DOI: https://doi.org/10.53555/nnmhs.v8i11.1436 Publication URL: https://nnpub.org/index.php/MHS/article/view/1436

ASSOCIATION BETWEEN CARDIOMETABOLIC RISK FACTORS AND COVID-19 SUSCEPTIBILITY, SEVERITY ANDMORTALITY: A SYSTEMATIC REVIEW

Lely Sustantine Totalia*

**Maranatha Christian University, Indonesia Email: lelysustantine@gmail.com*

Corresponding Author:-
lelysustantine@gmail.com

Abstract

The most recent outbreak of the coronavirus has caused widespread devastation across all aspects of human existence and has accelerated the spread of the disease throughout the globe. The coronavirus illness that has been identified in 2019 (COVID-19) has beengiven the name 2019-nCOV. This unique virus is the cause of the COVID-19 disease, which exhibits signs and symptoms that are akin to those of severe acute respiratory syndrome coronavirus 2. (SARS-COV2). Cardiometabolic disease is a group of metabolic abnormalities that increase the risk of type 2 diabetes (T2DM) and cardiovascular diseases (CVDs). These metabolic abnormalities include insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and hypertension (HTN). Environmental risk factors include smoking, leading a sedentary lifestyle, eating an unhealthy diet, and being poor. It is also possible to see it as a collection of interconnected pathophysiological abnormalities that take place in the cardiovascular system as well as other metabolic organs, which lead to an increased risk of type 2 diabetes and cardiovascular disease. According to the findings of study, persons who suffer from hypertension, diabetes mellitus type 2, and obesity are strongly associated with the susceptibility of the disease and the severity it manifests in COVID-19 patients. Althoughhigh blood pressure, also known as hypertension, is one of the most common cardiovascular comorbidities, it is not yet known whether or not the association betweenhigh blood pressure and COVID-19 is independent from advanced age.

Keyword: *Cardiometabolic Risk; COVID-19; Mortality; Severity*

INTRODUCTION

The current pandemic, known as coronavirus disease 2019 (COVID-19), was caused by an infection with severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2). According to an epidemiological update published by the World Health Organization on December 29, 2020, the global cumulative number of cases reported is over 79 million, and there have been over 1.7 million deaths as a result of the disease. Furthermore, there have been over 4 million new cases reported in just the past week alone.[1–3] There is compelling evidence that the risk of mortality is significantly increasedin patients who have comorbidities such as type 2 diabetes, high blood pressure, cardiovascular disease, cancer, chronic kidney disease, congestive heart failure, obesity, and smoking. This is despite the fact that the overall mortality rate remains low, rangingfrom 1.4% to 2.3%.[4,5]

Cardiometabolic disease refers to a group of metabolic abnormalities that increasethe risk of type 2 diabetes (T2DM) and cardiovascular diseases (CVDs), such as insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and hypertension (HTN), aswell as environmental risk factors such as smoking, sedentary lifestyle, poor diet, and poverty. It may also be viewed as a set of interrelated pathophysiological alterations to the cardiovascular system and other metabolic organs that result in an elevated risk of T2DM and CVD. It is a multifaceted illness with genetic, behavioral, and environmental variables, and there is growing evidence that lifestyle modifications and patient education can dramatically lower the risk of this condition.[6,7]

Metabolic syndrome, which depicts a widespread co-occurrence of previously described metabolic risk factors for T2DM and CVD, is on the illness progression spectrum to T2DM and CVD.[8] Currently, metabolic syndrome is defined as having any three of the following five characteristics, according to the Cardiometabolic Disease Staging (CDMS) system and the National Cholesterol Education Program's Adult Treatment Panel III: (1) abdominal obesity defined as a waist circumference of 40 inches in men and 35 inches in women, (2) serum triglycerides of 150 mg/dL or drug treatment for elevated triglycerides, (3) serum high-density lipoprotein (HDL) of 40 mg/dL in men and 50 mg/dL in women or drug treatment for low HDL, (4) blood pressure of 130/85 mm Hg or drug treatment for HTN, and (5) fasting plasma glucose of 100.[9]

This article investigate the sssociation between cardiometabolic risk factors and COVID-19 susceptibility, severity and mortality.

METHODS

Protocol

The guidelines that controlled the conduct of this systematic review were developed with the Preferred Reporting Items for Systematic Review and Meta-Analysis(PRISMA) 2020 checklist serving as the foundation.

Eligibility Criteria

This systematic review was created to examine articles on "Cardiometabolic"; "COVID-19"; "Mortality"; and "Disease severity". These are the subjects covered in the study that was considered. The following requirements must be met for your work to be taken into account: 1) Articles must be available online in their entirety; 2) Articles must be written in English; and 3) Articles must have been published after 2020, but prior to the preparation of this systematic review. Textual contributions of the following sort will not be accepted under any circumstances: 1) Editorial letters, 2) submissions without a Digital Object Identifier (DOI), and 3) article reviews and comparable submissions.

Search Strategy

The search for papers to be included in the systematic review began on 20 November 2022 using the PubMed and SagePub databases with the search terms "Cardiometabolic"; "COVID-19"; "Mortality"; and "Disease severity". Where *("cardiometabolic"[All Fields] OR "cardiometabolically"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR"covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]) AND ("severity of illness index"[MeSH Terms] OR ("severity"[All Fields] AND "illness"[All Fields] AND "index"[All Fields]) OR "severity of illness index"[All Fields] OR ("disease"[All Fields] AND "severity"[All Fields]) OR "disease severity"[All Fields])* is used as search keywords.

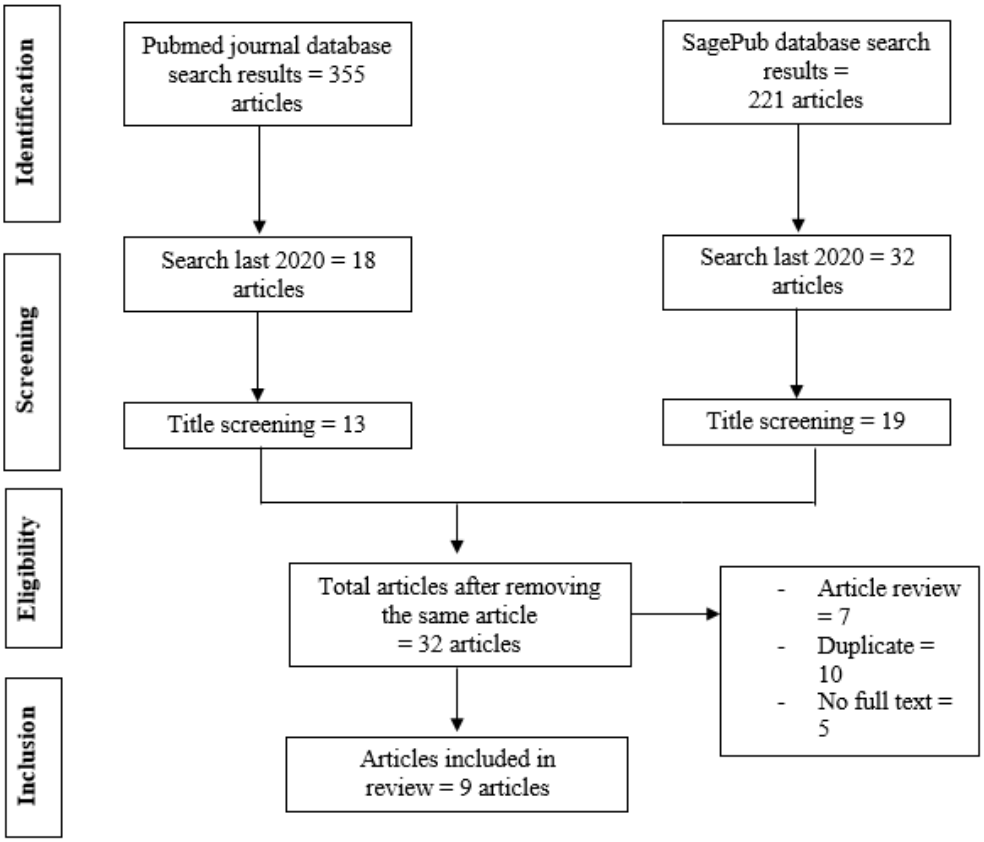

Figure 1. Article search flowchart

Data retrieval

After doing a literature review and reviewing the titles and abstracts of previouslypublished research, the study's author modified the inclusion and exclusion criteria. During the compilation of the systematic review, only those research projects that met each and every criterion were taken into account. It is possible to collect information about each individual study in the form of a title, author, publication date, study site of origin, research study design, and research variables.

Quality Assessment and Data Synthesis

To determine which studies were eligible for consideration, the authors conducted their own independent reviews of a subset of the studies listed in the titles and abstracts of the articles. The full texts of the studies that qualify for inclusion in the systematic review will then be read to determine which studies can be used for the review's purpose.

RESULT

Zhou *et al* conducted a study with 191 patients, 91 patients or 48%, were found to have a comorbid condition, with hypertension being the most prevalent (30%), diabetes(19%), and coronary heart disease (8%). Multivariable regression indicated increased risks of in-hospital death with older age (odds ratio [OR] = 110, 95% CI 103-117 / year increase; p = 00043), higher SOFA score (565, 261-1223; p <00001), and d-dimer >1
g/mL (1842, 264-12855; p= 00033). In survivors, virus shedding lasted 20 days (IQR 17–24), while non-survivors shed SARS-CoV-2 till death. Survivors shed virus for 37 days longest.[10] Zhang, *et al* (2020)[11] showed the most common co-existing conditions were hypertension (30.0%) and diabetes mellitus (12.1%).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size Characteristic	Result
Zhou, 2020[10]	China	Study retrospective	191 patients	48% were found to have a comorbid condition, with hypertension being the most prevalent (30%), diabetes (19%), and coronaryheart disease (8%).
Zhang, 2020[11]	China	Study retrospective	140 patients	The most common co-existing conditions were hypertension (30.0% of patients) and diabetes mellitus (12.1% of patients).
Huang, 2020[12]	China	Study retrospective	41 patients	Most of the infected patients were men (73%]; less than half had underlying diseases (32%), including diabetes (20%), hypertension (six15%), and cardiovascular disease (15%).
Onder, 2020[13]	Italy	Study retrospective	355 patients	30% of these patients were female. The mean age of these patients was 79.5 years. Among these patients, 30% ischemic heart disease, 35.5% diabetes, 24.5% had cancer, and stroke in 9.6% patients.
Docherty, 2020[14]	UK	Study retrospective	208 patients	The commonest comorbidities were chronic cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%), and chronic kidney disease (16%); 23% had no reported major comorbidity.
Stokes, 2020[15]	US	Study retrospective	5,817,385 patients	The most prevalent conditions were chronic heart disease (31%), simple diabetes (21%), non-asthmatic chronic lung disease (18%), and chronic renal disease (16%). Twenty-three percent of the patients did not have any major comorbidities that were recorded.
Zunyou, 2020[16]	China	Study retrospective	44,672 patients	Mortality rate was 10.5% for patients with CVD, 7.3% for those with diabetes, and 6% for those with HTN.
Wan, 2020[17]	China	Study retrospective	135 patients	43 individuals had an underlying condition, the most common of which were hypertension (13 patients, or 9.6%), diabetes (12 patients, or 8.9%), cardiovascular disease (7 patients, or 5.2%), and cancer 4 patients, or 3.0%.
Guan, 2020[18]	China	Study retrospective	1,590 patients	Hypertension was the mostcommon comorbidity, affecting 16.9% of patients, followed by diabetes, which affected 8.2%. Patients reported having a total of 130 comorbidities, making up 8.2% of the total.

Third study by Huang, *et al* (2020) showed most of the infected patients were men (30 [73%]); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Onder, *et al* showed their mean age of these patients was 79.5 years. Among these patients, 117 had ischemic heart disease, which accounts for 30% of the total, 126 had diabetes, which accounts for 35.5%, 72 had active cancer, 87 had atrial fibrillation, which accounts for 24.5%, 24 had dementia, which accounts for 6.8%, and 34 had a history of stroke, whichaccounts for 9.6%.[13]

Study in UK showed the most prevalent conditions were chronic heart disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%),and chronic kidney disease (16%). Twenty-three percent of the patients did not have any major comorbidities that were reported.[14] The reported frequencies of individual symptoms and underlying health conditions, in addition to asymptomatic cases that were not captured in case surveillances, likely underestimate the true prevalence of COVID-19patients and limit the ability to effectively estimate the risk of SARS-CoV-2 infection incardiometabolic disease patients. This limitation is shared by all of these studies.

Obesity is linked not just to high blood pressure, cardiovascular disease, and T2DM, but also to an increased risk of SARS-CoV-2 infection. 41.7% of COVID-19 patients who were hospitalized in the New York City area between March 2020 and April2020 were either overweight (body mass index [BMI] 25 kg/m2) or obese (BMI 30 kg/m2), according to a study that was conducted during that time period.[19] The number of COVID-19 cases was found to have a positive correlation with the prevalence of obesepatients and the mean BMI, according to the findings of a study that examined BMI of COVID-19 patients. These findings provided additional insight. A past diagnosis of metabolic syndrome was associated with 7 times increased odds of SARS-CoV-2 infection, according to a review of a commercial database that aggregated the electronic health records of 26 major healthcare systems located throughout the United States.[20,21]

Patients who suffer from cardiometabolic illness have a more bleak outlook, according to a research published by the Chinese Center for Disease Control and Prevention, despite the fact that the worldwide case-fatality rate of COVID-19 remains atabout 2.3%. Based on an analysis of 44,672 verified cases in mainland China, the death rate for patients with cardiovascular disease was 10.5%, while the mortality rate for thosewith diabetes was 7.3%, and the mortality rate for those with hypertension was 6%.[16] Other study with 43 individuals had an underlying condition, the most common of whichwere hypertension (13 patients, or 9.6%), diabetes (12 patients, or 8.9%), cardiovascular disease (7 patients, or 5.2%), and cancer 4 patients, or 3.0%.[17]

Hypertension was the most common comorbidity, affecting 16.9% of patients, followed by diabetes, which affected 8.2%. Patients reported having a total of 130 comorbidities, making up 8.2% of the total. After making adjustments for

age and smoking status, the following conditions were found to be risk factors for reaching the composite endpoints: COPD (hazard ratio [HR] (95% confidence interval [CI]): 2.681 (1.424–5.048), diabetes (1.59 (1.03–2.45)), hypertension (1.58 (1.07–2.32)), and malignancy (3.50 (1.60–7.64)).[18]

Patients who have COVID-19 are more likely to experience severe illness, according to a number of studies that were conducted and published in the course of this pandemic. These studies focused on cardiometabolic disease and its component diseases. Because of this, it is essential that patients who have such comorbidities be considered without delay for intensive surveillance or treatment, if it turns out that either of these options is required. These types of interventions are essential for protecting this vulnerable population while also attempting to alleviate the significant strain that severeCOVID-19 and other respiratory conditions put on the critical care resources available inhospitals.

DISCUSSION

There have been several studies that have provided information on individuals who suffer from cardiometabolic illness and their likelihood of contracting the SARS-CoV-2 infection. Zhou *et al.*[10] conducted a retrospective, multicenter cohort study of confirmed COVID-19 patients in China, between December 2019 and January 2020. They discovered that 48% of patients had at least one comorbidity, including 30% of patients with hypertension, 19% of patients with type 2 diabetes, and 8% of patients with cardiovascular disease. The three most prevalent comorbidities were type 2 diabetes, hypertension, and cardiovascular disease.[11,12]

It has been noted that other nations afflicted by the pandemic likewise have an alarmingly high frequency of comorbidities connected to cardiometabolic illness. A examination of dead COVID-19 patients in Italy,[13] which had a stunning overall case- fatality rate of 7.2% in March 2020, revealed that 30% of patients had ischemic heart disease, 24.5% of patients had atrial fibrillation, and 35.5% of patients had type 2 diabetes. 21 Similarly, a prospective observational cohort analysis of 16,749 COVID-19 patients in 166 UK hospitals revealed that among the identified comorbidities, chronic cardiac disease (29%) and simple T2DM (19%) were the two that occurred the most frequently.[14]

Numerous research that used COVID-19 individuals provide evidence that patients who suffer from cardiometabolic disease have a more severe form of their condition. Patients who got critical or fatal illnesses had a considerably increasedlikelihood of having underlying comorbidities such as high blood pressure, cardiovascular disease, and type 2 diabetes.[16–18] Unsurprisingly, similar incidence is alsoobserved in samples from the United States, and as of May 2020, the conditions cardiovascular disease (32%) and type 2 diabetes (30%) were the most prevalent underlying comorbidities in COVID-19 cases.[15]

The reported frequencies of individual symptoms and underlying health conditions, in addition to asymptomatic cases not captured in case surveillances, likely underestimate the true prevalence of COVID-19 patients and limit the ability to effectively estimate the risk of SARS-CoV-2 infection in patients with cardiometabolic disease.[22] This limitation is common to all of these studies and affects the ability to estimate the risk of SARS-CoV-2 infection in patients with cardiometabolic disease.[23,24] Although high blood pressure, often known as hypertension, is one of the most common cardiovascular comorbidities, it is not yet known whether or whether the link between high blood pressure and COVID-19 is independent from advanced age.[25,26]

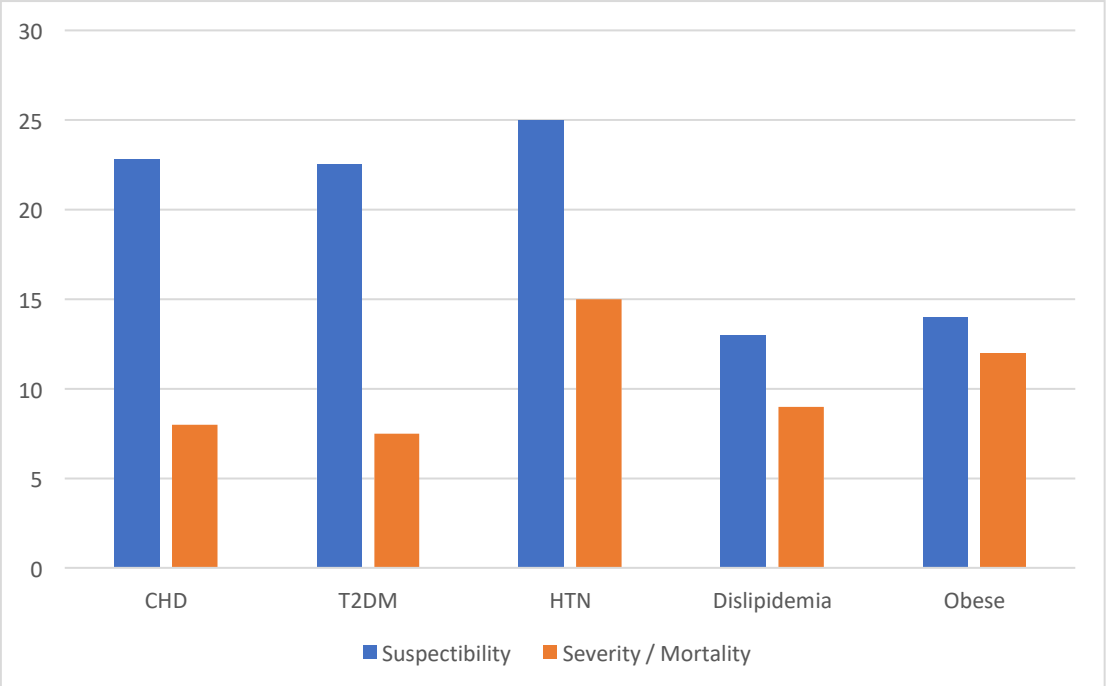

Figure 2. Percentage of comorbidities based on susceptibility and severity/mortality

In the research conducted by Kulkarni et al., the cause for the correlation betweenHTN and the severe form of COVID-19 was investigated. The researchers concluded thatthe correlation may be explained by the high incidence of hypertension in people who areolder.[25] The Centers for Disease Control and Prevention (CDC) says that around 63% ofpersons over the age of 60 have hypertension. On the other hand, damage to end organs in hypertension individuals is a possible alternate cause. Left ventricular hypertrophy andfibrosis are two typical consequences of hypertension, and both of these conditions may render the heart much more susceptible to infection by SARS-COV2.[27]

The idea that the SARS-COV2 virus enters host cells through angiotensin converting enzyme 2 (ACE2) has created questions regarding whether or not patients withunderlying hypertension should continue therapy with ACEI or ARB or whether or not they should stop using these medications. The human angiotensin converting enzyme2 (ACE2) is a type of carboxymonopeptidase that is bound to the endothelium and has a single active site in its catalytic region. Its expression is primarily limited to the endothelial cells that line the arteries, arterioles, and venules in a variety of organs, including the heart, lungs, and kidneys.[27]

An analysis of the current research that is available regarding the relationship between obesity and COVID-19 patients, and more specifically, the proinflammatory state as a mediator, is something that needs to be taken into consideration. This is becauseobesity and increased BMI are associated with increased susceptibility to and severity of SARS-CoV-2 infection and its complications. Studies conducted in the past have demonstrated that patients who suffer from cardiometabolic disease have elevated levelsof proinflammatory markers, which is evidence of a dysregulation of the immune system.[28–30] This, in turn, leads to immune responses that are less than optimal. Components of cardiometabolic disease such as excess adipose mass are known to upregulate the levels of key immune factors such as C-reactive protein, tumor necrosis factor alpha, interleukin-6 (IL-6), and many other adipokines that are involved in chronicinflammatory conditions. This is because excess adipose mass makes it easier for the bodyto store more fat.[31]

CONCLUSION

According to research, individuals who have hypertension, diabetes mellitus type2, and obesity are substantially related with illness susceptibility and severity in COVID-19 patients.

REFERENCE

[1]. He F; Deng Y; Li W; et al. Coronavirus disease 2019 (COVID-19): what we know?J Med Virol. 2020;
[2]. Guan WJ; Ni ZY; Hu Y; et al, Guan WJ, Ni ZY, Hu Y, et al, Guan WJ; Ni ZY; HuY; et al. Clinical characteristics of coronavirus disease 2019 in China. N Eng J Med. 2020;382(18):1708–20.
[3]. Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. BioRxiv.
[4]. 2020;2(7):93–7.
[5]. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. April 2020;382(18):1708–20.
[6]. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. PLoS Med. September 2020;17(9):e1003321.
[7]. Sinclair AJ, Abdelhafiz AH. Cardiometabolic disease in the older person: prediction and prevention for the generalist physician. Cardiovasc Endocrinol Metab. September 2020;9(3):90–5.
[8]. Hertle E, Stehouwer CDA, van Greevenbroek MMJ. The complement system in human cardiometabolic disease. Mol Immunol. Oktober 2014;61(2):135–48.
[9]. Ralston J, Nugent R. Toward a broader response to cardiometabolic disease. Nat Med. November 2019;25(11):1644–6.
[10]. Fauci AS, Jameson JL, Kasper D, et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.
[11]. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). Maret 2020;395(10229):1054–62.
[12]. Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. Juli 2020;75(7):1730–41.
[13]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). Februari 2020;395(10223):497–506.
[14]. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of PatientsDying in Relation to COVID-19 in Italy. JAMA. Mei 2020;323(18):1775–6.
[15]. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. bmj.
[16]. 2020;369.
[17]. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22- May 30, 2020. MMWR Morb Mortal Wkly Rep. Juni 2020;69(24):759–65.
[18]. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and

Prevention. Vol.323, JAMA - Journal of the American Medical Association. American Medical Association; 2020. hal. 1239–42.
[19]. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. Juli 2020;92(7):797–806.
[20]. Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidityand its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. Mei 2020;55(5).
[21]. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW,et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. Mei 2020;323(20):2052–9.
[22]. Ghoneim S, Butt MU, Hamid O, Shah A, Asaad I. The incidence of COVID-19 inpatients with metabolic syndrome and non-alcoholic steatohepatitis: A population-based study. Metab open. Desember 2020;8:100057.
[23]. Yanai H. Significant Correlations of SARS-CoV-2 Infection With Prevalence of Overweight/Obesity and Mean Body Mass Index in the SARS-CoV-2 Endemic Countries. Cardiol Res. Desember 2020;11(6):412–4.
[24]. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS- CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun. Oktober 2020;11(1):5493.
[25]. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. Februari 2011;11(2):85–97.
[26]. Hotamisligil GS. Inflammation and metabolic disorders. Nature. Desember
[27]. 2006;444(7121):860–7.
[28]. Kulkarni S, Jenner BL, Wilkinson I. COVID-19 and hypertension. J Renin Angiotensin Aldosterone Syst. 2020;21(2):1470320320927851.
[29]. Perumareddi P. Prevention of hypertension related to cardiovascular disease. Prim Care Clin Off Pract. 2019;46(1):27–39.
[30]. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol. Maret 2020;94(7).
[31]. Rabaan AA, Al-Ahmed SH, Garout MA, Al-Qaaneh AM, Sule AA, Tirupathi R, et al. Diverse Immunological Factors Influencing Pathogenesis in Patients with COVID-19: A Review on Viral Dissemination, Immunotherapeutic Options to Counter Cytokine Storm and Inflammatory Responses. Pathog (Basel, Switzerland). Mei 2021;10(5).
[32]. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID- 19): A Review. JAMA [Internet]. 25 Agustus 2020;324(8):782–93. Tersedia pada:https://doi.org/10.1001/jama.2020.12839
[33]. Chua RL, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, et al. COVID- 19 severity correlates with airway epithelium-immune cell interactions identifiedby single-cell analysis. Nat Biotechnol. Agustus 2020;38(8):970–9.
[34]. Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol. 2020;10(9):200160.