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Preface

We would like to present, with great pleasure, the inaugural volume-7, Issue-3, March 2021, of a scholarly journal, *International Multispeciality Journal of Health*. This journal is part of the AD Publications series *in the field of Medical, Health and Pharmaceutical Research Development*, and is devoted to the gamut of Medical, Health and Pharmaceutical issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Medical, Health and Pharmaceutical as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical statistics investigations. Its mission is to become a voice of the Medical, Health and Pharmaceutical community, addressing researchers and practitioners in below areas

Clinical Specialty and Super-specialty Medical Science:

It includes articles related to General Medicine, General Surgery, Gynecology & Obstetrics, Pediatrics, Anesthesia, Ophthalmology, Orthopedics, Otorhinolaryngology (ENT), Physical Medicine & Rehabilitation, Dermatology & Venereology, Psychiatry, Radio Diagnosis, Cardiology Medicine, Cardiothoracic Surgery, Neurology Medicine, Neurosurgery, Pediatric Surgery, Plastic Surgery, Gastroenterology, Gastrointestinal Surgery, Pulmonary Medicine, Immunology & Immunogenetics, Transfusion Medicine (Blood Bank), Hematology, Biomedical Engineering, Biophysics, Biostatistics, Biotechnology, Health Administration, Health Planning and Management, Hospital Management, Nephrology, Urology, Endocrinology, Reproductive Biology, Radiotherapy, Oncology and Geriatric Medicine.

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It includes articles related to Pathology, Microbiology, Forensic Medicine and Toxicology, Community Medicine and Pharmacology.

Basic Medical Science:

It includes articles related to Anatomy, Physiology and Biochemistry.

Spiritual Health Science:

It includes articles related to Yoga, Meditation, Pranayam and Chakra-healing.

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within

that community who supported the idea of creating a new Research with *IMJ Health*. We are certain that this issue will be followed by many others, reporting new developments in the Medical, Health and Pharmaceutical Research Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IMJ Health* readers and will stimulate further research into the vibrant area of Medical, Health and Pharmaceutical Research.



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A Review of Smoking on Cardiovascular Disease: Impact on Human Health

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Abstract— Cardiovascular diseases (CVD) are the leading cause of global morbidity and mortality. They also inflict huge direct and indirect financial costs on the worldwide society. With the ready availability of affordable therapeutics globally, and the relatively slow development of newer therapeutics, lifestyle behaviors are gaining importance, both as preventive and therapeutic interventions. Smoking tobacco is consistently and strongly related with a higher risk of CVD incidence, adverse progression, and increased mortality. Smoking is deleteriously associated with most cardiovascular diseases. Smokers die of more CVDs than from any other cause. Cessation of smoking is therefore paramount in improving worldwide CVD health. This paper reviews the negative effects of smoking on cardiovascular diseases.

Keywords— Smoking, Cardiovascular Diseases, Lifestyles, Modifiable Risk Factors, Nicotine.

I. INTRODUCTION

Tobacco is consumed by over a billion people around the world¹. Smoking is the most common mode of its use². This is done using products like cigarettes, e-cigarettes and water pipes³. Smoking tobacco exposes individuals to tobacco related noxious gaseous and particulate matter in several ways⁴⁻⁶. Most commonly, smoke enters the smoker's mouth directly from the cigarette being smoked and this is known as the first-hand smoke or mainstream smoke⁴. Side-stream cigarette smoke emanates from the burning ends of a cigarette and along with the exhaled main-stream smoke, results in second-hand smoke that could be inhaled by others⁵. Third-hand smoke is the residue from tobacco products that cling to surfaces such as skin, hair, clothing, and furniture⁶. These pollutants resist removal with traditional cleaning methods and may persist on these surfaces for several months. Tobacco is also consumed by non-smoking methods⁷. The smokeless tobacco products include loosely chewed tobacco leaves, tobacco paste and several tobacco-based concoctions such as naswar, gutka, and snuff⁸. The ingredients in these products are mainly absorbed via the mucous membranes of the mouth and nose.

Tobacco is highly addictive, primarily due to its nicotine content^{9,10}. All tobacco forms provide, besides nicotine, a plethora of harmful substances, many being extremely toxic and cancer provoking¹¹. These include many harmful nitrosamines and polycyclic aromatic hydrocarbons^{12,13}. Water pipe smoking results in large amounts of smoke being inhaled during a single smoking session and exposes the smoker to similar harmful substances as are present in cigarette smoke¹⁴. Inhaled e-cigarette vapor is usually lower in carcinogens and other toxins but is still harmful¹⁵. Smokeless tobacco also contains nicotine and more than 20 carcinogens, which enter the body via the oral and nasal mucous membranes¹⁶.

Tobacco smoking adversely affects literally every organ in the human body¹⁷. Tobacco smoke has a several thousand compounds, including several toxic ones, such as benzene, formaldehyde, benzopyrene, carbon monoxide, acrolein, and metals¹⁸. The respiratory tract is the first to be hit with these, (before disseminating all over the body via the blood stream) causing inflammation, irritation, asphyxiation, carcinogenesis, and other deleterious effects¹⁹. Further dissemination, mainly via the blood stream, results in the development of many other serious disorders including several forms of cancer²⁰. Smoking also affects pregnancy, causing a wide range of complications²¹. Infants exposed to cigarette smoke, either during the prenatal period or after birth have an increased risk of sudden death, orofacial clefts, periodontal disease, and dental caries²². Smoking accelerates aging, and smokers often develop wrinkles prematurely²³. Cigarette smoking greatly reduces

the quality of life²⁴. It is estimated that almost half of the smokers lose about 20 years of healthy life²⁵. In 2017, 182 million disability-adjusted life-years (DALYs) were attributed globally to tobacco use²⁶. Smokers over their lifetime demonstrate a higher mortality risk when compared to never smokers²⁷. According to the Global Burden of Disease Study, in 2015, worldwide, one out of ten deaths was due to smoking²⁸. Tobacco-related diseases are estimated to claim more lives than those due to AIDS, malaria and tuberculosis combined²⁹. The estimated economic cost associated with smoking is 1.8% of global gross domestic product³⁰.

Smoking cessation before the age of 40 is associated with a reduction of more than 90% of the excess morbidity and mortality³¹. Cessation at the age of 30 eliminates nearly all the excess risk. Besides bestowing a healthier life, cessation also increases life expectancy³¹. Jha et al estimated that smokers who started smoking early in adult life, gain almost 10, 9, 6, and 4 years of increased life if they stop smoking at ages of 30, 40, 50, or 60 years of age, respectively, compared to those who continue to smoke³².

II. DISCUSSION

The major CVDs are coronary heart disease (CHD) high blood pressure (HTN), stroke, heart failure (HF), cardiac arrhythmias, peripheral arterial disease (PAD), deep vein thrombosis (DVT) and vasculogenic erectile dysfunction (ED)³³. These impart the greatest non-communicable diseases burden globally and this is expected to rise globally in the coming years³⁴. They cause considerable disability and are responsible for an enormous number of deaths^{35,36}. They are responsible for a huge financial burden worldwide³⁴.

Smoking exerts adverse effects on several CVDs, resulting in poor outcomes³⁷. It is estimated that globally, smoking related CVD deaths exceed those from respiratory diseases or all forms of cancer combined³⁸. A smoker has approximately 10 years shorter lifespan than a nonsmoker³⁹. Smoking cessation is associated with a gradual reversion of the harmful cardiovascular effects⁴⁰. It reduces mortality and increases longevity⁴¹.

The relationship between smoking and CVD risk is non-linear⁴². It is estimated that 80% of the risk of smoking >20 cigarettes/day comes from smoking less than 3 cigarettes/day⁴³. Even smoking 1 cigarette/day is associated with 30–50% of the risk of CHD and 34–65% of the risk of stroke that would occur with smoking 20 cigarettes/day⁴⁴. Deleterious effects are also seen with low-tar cigarette, filtered cigarette, e-cigarette, cigar pipe, and water-pipe smoking⁴⁵. Nonsmokers exposed to passive smoke also demonstrate a 25–30% increased CV risk⁴⁶.

Tobacco smoking plays a critical role in the maintenance and development, and progression of atherosclerosis via several mechanisms⁴⁷. Tobacco smoking related chemicals increase low-density lipoprotein cholesterol levels, decrease high-density lipoprotein cholesterol level, increase inflammation, increase insulin resistance, increase catecholamines, increase the amount of fibrinogen, increase reactive oxygen species, and enhance platelet aggregation⁴⁷.

2.1 Smoking and HTN

According to the WHO, one in four men and one in five women have elevated BP globally and its prevalence is increasing steadily^{48,49}. Elevated BP increases the risk for coronary heart disease, PAD, stroke, kidney failure, and heart failure⁵⁰. It also increases CVD mortality⁵¹. It accounts for approximately 45% of all global CVD morbidity and mortality⁵².

The adverse relationship between smoking and hypertension is well documented⁵³. In the Physicians' Health Study, the risk of incident hypertension was increased by 15% in current smokers compared with never smokers⁵⁴. In a recent study, a more than 5 pack-years smoking exposure increased the risk of BP by more than 30%⁵⁵. Even passive smoking, after adjustments for several confounding factors, was found to be associated with a higher rate of hypertension in the exposed individuals, when compared to those not exposed to the secondhand cigarette smoke⁵⁶. Besides smoking promoted atherosclerosis, the sympathetic nervous system and the baroreflex-system also play a deleterious role⁵⁷⁻⁵⁹.

2.2 Smoking and CHD

CHD, or coronary artery disease/ischemic heart disease, is the most common CVD⁶⁰. Its prevalence is increasing in the middle- and low-income countries⁶¹. It is primarily caused by atherosclerosis, which leads to a flow-limiting stenosis of large epicardial coronary arteries, initially resulting in angina⁶². A plaque rupture or erosion can provoke superimposed atherothrombosis and vessel occlusion, leading to a myocardial infarction, or even death⁶³. It is responsible for an enormous amount of global disability⁴⁹. This imparts a heavy disability-adjusted life year (DALY) burden and smoking remains the number one CHD killer in the world^{49,65}.

Smoking is strongly linked with CAD⁶⁵. Smokers are two to four times more likely to develop CHD⁶⁶. In women, smokers between the ages of 35–39, almost triple their risk of CHD if they smoke just 1–4 cigarettes a day⁶⁷. The INTERHEART study found that smokers have a 1.95-fold increased risk of developing non-fatal myocardial infarction when compared to non-smokers⁶⁸. Hackshaw et al. reported that while smoking one cigarette per day increased the excess CHD risk by 40–50%, smoking 5–20 cigarettes per day increased the excess risk to only 55–65% - indicating that the smoking-cad relationship is non-linear⁶⁹. Passive smoking also increases the risk of ischemic heart disease⁷⁰. Smoking increases mortality⁷¹. One study showed that men smoking 20 cigarettes per day were twice as likely to die from CHD, when compared with never smokers⁷¹. Smoking cessation can reduce CHD mortality risk by around 36%⁷². This is impressive, when compared to a 29% reduction with statins, a 23% reduction with either beta-blockers or angiotensin-converting enzyme inhibitors, and a 15% reduction with aspirin⁷². Smoking cessation is therefore strongly recommended for all coronary artery disease patients by most major cardiology associations⁷³. The pathological basis of CHD is atherosclerosis, which is enhanced by smoking^{74,75}.

2.3 Smoking and Stroke

Stroke is characterized by a sudden onset of a neurological deficit due to a vascular cause and typically occurs after the age of 50 years⁷⁶. Vascular stroke may be ischemic or hemorrhagic or could result from a subarachnoid hemorrhage⁷⁶. Ischemic stroke is the most common⁷⁷. The Global Burden of Disease collaborators in a report published in 2018, estimated that the global lifetime risk of stroke from the age of 25 years was one in four and that the risk was twice as high for ischemic than hemorrhagic stroke⁷⁸. Stroke is associated with considerable functional disability⁷⁹. It is the second leading cause of death worldwide⁴⁹. The total number of strokes, the related DALY burden, and deaths, are steadily increasing globally, with the bulk occurring in the medium- and low-income world⁴⁹.

Smoking is a major risk factor for stroke⁸⁰, irrespective of the age of the individual^{81,82}. This increased risk appears to be dose-dependent⁸³, and the risk declines with smoking cessation⁸⁴. As noted with CHD, the risk is high even with smoking only one cigarette a day⁸⁵. Smoking one cigarette a day represents approximately 41% of the excess relative risk of getting a stroke when compared to the risk associated with smoking 20 cigarettes a day⁸⁵.

2.4 Smoking and Heart Failure

HF affects 2–4% of the global population, according to the World Health Organization⁸⁶. It is characterized by several functions restricting symptoms, such as shortness of breath, fatigue, and swelling of the ankles⁸⁷. These show frequent exacerbations and these result in repeated hospitalizations⁸⁷. The prognosis is extremely poor, and the mortality rate is high, with almost 50% of HF patients dying within 5 years⁸⁸. The main therapeutic goal in HF management is to reduce symptoms, decrease progression, diminish mortality, and improve the quality of life⁸⁹.

Smoking is associated with an increased risk of heart failure⁹⁰, and this is seen in both HFrEF (heart failure with reduced ejection fraction) and HFpEF (heart failure with preserved ejection fraction) after adjusting for other CVD risk factors⁹¹. The smoking-HF relationship is related to the amount and duration of smoking in HF patients⁹². Smokers not only demonstrate a reduced efficacy to treatment but are also more likely to experience undesirable long-term outcomes⁹³. Unfortunately, about 16% of HF patients continue to smoke⁹⁴. Exposure to second-hand smoke in HF patients is also detrimental and leads to a further reduction their quality of life⁹⁵. Active smoking increases mortality in HF patients⁹⁶. Even smoking in future donors results in a higher incidence of graft failure following heart transplantation and is associated with an increase in mortality⁹⁷. Smoking cessation is the leading modifiable risk factor for HF⁹⁸. The risk of HF declines steadily with increasing duration following smoking cessation⁹⁰.

The increased risk of HF and worse progression in existing HF in smokers are mediated via multifactorial pathways⁹⁹. These included increased inflammation, oxidative stress, impaired endothelial function, increased systemic vascular resistance, atherosclerosis, and ischemic heart disease¹⁰⁰⁻¹⁰³. They also demonstrate sympathetic predominance, increased pulmonary vascular resistance, toxic effects of inhaled carbon monoxide and harmful structural changes in the ventricles¹⁰⁴⁻¹⁰⁶.

2.5 Smoking and Arrhythmias

Atrial fibrillation (AF) is a common arrhythmic disorder¹⁰⁷. Its prevalence is higher in the elderly¹⁰⁸ and in individuals with other cardiovascular risk factors¹⁰⁹. It is a major risk factor for stroke, heart failure, and cognitive dysfunction, and the former two often being the first manifestations of AF¹¹⁰. Patients with established AF have a five-fold increase in their risk of stroke compared to those without this arrhythmia¹¹¹. It also reduces the individual's quality of life and is associated with increased mortality^{112,113}. According to Dai et al., AF contributed to about 290,000 deaths globally in 2017¹¹⁴.

The link between smoking and increased risk of developing AF is well established^{115,116}. A prospective, population-based study showed that the increased risk of developing atrial fibrillation was increased in both current and former cigarette smokers¹¹⁷. Similar conclusions have been reached in several other studies^{118,119}. Chamberlain et al found that current smoking increased the incidence of AF more than two-fold¹¹⁸. Former smokers also demonstrate a higher risk, although this risk is lower than that seen in current smokers¹¹⁹. Secondhand smoke exposure during gestational development and childhood also increases the risk of AF in later in life¹²⁰. Quitting smoking reduces the risk of AF¹²¹.

Even ventricular tachyarrhythmia's are increased in smokers with ischemic left ventricular dysfunction¹²². Ventricular arrhythmias are a major cause of sudden cardiac death¹²³. Cigarette smoking is pro-arrhythmic due to the combined effects of nicotine, carbon monoxide, and pro-cyclic aromatic hydrocarbons^{124,125}.

2.6 Smoking and Valvular Diseases

Severe calcification of the aortic valve invariably results in impaired left ventricular outflow¹²⁶. The prevalence of moderate to severe aortic valve stenosis (AS) increases with age¹²⁶. Shortness of breath eventually develops in these patients and symptomology gradually progresses to angina, heart failure, and syncope¹²⁷. Once symptoms develop, mortality is extremely high, and more than half of AS patients die within 2 to 3 years¹²⁸. Treatment of severe aortic stenosis includes aortic valve replacement, either via a surgical or percutaneous approach¹²⁹. Globally, the prevalence of aortic valve calcification has steadily increased over the last 3 decades⁴⁹.

Several observational studies have established that smoking increases the risk of aortic valve stenosis¹³⁰⁻¹³³. Thanassoulis et al reported that greater cigarette use was associated with elevated odds for aortic valve calcification (AVC), even after adjusting for other cardiovascular factors¹³¹. In the MESA study, the risk for incident AVC was more than doubled in active smokers relative to never smokers, independent of other clinical factors¹³². The Cardiovascular Health Study reported 35% increased odds for aortic stenosis in smokers¹³³. This increased risk of aortic valve stenosis associated with smoking has also been noted in several prospective cohort studies¹³⁴. Stenotic aortic valve disease is pathologically like atherosclerosis, with lipoprotein deposition, chronic inflammation, and active leaflet calcification¹³⁵.

2.7 Smoking and Aortic Aneurysm

An aortic aneurysm, either thoracic or abdominal, is defined as a permanent localized dilatation of the vessel at least 150% compared to a relative normal adjacent diameter or with a maximal transverse diameter that exceeds 30 mm^{136,137}. It is estimated that abdominal aortic aneurysms, have a prevalence of 1.4% in those studied aged 50 to 84¹³⁸. They are potentially life-threatening, as rupture carries an extremely high mortality rate of 80–85%¹³⁹.

There is a strong association between smoking and the risk of developing abdominal aortic aneurysms, both in current and ex-smokers^{140,141}. It is estimated that smokers are almost 4 times more likely to die from aortic aneurysm than nonsmoking men and women¹⁴². Thoracic aortic aneurysms are uncommon but smoking also appears to increase the risk of their occurrence¹⁴³. Although decline in smoking has reduced their prevalence in some areas, abdominal aortic aneurysms continue to increase morbidity and mortality, in most parts of the world⁴⁹. Isolated aortic aneurysms develop from complex mechanisms, including apoptosis of vascular smooth muscle cells, oxidative stress, and inflammation¹⁴⁴.

2.8 Smoking and Peripheral Artery Disease

PAD is an atherosclerotic disease involving the pelvic and leg arteries¹⁴⁵. It is characterized by intermittent claudication¹⁴⁶. As the disease progresses, pain occurs at rest and the critical limb ischemia ultimately leads to tissue necrosis and amputation¹⁴⁷. PAD is a cardiovascular disease equivalent and is associated with a high rate of non-fatal and fatal cardiovascular events¹⁴⁸. PAD is diagnosed by measuring the ankle brachial index (ABI), and an ABI < 0.90 is extremely sensitive, and specific for a diagnosis of PAD^{149,150}. It affects more than 200 million people worldwide¹⁵¹. Its global prevalence and its associated mortality is rising⁴⁹.

Smoking is causally associated with PAD¹⁵². It is estimated that almost 80% if individuals with PAD smoke or have smoked in the past¹⁵³. Not only is the risk of PAD in smokers increased several-fold, but continuation of smoking also worsens prognosis in these individuals^{154,155}. Smoking is also associated with restenosis after endovascular revascularization, graft failure and amputation in PAD patients¹⁵⁶. Individuals smoking more than 1 pack per day have significantly greater adverse limb complications at one year, compared to those who smoked less¹⁵⁷. Continued smoking also increases the risk of myocardial infarctions and premature death in patients with PAD¹⁵⁸. Cessation of smoking helps reduce symptoms of

claudication in these patients but also helps reduce cardiovascular morbidity and mortality^{159,160}. PAD is an atherosclerotic disease and smoking promotes the pathogenesis of atherosclerosis, the primary pathology in these patients¹⁶¹.

2.9 Smoking and Erectile Dysfunction

ED is defined as a consistent or recurrent inability to attain or maintain a rigid penile erection suitable for satisfactory sexual intercourse¹⁶². It is a common male disorder and is expected to affect more than 320 million men worldwide by 2025^{163,164}. Causes may be endocrine or non-endocrine, and non-endocrine vasculogenic etiology is present in about 80% of cases¹⁶⁵. It is associated with many comorbidities and risk factors including increasing age, obesity (BMI>30 kg/m²), excessive alcohol intake, diabetes mellitus, other cardiovascular diseases, depression, and several other psychological disorders¹⁶⁶. It is usually a part of a more widespread atherosclerotic vascular disease and is known to be a strong predictor of other cardiovascular disorders, especially coronary artery disease¹⁶⁷. Its presence significantly reduces the quality of life in men and their partners¹⁶⁸.

Several epidemiological and prospective studies have shown that smoking increases ED^{169,170}. This adverse relationship has been noted in both former as well as current smokers¹⁷¹. He et al studied the association between smoking and ED among 7684 men without vascular disease¹⁷². The odds ratio of erectile dysfunction was 1.41 for cigarette smokers compared with never smokers¹⁷². Comparable data was obtained in men aged 40–70 years followed for up to 10 years, with the likelihood of developing ED being double in smokers¹⁷³. In a cross-sectional study of Chinese men in Hong Kong, smoking of ≥ 20 cigarettes daily was associated with a 50% increase of having ED¹⁷⁴. Smoking also increases the risk of ED in patients with other CVD risk factors¹⁷⁵⁻¹⁷⁷. The relationship between smoking and ED appears to be dose dependent¹⁷². In one study, penile rigidity during nocturnal erection inversely correlated with the number of cigarettes smoked per day¹⁷⁴. Smoking in ED is a modifiable risk factor and smoking cessation improves ED^{178,179}. This benefit has been noted in middle aged adults regardless of pack-year smoked¹⁸⁰.

Penile erection is largely caused by the presence of sufficient blood flow into the erectile tissue, simultaneous arterial endothelium-dependent dilatation, and sinusoidal endothelium-dependent corporal smooth muscle relaxation^{181,182}. This dilatation is impaired resulting in reduced blood flow to the penis in smokers, due to impaired nitric oxide (NO) synthesis and degradation¹⁸³. NO is the main neurotransmitter mediating vascular actions in the penile vasculature. Further, smoking results in the development of atherosclerosis in the internal pudendal and common penile arteries¹⁸⁴. Smoking may also cause ultrastructural damage to the corporal tissue¹⁸⁵.

2.10 Smoking and Venous Disease

DVT of the lower extremities is a common venous disorder and is associated with significant morbidity and a high rate of recurrence^{186,187}. These patients are at an extremely high risk of developing pulmonary embolism (PE)¹⁸⁸. PE is third most common cause of cardiovascular death in hospitalized patients in the West after stroke and heart attack¹⁸⁹. Acute PE is a significant cause of mortality worldwide, accounting for over 100,000 deaths in 2018 alone¹⁹⁰. Early diagnosis and intervention are paramount as 70% of deaths occur within the first hour of its occurrence¹⁹¹.

The increased risk for developing venous thrombo-embolism (VTE) with smoking has been determined by systemic meta-analytic studies^{192,193}. Kaptoge and group analyzed data from more than 1.1 million participants in 76 cohorts, and found that, smoking was associated with higher risk of VTE¹⁹⁴. El-Nasser recently re-confirmed this adverse link¹⁹⁵. Excess risk for VTE in smokers is also related to hospitalization¹⁹⁶. This risk is more during the first 12 weeks in smokers if there was surgery involved¹⁹⁷. Smoking induces endothelial dysfunction, along with oxidative stress and thrombo-inflammation and these contribute to the venous complications^{198,199}.

2.11 Smoking and other CVD risk factors

Smoking also aggravates many other CVD risk factors, such as diabetes mellitus²⁰⁰, dyslipidemia²⁰¹, insulin resistance²⁰², metabolic syndrome²⁰³, systemic inflammation²⁰⁴, and renal failure²⁰⁵.

III. CONCLUSION

The relationship between tobacco intake and the increased risk of CVDs is well established. The major mode of tobacco use is by smoking cigarettes. This is the number one preventable cause of CVDs. Further, quitting smoking after a major cardiovascular event is also the most effective secondary prevention measure²⁰⁶. The risks of CVDs drop dramatically following smoking cessation, irrespective of the age at cessation. Smoking cigarettes is also the number one preventable

cause of CVD mortality²⁰⁷. These risks are also increased with smokeless tobacco. Cessation of cigarette smoking dramatically reduces the risk of premature death from all smoking-related diseases²⁰⁸. The health risks associated with smoking show a dose-response relationship and there is no lower limit for deleterious effects²⁰⁹. No exposure to tobacco is safe for the cardiovascular system.

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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.

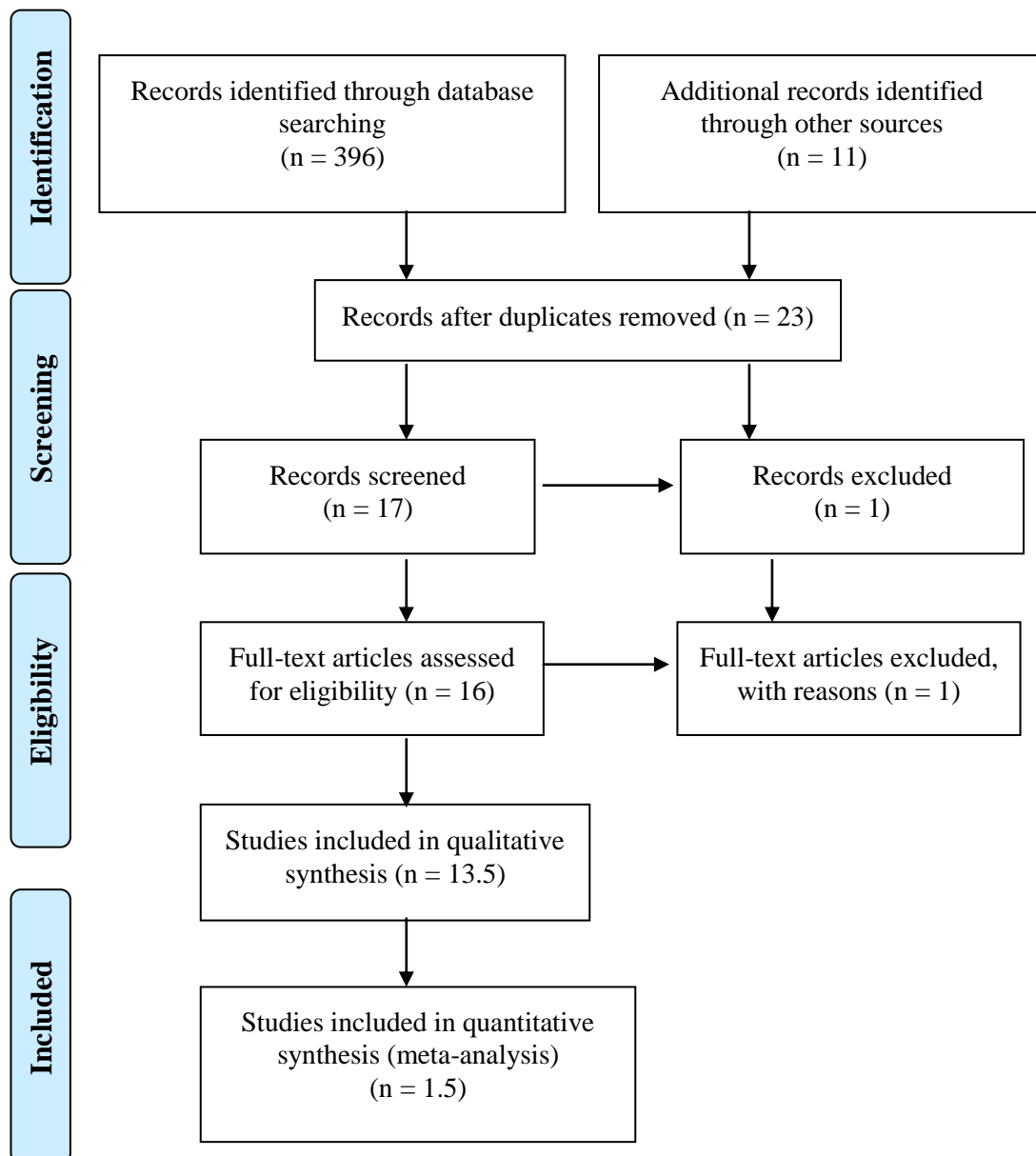


FIGURE 1: Flowchart how to select 15 references that support the lymphopenia mechanism in COFID-19

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 <i>IJID</i> 95(x):304-7	Cross-sectional	ICU pts. 191 COVID-19 pts	D-Dimer Lymphopenia	Mild vs. severe vs. fatal
[7]	Bani-Sadr 2020 <i>Int J Antimicrob Agents</i> 106077	Cross-sectional Before, after	257 COVID-19 pts. 27 March 2020	Lymphopenia < 1G/L	Corticosteroid (vs CPT)
[8]	Gupta A 2020 <i>Med Hypotheses</i> 143(June): 110122	Hypothesis	Early clinical course	Lymphopenia IL-6 >> TNF-a >>	receptor antagonist Prostaglandin signaling
[9]	Zhao Q 2020 <i>IJID</i> 96(x): 131-5	SR and MA	2282 with and without severe	Lymphocyte count-severity	<1.5x10 ⁹ /L: severe
[10]	Yang J 2020 <i>New Microbe New Infect</i> 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 <i>Med Hypotheses</i> 143 (July): 110111	Hypothesis	Severe stage	Lymphopenia and cytokine storms	NF-KB pathway through var mechanism
[12]	Khan S 2020 <i>Saudi Pharm J</i> 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 Arbutol hydrochloride
[13]	Toledo 2020 <i>ClinChimActa</i> 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 <i>Thromb Res</i> 193 (March):110-115	Review	1099 COVID-19 pts.	Lymphopenia then thrombocytopenia	Both as pts. Prognosis with COVID-19
[15]	Zhang J 2020 <i>Brain Behav Immun</i> 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 <i>Travel Med Infect Dis</i> 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 <i>Clin Chim Acta</i> 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 <i>DRCP</i> 167(x): 108338	Retrospective	255 pts: 41 ICU	Lymphopenia Higher IL-6	ICU/death Diabetes>>
[18]	Finelli C 2020 <i>Adv Biol Regul</i> 77(July):100742	Retrospective	46 multicentre CPT in Italy	Lymphopenia	Prognostic evaluation
[19]	Lv Z 2020 <i>Microbes Infect</i> 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,¹¹ Mozafari 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 $<1.5 \times 10^9/L$ 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.

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