagnosis the white blood cell counts is low (30.1 %) and 45.2 % have decreased lymphocytes. Multiple patchy ground-glass shadows outside of the patient lungs were commonly observed, and a single sub-pleural sheet of ground glass shadow with enhanced vascular bundles was also found located under the pleura.[36]

Lymphocyte counts below 0.8×10^9/L cannot be used to predict severe and critical groups from the ordinary group.[35] Family clustering in the later period,[35] should be a screen with thrombocytopenia to triage, much more the incubation period was relatively long, and the incidence was relatively hidden, but the virulence was relatively low.[35]

In COVID-19 patients, the peripheral blood inflammatory cells (PBICs) changes are related to blood routine and lymphocyte subsets. Under clinical classifications, disease-associated phases, and one-month outcomes, the inflammatory cell levels are compared. Based on blood routine and lymphocyte subsets, patients of non-severe type vs. the patients of severe type suffered from significantly decreased counts of lymphocytes, eosinophils, basophils, but increased counts of neutrophils.[37] These PBICs alterations got improved in the recovery phase, but persisted or got worse in the aggravated phase.[37]

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VI. CONCLUSION

In facing the COVID-19 pandemic, most countries feel not early to diagnosis mild COVID-19 on doing fast quarantine, which right possible diagnosis could be done by thrombocytopenia alone or parallel with lymphocytopenia. Thus, Thrombocytopenia might become a sentinel of COVID-19, and it serves attention during mild COVID-19 triage.

CONFLICT OF INTEREST

Nothing

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