Sahlgrenska Academy

ECG patterns, cardiovascular aspects and clinical outcomes among Covid-19 patients at Sahlgrenska University Hospital

Degree project in Medicine

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Table of content

1. Abbreviations and acronyms

ACE-2	Angiotensin converting enzyme 2
ACE-inhibitors	Angiotensin Converting Enzyme Inhibitors
ACS	Acute coronary syndrome
AF	Atrial fibrillations
ALAT	Alanine aminotransferase
AMI	Acute myocardial infarction
ARB	Angiotensin Receptor Blockers
ARDS	Acute respiratory distress syndrome
ASAT	Aspartate aminotransferase
AV	Atrioventricular
BMI	Body mass index
CK	Creatinine kinase
COPD	Chronic obstructive pulmonary disease
CoV	Coronavirus
Covid-19	Coronavirus disease 2019
CRP	C-reactive protein
CRS	Cytokine release storm
CS	Cardiac shock
CT	Computer tomography
CT-value	Cycle threshold-value
CV	Cardiovascular
CVD	Cardiovascular disease
ECG	Electro cardiography
ECMO	Extra Corporeal Membrane Oxygenation
GP-130	Glycoprotein-130
HF	Heart failure
HFpEF	Heart failure preserved ejection fraction
HFrEF	Heart failure refractory ejection fraction
ICU	Intensive care unit
IL-6	Interleukin-6
IL-6r	Interleukin-6 receptor
INF	Interferons
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
MERS	Middle east respiratory syndrome
NF-κB	Nuclear factor kappa beta
NSPS	Nonstructural proteins
NSP3	Nonstructural protein 3
NSTEMI	Non-ST-elevation myocardial infarction
NT-pro-BNP	N-terminal prohormone of brain natriuretic peptide
PCR	Polymerase chain reaction

PE	Pulmonary embolism
QTc	Duration from QRS complex to T-wave
Q-wave	Pathologic abnormal wave at start of QRS complex
RAAS	Renin angiotensin aldosterone system
RBBB	Right bundle branch block
RBD	Region binding domain
S-protein	Spike-glycoprotein
S1	Spike-glycoprotein subunit 1
S2	Spike-glycoprotein subunit 2
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ST	Section on ECG between J-point and T-wave
STAT	Signal transducer and activator of transcription
STAT 1	Signal transducer and activator of transcription 1
STAT 3	Signal transducer and activator of transcription 3
STEMI	ST-elevation myocardial infarction
TNT/TNI	Highly sensitive cardiac troponin T/I
OR	Oddsratio
ORF	Open reading frame
VT	Ventricular Tachycardia
VTE	Venous thromboembolism

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Abstract

Introduction: Coronavirus disease 2019 (Covid-19) is a viral infectious disease classified as a pandemic since March 2020. Severity of disease varies from asymptomatic to need of treatment at intensive care unit (ICU) and death. Covid-19 is primarily a respiratory disease but can cause complications in several organs, including cardiovascular (CV) complications.

Aim: To investigate how specific ECG-changes, symptoms, lab values and comorbidities correlate to severity of Covid-19-disease.

Methods: This is an observational cohort study of medical database information including 238 patients treated at Sahlgrenska University hospital between March and May 2020 with confirmed Covid-19 disease and available ECG at admission. Patients were divided into 2 groups; patients that needed treatment at ICU or died in-hospital (ICU/death) and patients who were not in need of ICU treatment and survived (not ICU/death).

Results: No specific ECG-alteration was associated with a higher risk of ICU/death, although presence of any ECG-abnormality (OR 2.1, p-value 0.007) showed an increased risk of severe disease. Also, patients with male sex (OR 2.0, *p*-value 0.028)**,** increased CRP (OR 1.01, *p*-value<0.001), dyspnea (OR 2.6, *p*-value 0.002) pulmonary rales (OR 1.8, *p*-value 0.031), low saturation (OR 0.84, p-value <0.001) and high viral load (OR 0.94, p-value 0.024) showed a significantly increased risk of ICU/death. Medication with beta-blockers (34% vs 20%, *p*-

value 0.01) and Warfarin (5% vs 0-7%. *p*-value 0.04) was more common in the ICU/death group, but the groups did not differ significantly regarding comorbidities or age.

Conclusions: ECG-alterations was associated with need of ICU treatment and death, which might indicate that viral engagement of the CV system leads to an increased risk of severe disease. The most prominent risk factors for need of ICU treatment or death in this study were lung engagement together with lab values of elevated CRP/TNT/Creatinine and high viral load in patients.

Keywords: Covid-19, risk factors, ECG, cardiovascular disease, comorbidities, clinical outcome.

Introduction

Overview

In late 2019, a yet unknown virus rapidly spread in Wuhan, China, today known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing Coronavirus disease 2019 (Covid-19). It has since 11 March 2020 been classified as a pandemic by the World Health Organization (1, 2) and the numerous people infected has proven to be a challenging task for healthcare establishments worldwide. Until recently, there were no preventive or curative treatments, but in the last few months several vaccines have been approved, and on April 17th, 863 million doses of Covid vaccine had been administered worldwide (3). Covid-19 primarily affects the respiratory system, sometimes causing viral pneumonia, but can affect several organs in the body, such as the cardiovascular (CV) system, the digestive system, the urinary system and the nervous system (4-8). Severe complications of Covid-19 include pulmonary ground-glass changes, CV complications such as myocarditis, acute myocardial infarction (AMI), noncoronary myocardial injury, enlarged left ventricle, pulmonary embolism (PE) and Acute Respiratory Distress Syndrome (ARDS) (6, 7, 9). Previous research indicates a higher risk of severe disease or complications in Covid-19 patients with underlying cardiovascular disease (CVD) (10-13). In this study we will investigate the effects of ongoing SARS-CoV-2 infection from the CV point of view by investigating electrocardiographic (ECG) patterns, previous medical history, symptoms on admission and in-hospital complications in correlation to need of intensive care unit (ICU) treatment or death.

Genome and structural composition of SARS-CoV-2

Coronaviruses (CoVs) is part of the family Coronaviridae, subfamily of Coronaviridae, order Nidovirales and realm Riboviria. CoVs are composed of enveloped genomes consisting of single stranded positive-sense RNA. The subfamily is further divided into genera of alpha-,

beta-, gamma- and delta- CoVs based on type of spike glycoprotein (S-protein) (5). Only the first two infect mammals. SARS-CoV-2 has a spherical shaped envelope, belongs to the beta CoV genus with a genome size of 29.8-29.9 kbp (fig.1).

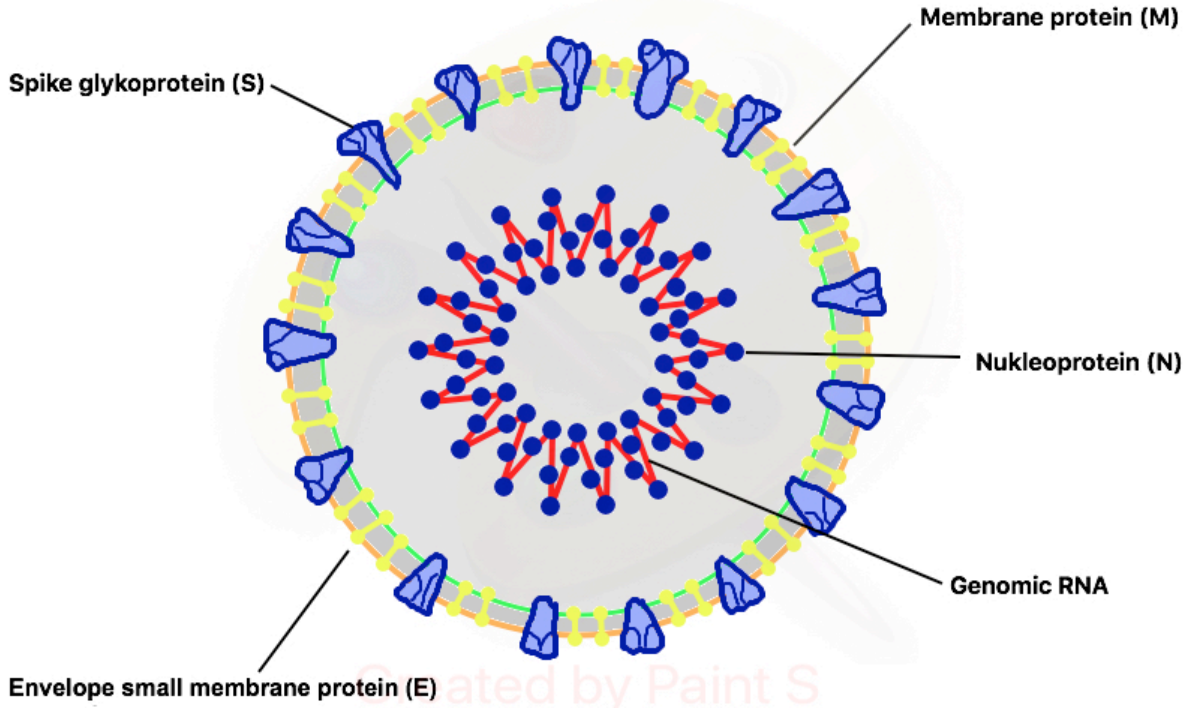

Figure 1. SARS-CoV-2 virus, shape and structure. The RNA-strand is encapsulated in a spherical envelope containing spike proteins, membrane proteins and envelope protein.

Genomic sequencing was initiated early in Wuhan, China, by examining bronchoalveolar lavage fluid samples of initial patients using next generation sequencing technology, providing a template to compare later mutations of viral strains to (1). The genome of SARS-CoV-2 consists of single strain RNA. Located at the 5'-end are two open reading frame (ORF) regions that together contain all non-structural proteins, next follows genes encoding the structural proteins spike, envelope, membrane and nucleocapsid (5). Gene order and location can be used to establish relationship with other virus strains of similar origin (1). The order of genes encoding accessory proteins in SARS-CoV-2 showed 73.8-78.6% similarity to SARS-CoV, 85.3% to pangolin CoV GX/P2V and 96.1% to bat CoVZXC21, and therefore

the bat virus CoVZXC21 is now assumed the origin of SARS-CoV-2, although probably with a yet undetermined intermediate host (1, 5).

One key gene believed to be involved in immunomodulating pathogenesis inducing severe Covid-19 is nonstructural protein 3 (NSP3). NSP3 affects immune cells by altering nuclear factor kappa beta (NF-κB) signaling, as well as increasing activity of signal transducer and activator of transcription 1 (STAT1) (5). Both NF-κB, STAT1 are suggested as important proteins in the formation of the cytokine release storm (CRS) observed in patients with severe SARS-CoV-2 infections associated with high mortality (5, 14). There are also studies indicating that a dysregulation between different STAT proteins might cause CRS in COVID-19 (5, 15) indicating that the mechanism is not yet fully understood. Another

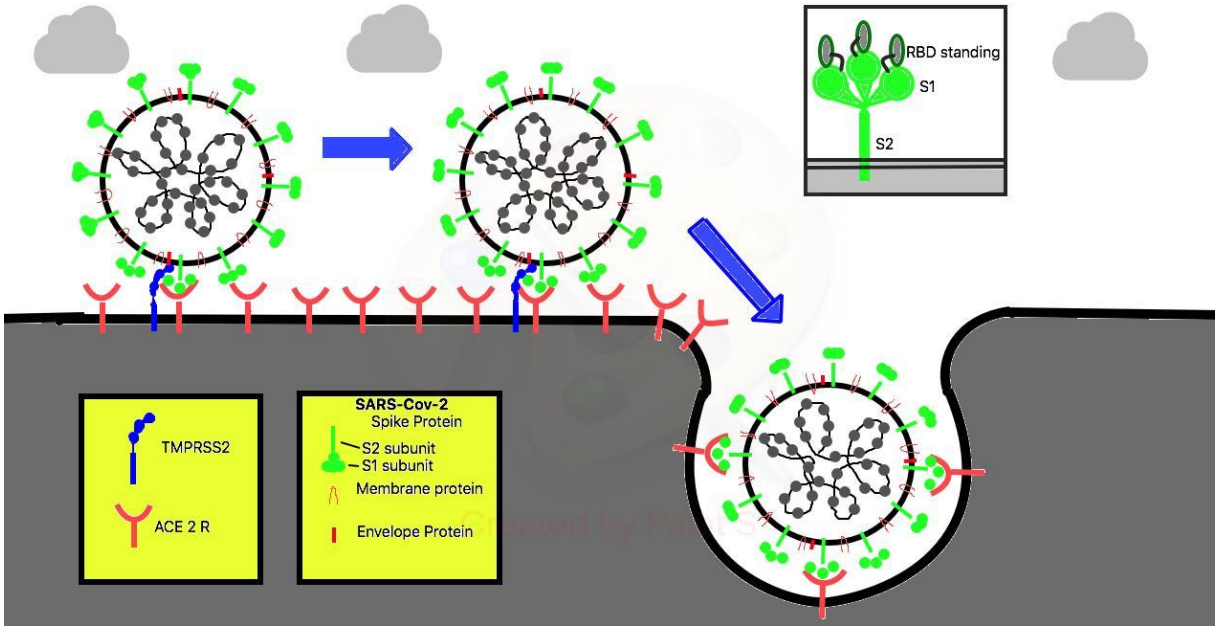

Figure 2. Viral entry into the host cell. Transmembrane serine protease (TMPRSS2) cleaves spike protein into subunits exposing region binding domain of spike glycoprotein (S-protein). Region S1 binds to angiotensin converting enzyme 2 (ACE-2) after which S2 subunit fuses viral envelope with the host cell membrane.

SARS-CoV-2 protein of interests the spike (S)-protein, freely rotating around the virus. The S-protein is composed of 2 subunits named S1 and S2. S1 forms a trisomy configuration and acts as receptor binding domain (RBD) with ability to bind ACE-2 on host cells. The S1

trisomy complex further has motile properties able to form a contracting hinge, pulling the viral envelope closer to the cellular membrane upon S1-ACE-2 binding (5). Thereafter, S2 fuses virus envelope to the host cell membrane enabling viral genome to enter the host cell cytoplasm (fig. 2) (5).

Coronavirus diseases; SARS/MERS/Covid-19

Infections by CoVs are not new, for decades CoVs have been known to cause mild respiratory diseases in humans and domesticated animals (5). A change in severity of infection has been observed since the start of the new millennium, new CoVs with more pathological characteristics have appeared (1, 5). SARS-CoV-2 marks the third CoV causing severe respiratory illness in humans. This alteration in severeness was first observed in 2002 with Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV, infecting 8422 humans. The next new severe CoV disease was Middle East Respiratory Syndrome (MERS) in 2012 caused by MERS-CoV, infecting approximately 1800 humans (5). A total of six known new CoVs then preceded the Covid-19 pandemic, two alpha and four beta subtypes, but none with similar virulence or pathological features as SARS-CoV-2 (1)(1). Infection by SARS-CoV and MERS-CoV share many potential complications with SARS-CoV-2, such as myocarditis, arrhythmias and heart failure (HF)(5).

Viral and pathological properties of SARS-CoV-2

Covid-19 is believed to spread via droplets and direct or indirect contact, with an incubation time of 2-14 days. Infection is initiated through the upper respiratory tract and entry to the host cell is carried out by S-protein binding to ACE-2, same as SARS-CoV (1, 4, 5). ACE-2 in the host cell membrane is necessary for the virus to enter the host cell. ACE-2 is present on many types of cells in the body explaining the variety of organs that can be engaged in Covid-

19 disease. Organs with cells expressing excessive levels of ACE-2 are lung tissue, heart, arteries, kidney and intestines (5), and consequently, involvement of these organs is often seen in severe infection (4, 5). Furthermore, mucosa of the oral cavity expresses ACE-2, which indicates likely entry point of infection. SARS-CoV-2 has a higher affinity to ACE-2 compared to SARS-CoV, as well as altered S-protein cleavability into S1-S2 subunits (1, 5). This upregulates availability of S1, which propagates pathogenic properties and might in part explain SARS-CoV-2s more rapid spreading profile (1). Another reason that SARS-CoV-2 spreads more rapidly is that the virus resides in the upper respiratory tract allowing for spread of infection during early incubation in contrast to SARS-CoV which primarily resides in the lungs (15). When viral infection is established the innate immune system responds by producing interferons (IFN), this subsequently upregulates expression of ACE-2 promoting further viral attachment and infection of host cells in early infection (4, 5). Nonstructural proteins (NSPS) in the viral genome regulate host immunological response by blockade of host-RNA transcription, downregulation of antiviral activity (IFN), host-RNA degeneration, blockage of cell cycle, regulation of mitochondrial function and induction of pathologic immune signaling (5, 15). SARS-CoV-2 is also believed to have immunomodulating features through direct infection of innate monocytes, T-lymphocytes and dendritic cells, seen clinically as lymphocytopenia in patients with severe Covid-19 (4, 15). CRS has been observed in patients with severe SARS, MERS and Covid-19, this is a result of dysregulation of cytokine expression by immune cells due to viral hi-jacking of signal transmission, especially interleukin-6 (IL-6) overexpression is linked to CRS (4). Elevated blood levels of IL-6 and other proinflammatory cytokines is a clinical hallmark of severe Covid-19 and subsequent CRS, resulting in systemic inflammation potentially affecting the multiple organs including CV system (4, 5, 15).

Cytokine release storm

CRS is an umbrella term describing systemic hyper inflammation essential in pathology of SARS-CoV-2 and a feared end point (16). CRS is caused by excessive release of cytokines, mainly IL-6, leading to multiorgan engagement with subsequent failure if not adequately treated (4). In a study by Matsuyama et al. published in October 2020 it is suggested that SARS-CoV-2 proteins inhibit functions of STAT1 and INF in order to evade immune response, resulting in a compensatory elevated expression of signal transducer and activator of transcription 3

(STAT3). STAT3 normally exists in equilibrium with STAT1. This causes a compensatory and devastating positive feedback loop causing massive expression of cytokines (mainly IL-6) resulting in the systemic inflammation observed in Covid-19 (15), although other pathways are possible.

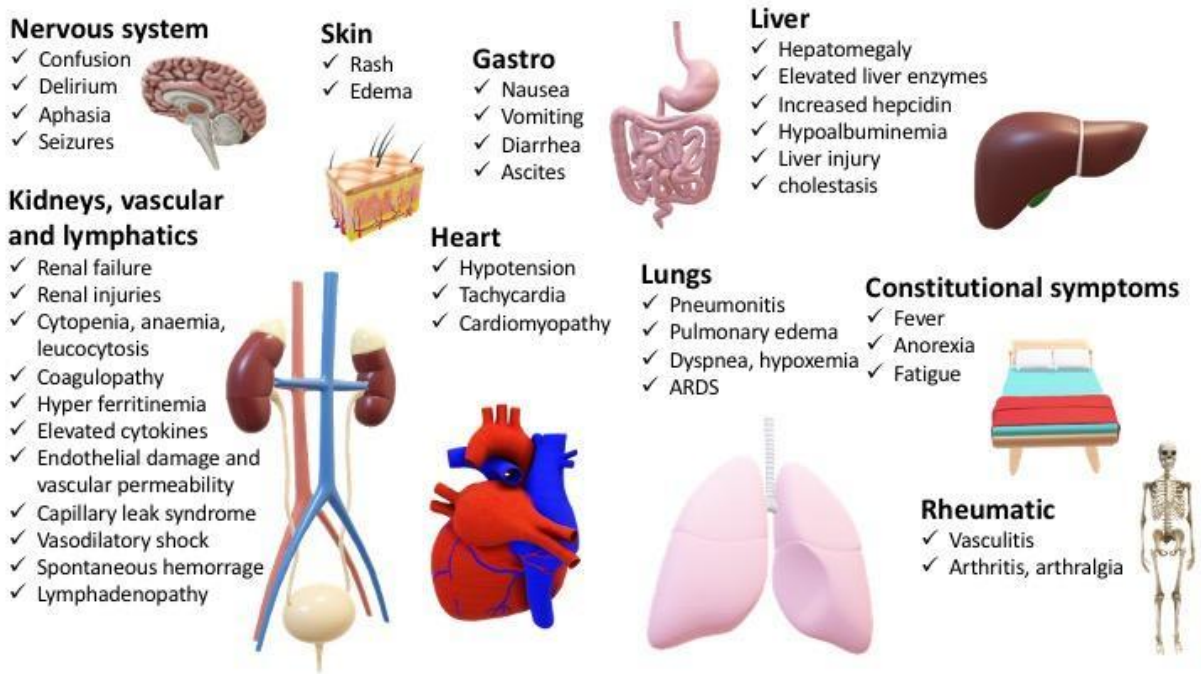

Figure 3. Effects of cytokine release storm (CRS)in Covid-19. CRS can affect several organ systems such as the nervous system, kidneys, skin, gastrointestinal system, heart, lungs, liver, arteries and joints.

Hypotension/vasodilatory shock, tachycardia, cardiomyopathy, dyspnea, hypoxemia, ARDS, vasculitis, coagulopathy, renal failure and endothelial damage are all systemic effects of CRS that can be observed in patients with Covid-19 (4, 16) (fig.3).

There are two pathways to IL-6 transmission, cis-signaling and trans-signaling. IL-6 has to form a complex with IL-6 receptor (IL-6r) and Glycoprotein-130 (Gp-130) to initiate cellular response. Gp-130 is expressed in most cells, and IL-6r can be found on hepatocytes, some epithelial cells and certain leukocytes, or in a free form circulating in plasma. Cis-signaling is conducted through membrane bound IL-6r and trans-signaling via circulating IL-6r (4, 5). Since activation of IL-6 signaling through trans-pathway is conducted via free IL-6r in plasma it has potential to affect all cells expressing GP-130 and therefore believed causative of the systemic inflammation defining CRS (15). Response of IL-6 trans-signaling depends on cell type activated but is always inflammatory in nature (5). Trans-signaling can be a potential target of treatment in severe Covid-19 and inhibition of trans-signaling by Tocilizumab, a monoclonal antibody, is now tested as treatment of severe Covid-19 (4). A British study showed decreased mortality in Covid-19 patients with systemic inflammation when treated with Tocilizumab (17). Siltuximab is a direct IL-6 interacting antibody affecting both pathways and has been studied in several other diseases where CRS is observed and is now evaluated in a European phase III study as treatment in patients with severe Covid-19 (4, 18). To understand Covid-19s impacts on the CV system understanding of the pathological immune response is vital, since most complications, both direct occlusion of coronary artery and myocarditis can be related to dysregulation of immune response caused by viral activity (16).

Pathophysiology – Cardiovascular implications/complications

A variety of complications can be seen in patients with Covid-19 and a minority of patients develop Covid-19 CV syndrome (16). Covid-19 is a predominantly respiratory disease and as such, lung tissue damage is common. This may lead to increased cardiac workload and patients with underlying CVD, especially patients with HF have a reported increased risk of CV complications of Covid-19 (12, 19). However, damage to lung tissue alone does not explain the CV complications documented in patients with Covid-19. In patients suffering from Covid-19, as well as both preceding CoV infections with severe respiratory disease (SARS and MERS), CV complications and manifestations have been described in form of myocarditis, arrhythmias, hypotension, sudden cardiac death with elevation of precursor cardiac injury biomarkers (5, 12, 14). Autopsies of patients deceased in Covid-19 have shown virus infected cardiomyocytes and monocytes in cardiac tissue, indicating that inflammatory processes induced by SARS-CoV-2 infection can cause direct cardiac damage (4, 14, 20). Cardiomyocyte damage can also be caused by inflammation elevated cytokine levels (16). Elevation of cardiac troponin T (TNT /TNI) biomarkers correlates to clinical severity of disease indicating CV involvement as a risk factor of severe Covid-19 (12, 20, 21). As seen in previous CoV diseases SARS and MERS, virus replication in myocardiocytes has been detected also in patients with Covid-19 believed to cause acute myocarditis (16, 20). Ischemia and myocarditis are believed to be the dominant causes of TNT/TNI elevation linked to worse prognosis of Covid-19 infection (12, 16). In fatal cases a progressive elevation of both TNT/TNI and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is commonly seen (1). ACE-2 is part of the Renin Angiotensin Aldosterone System (RAAS) converting angiotensinogen to active angiotensin 2 that is involved in regulation of blood pressure and anti-inflammatory function (5). It has been suggested that medication targeting RAAS might affect severity of Covid-19 disease, since one of the components in RAAS, ACE-2, is directly

targeted by SARS-CoV-2 (5). Still, medication with ACE-inhibitors has not been correlated to a higher risk of severe disease in previous studies (22-24).

The following potential CV complications are known to be associated with SARS-CoV-2 infection: ACS with occlusion (STEMI/NSTEMI), ACS without occlusion, myocarditis due

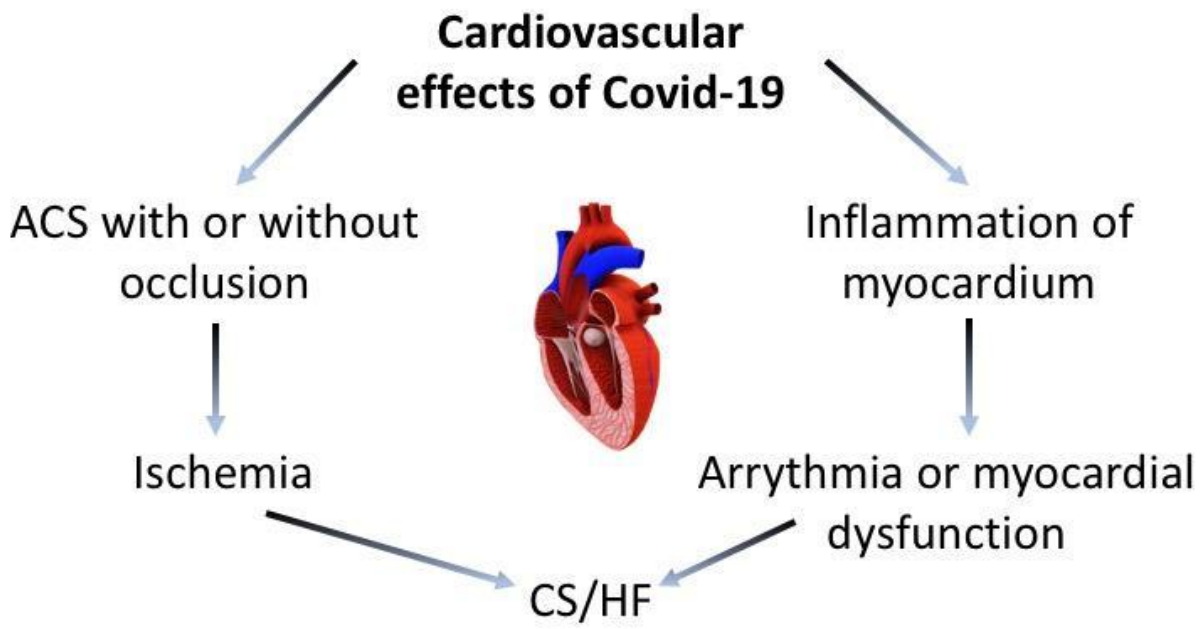

Figure 4. CV effects of Covid-19. Two pathways for SARS-CoV-2 to affect heart function. SARS-CoV-2 infection can cause cardiac shock or heart failure through two different pathways. First pathway is when occlusion or inflammation of coronary arteries cause ischemia in cardiomyocytes leading to cardiac shock or heart failure. Second pathway is when myocardial inflammation induces arrhythmias or loss of cardiac pump function leading to cardiac shock or heart failure. ACS = acute coronary syndrome. CS/HF = cardiac shock/heart failure.

to cytokine dysregulation or viral entry to cell/or immune cells effects on myocardium, stress induced cardiomyopathies, arrhythmias, HF/CS, pericardial effusion with or without tamponade and thromboembolic complications (14, 20, 21, 25). SARS-CoV-2 infection's direct effect on the CV system, focusing on the heart, can be split into two main pathways with similar outcome. The first pathway is when acute coronary syndrome (ACS), with or without coronary artery occlusion, leads to cardiac shock (CS) and/or HF. The second pathway is when inflammation of myocardium with subsequent arrhythmia or myocardial dysfunction leads to CS/HF (12, 16) (fig.4).

In the first pathway it is believed that hyper/hypo-coagulopathy, associated with Covid-19 (4), can cause plaques to become unstable, which together with systemic hyperinflammation and vascular instability can induce rupture in pre-existing vascular plaques, causing coronary occlusions (16). In cases with non-occlusive ACS, it is believed that inflammation of microvascular walls supporting the myocardium leads to hypoperfusion and ischemic infarction (12, 14, 16). In the second pathway leading to CS/HF, arrhythmias and myocarditis are linked to myocardial inflammation, with myocyte damage not due to oxygen deprivation but to inflammatory immune response. This leads to electrical conduction failure, resulting in arrhythmias and/or loss of pump function (12, 14, 16). The commune factor of both described pathways leading to CS/HF is hyper inflammation of tissue (4), disrupting functional cardiac output (12, 14). It has been suggested that an upregulation of ACE-2 in cardiac cells propagates myocardial inflammation as well as viral infection of pericytes, inducing vascular inflammation (5, 16), although this is not yet fully understood. Proposed risk factors for myocarditis during Covid-19 disease are as follows: preexisting CVD, microvascular/thrombotic injury, stress induced cardiomyopathies, CRS, viral myocarditis, hypoxemia, ventricular/atrial arrhythmias, hypotension/shock.

ECG and alterations in Covid-19

Electrocardiography **(**ECG) is a fast and effective clinical examination of the heart, enabling detection of several pathologies in the heart, including coronary heart disease, arrhythmias, failure in electrical conduction, cardiac hypertrophy (26). It's a measurement of electrical activity of the heart muscle over time. It allows for electrical activity to be interpreted by physicians to diagnose myocarditis, AV-blockades, ischemia, left ventricular hypertrophy, LBBB, RBBB, ectopic electrical activity, previous coronary events and strain on cardiac tissue, among other conditions (27, 28).

While the European society of cardiology declare that no specific alteration on ECG has been observed generally connected to Covid-19 (14). Infection is however associated with cardiac injury, detected as elevated cardiac troponins, although these injuries are not typically detected by ECG. Therefore, diagnostic criteria for cardiac events during Covid-19 infection are the same as in uninfected patients (14). A study by Wang *et.al.* describe higher frequents of ST-segment alterations, sinus tachycardia, atrial fibrillations (AF) and ventricular tachycardia (VT) in patients with severe Covid-19 or in critically ill condition. In the critically ill patient group ST-alterations, associated with myocarditis, was the most common alteration among patients with abnormal ECG (48.5%). Sinus tachycardia, atrial arrhythmia and RBBB was also shown in high frequencies among patients with altered ECGs (30%, 13% and 12%) (29). Bergamaschi *et.al. found* that ECG alterations are present in high frequencies among patients with severe Covid-19 disease. They suggest that ECG should be recorded at admission of Covid-19 patients to in-hospital treatment, to serve as baseline if additional recordings are made, and to and to reveal cardiac engagement in Covid-19 at an early stage (21).

Symptoms associated with CV engagement in Covid-19

Chest Pain: a frequent symptom of Covid-19, in some cases due to coronary events such as type 2 myocardial infarction but more often related to viral pneumonia (14).

Dyspnea: Shortness of breath is commonly linked to pneumonia, ARDS or CVD and is very common in patients with Covid-19 infection (12). There is a strong correlation between dyspnea and severity of disease, up to 92% of ICU admitted patients experience dyspnea compared to 31-55% of patients receiving in-hospital, but not ICU, treatment (14).

Cough: Dry/unproductive cough is the most common type of cough, but productive cough is also frequent in patients with Covid-19 disease. 59.4-81.1% of Covid-19 patients experience cough regardless of infection severity (14).

Respiratory distress: Patients with adult respiratory distress syndrome (ARDS) show ground glass opacifications on CT (fig. 5). ARDS is an umbrella term defining respiratory failure with declining O2 and rising Co2. Mortality in patients with ARDS in Covid-19 is high, estimated 52-53%, and a high prevalence of ARDS has been reported in patients with severe Covid-19 disease (14).

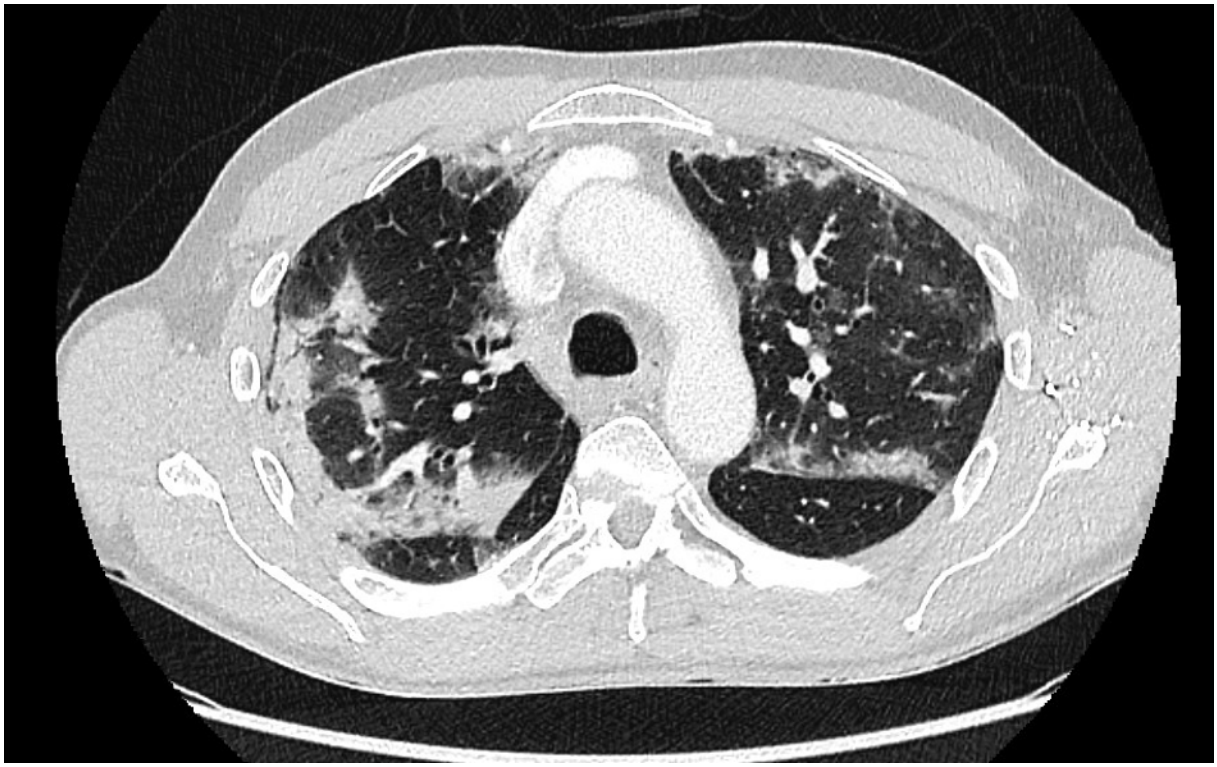

Figure 5. Ground glass opacifications in lung of Covid-19 patient. Picture obtained from computer tomography (CT) scan of lung tissue in a patient with Covid-19, showing ground glass opacifications.

Cardiogenic shock (CS): Covid-19 patients with ACS, myocarditis and sepsis are all considered to have CS. Underlying cardiac conditions play a key role in risk of developing CS when infected by SARS-CoV-2, such as HF or previous AMI (12, 14).

Comorbidities

While risk factors of severe disease during infection by SARS-CoV-2 are many and not yet fully understood, several comorbidities have been reported as risk factors for both severe disease, complications and increased mortality (14). Elderly patients with risk factors are especially vulnerable as seen in several studies (6, 14, 19, 24, 30). In this study, we focus particularly on pre-existing CVD, but several other reported risk factors have been taken into consideration. In a study by Matsuyama *et al*. the most common comorbidities in patients in need of ICU care or deceased from Covid-19 were hypertension, diabetes and obesity (15). A study from the Netherlands by Collard *et al*. concluded that hypertension, diabetes and hyperlipidemia are significant risk factors of severe disease of Covid-19 and patients with two risk factors or more have a significantly increased risk of mortal outcome within the first 21 days of hospitalization. They further report old age, male sex and obesity as predisposing risk factors of increased severity of Covid-19 disease (19). A meta-analysis from Weifang Medical University published in April 2020 by Eastin *et al*. covering 6 retrospective studies including a total of 1558 patients, shows that patients with hypertension, chronic obstructive pulmonary disease (COPD), CVD, Cerebro-VD and diabetes have a significantly higher risk of developing severe Covid-19. This study detected no significant correlation between severe Covid-19 and previous liver disease, renal failure or malignancy (31). Another study by Fadl *et al*. reported that hypertension is the most common risk factor (18.6%) for need of in-hospital care followed by CVD (14.4%) and diabetes (11.9%). Other factors had lower impact on clinical outcome and severity of Covid-19 such as liver disease, smoking, pregnancy and autoimmune disease (32). These studies have different definitions of severe disease, which can make interpretation of results difficult; some studies use clinical symptoms, others use treatment at ICU department to define severe disease.

Risk factors and severity of Covid-19

Infection by SARS-CoV-2 has a wide range of severity spanning from asymptomatic to respiratory failure, multi-organ failure, ARDS, AMI and CS and death (4, 14, 30). Rapid viral replication in lung tissue with subsequent excessive immune response is the most common reason for severe complications (1, 4). The amount of viral load in patients has been correlated to a more severe disease (15). Several studies indicate that age is the most dominant risk factor for severe disease, but all ages are susceptible to the entire range of severity, spanning from non-symptomatic to mortal disease (1, 14, 21). When infected by SARS-CoV-2, studies have indicated that around 80% of patients did not suffer from severe illness, but rather had few to no symptoms of the disease (2, 9). In cases with severe illness, multiorgan engagement and long duration at the ICU was commonly seen (12). An early study by Driggin *et al*. reported that 81.4% had mild, 13.9% severe and 4.7% critical Covid-19 disease with a 3.8% overall fatality rate (2). Other early reports from China showed similar results; asymptomatic/mild disease 81%, severe disease 14%, and critical disease 5% (10, 11). However, in a review published in September 2020, overlooking 86 studies and 91,621 patients, mortality was estimated to be 0.3-2.8% (33). Another study by Hu *et al*. concluded that men above 60 years of age with comorbidities are more likely to develop ARDS and need in-hospital care, as well as AMI and CS, while younger individuals are more likely to be asymptomatic or suffer mild symptoms (1). It has also been shown that cases of critical illness with need of ICU care have higher levels of cytokines in plasma indicating CRS (4). A study by Eastin *et al*. from China included 1099 patients from 552 hospitals where 926 patients had non-severe disease, whereas 173 were severe cases in need of ICU care, invasive ventilation or death (31). Most common symptoms in this study were cough (67.8%) followed by fever (43.8% on admission rising to 88.7% during hospital stay). Uncommon symptoms were nausea/vomiting (5%) and diarrhea (3.8%). In laboratory findings 83.2% patients had

lymphocytopenia and 36.2% had thrombocytopenia, most patients had elevated levels of CRP (30). Aspartate aminotransferase/alanate aminotransferase (ASAT/ALAT), creatinine kinase (CK) and D-dimer, were elevated in patients with severe disease and with fatal outcome in higher prevalence in previous studies (16, 31), D-dimer, CRP and lymphocytopenia have been observed in direct correlation to severity (15). High CRP levels are commonly seen in Covid-19, which is unusual in viral infections (15). Chest CT scans were performed on 975 patients and revealed abnormalities in 86.2% of patients with Covid-19. Most common were ground glass opacity (56.4%) and bilateral shadow (51.8%) (31). Patients with severe disease had pre-existing illnesses to a higher extent than patients with non-severe disease (38.7% vs 21%) (14, 19, 31).

To summarize, many studies have investigated the properties of the SARS-CoV-2 virus, its pathophysiology as well as risk factors for severe disease in Covid-19. The true mortality and severity of Covid-19 infection is still unclear and hard to estimate, both due to a vast number of asymptomatic patients not tested, as well as uncertainty in country specific reporting of Covid-19 cases and death. For calculating the true mortality, it has been proposed that excess mortality might be superior to crude reported deaths (12, 14). More research will be needed before the mechanisms of infection, complications and risk factors are fully understood.

Aim

The aim of this study was to provide better understanding of the CV aspects of the Covid-19 infection by describing ECG changes, in-hospital CV complications, implications of pre-existing CVD and effect on overall clinical outcome. Although initially designed as a strict ECG/CV study we also included clinical values, medical history and medication in our analysis to confirm previous findings regarding progression and possible risk factors of adverse outcome in patients with Covid-19. We also analyzed the most common symptoms of Covid-19 as well as the association between presenting symptoms and clinical outcome. The primary endpoint was the composite of need of ICU treatment or in-hospital death and our research questions were the following:

1. Are there any frequent or specific ECG changes correlated to severity in patients with Covid-19?
2. Are ECG changes related to clinical outcome and in-hospital complications?
3. Which are the main CV complications of Covid-19?
4. How does pre-existing CVD affect the clinical outcome of Covid-19?
5. What symptoms and lab values are correlated to severity of the disease?

Materials and methods

Patient selection

In this observational cohort study, we included all patients ≥18 years old with positive PCR test for SARS-CoV-2 and available admission-ECG at admission to Sahlgrenska University Hospital from March to May 2020. Patients who were admitted only for the cause of isolation of infection, i.e., not because of clinical symptoms requiring hospitalization, were excluded as well as patients with missing admission ECG (ECG within 24 hours of admission to in-hospital care). Among a total of 439 patients, 34 patients were not in need of in-hospital care and for 167 patients no admission ECG was available, leaving a total of 238 patients to be included in the study.

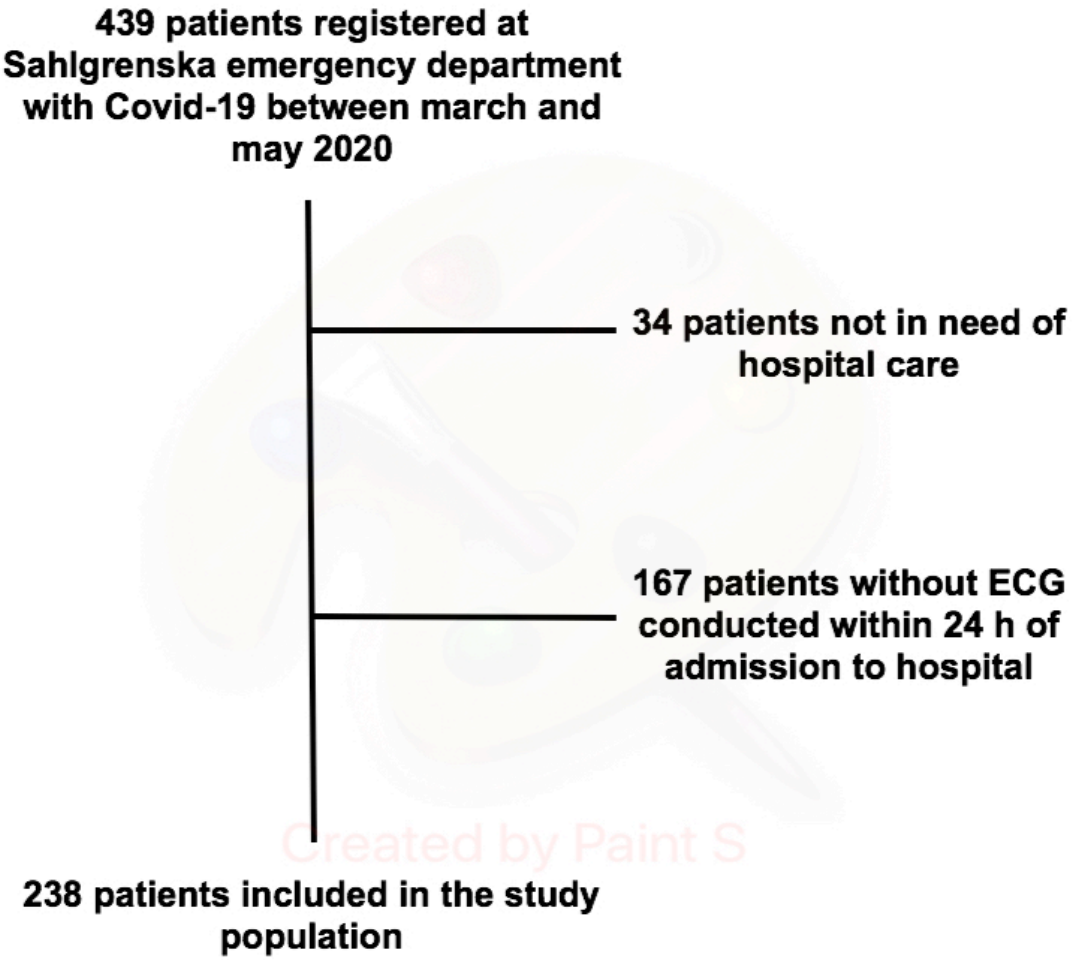

Figure 6. Study flow chart of patient selection.

Data collection

Information regarding baseline characteristics, presenting symptoms, detailed medical history, presenting clinical parameters, laboratory values and in-hospital complications was extracted from the patient's medical charts in the journal system Melior. Detailed ECG data (baseline admission ECG) for all patients were collected and analyzed by trained medical students and experienced physicians.

ECG analysis

ECGs were recorded at a paper speed of 50 mm/s and an amplification of 10 mm/mV. ST-segment deviation was measured from at the J-point from the isoelectric line to the nearest 0,5 mm, T-wave and Q-wave amplitude was measured from the isoelectric line to peak or nadir to the nearest 0,5 mm. Values for heart rate, PQ-interval, QRS-duration, QRS-axis and QT-time were electronically derived using EC web view (by Cardiolex version 4.1.4.47) and Bazett's formula was used to calculate the corrected QT interval (QTc). All ECG-definitions used in this study are summarized in Table 1

Statistical analysis

Statistical differences of baseline characteristics, presenting symptoms and signs, ECG-changes and in-hospital complications were calculated between patients in two separate groups; ICU/death and not ICU/death. In the group labeled ICU/death we included all patients that at some point of hospitalization needed care at ICU and/or suffered a fatal outcome in Covid-19 within 2 weeks of discharge from hospital. In the not ICU/death group we allocated patients that were in need of hospital care but not at ICU and who survived Covid-19. For continuous normally distributed variables (blood pressure at admission, heart rate, breaths per minute, body mass index (BMI), CT-value (Cycle threshold-value) and creatinine levels in

plasma) we calculated mean and standard deviation. Student's T-tests were used to calculate differences between groups for continuous normally distributed variables. For variables that were not normally distributed (saturation at admission, CRP, TNT, NT-pro-BNP, LWMH, electrical axis, PQ-interval, QTc-interval and QRS duration) we calculated median and interquartile range and for categorical variables we calculated percentages. We used Mann-Whitney U-test to determine differences for continuous, not normally distributed variables and Chi-Square tests for categorical variables. For the ECG- and clinical predictors of ICU treatment or death univariable logistic regression was used to calculate Odds Ratio (sex, dyspnea, pulmonary rales, saturation 0_2, SARS-Cov-2 CT-value and CRP at admission found in table 6). No multivariable analysis was applied to the data in this study.

Ethics

This study has been approved by the Swedish Ethics Review Authority (DNR 2020-01569). All patient related data collected in this study is kept separate from personal information to ensure patient integrity and confidentiality. This project is part of a larger study that was approved by the Ethics committee, adding retrospective analysis of. UCG is utilized to find correlation between cardiac anomalies and response to experimental medication such as Klorokin Phosphate, myocarditis and Takosubosyndrome in addition to presented data in our study.

Student's contribution:

The student has contributed to the study by collecting patient data, medical history, lab values, clinical data and data on clinical outcome, and written the thesis.

Table 1. ECG definitions used to analyze ECGs at admission.

Variable	Definition
Heart rate	Number of heart rhythm cycles per minute
Sinus rhythm	Regular rhythm, P waves should be upright in lead II
Atrial fibrillation	Variable irregular ventricular rhythm, absence of p-waves
Atrial flutter	Narrow complex tachycardia, regular atrial activity at approx. 300 BPM, flutter waves ("saw-tooth"), ventricular rate 2:1 block = 150 bpm, 3:1 block = 100 bpm, 4:1 block = 75 bpm
Other rhythm	Other rhythm than sinus rhythm, atrial fibrillation or flutter
Long QTc	Corrected (according to Bazzet's formula) QT interval > 440ms if male and >460ms if female
Normal AV conduction	PR interval <220ms, P-wave followed by QRS without alteration in PR interval or missing QRS complex.
Q-wave pathology	Negative deflection preceding R-wave with duration >40ms or 2 mm deep or > 25% of QRS-amplitude
Normal QRS morphology	QRS<120ms without signs of Right or left bundle branch block, pathologic Q-wave or alteration of electrical axis.
Right bundle branch block (RBBB)	QRS>120ms. RSR' patterns (M-shaped QRS) in leads V1-3. Wide S wave in lateral leads
Left bundle branch block (LBBB)	QRS>120ms; dominant S wave in V1; broad monophasic R wave and absents of Q wave I lateral leads

	Prolonged R peak time > 60ms in leaf precordial leads
Other QRS morphology	Other QRS-morphology than normal, LBBB or RBBB. LAH (LAH=Left axis deviation (-45 to -90 degrees); "qR-complexes" in leads I and aVL; "rS complexes" in leads II, III, aVF; QRS-duration normal or slightly prolonged
Low QRS amplitude	QRS complex with amplitude ≤ 5mm in all limb leads or ≤ 10 mm in all precordial leads
ST-elevation	≥1mm elevation of ST segment measured at the J-point in any two anatomically consecutive leads
ST elevation with reciprocal changes	ST-depression ≥1 mm 60 ms after J-point in electrically opposite leads to the observed ST-elevation
ST-depression	≥1mm depression of ST segment measured 60 ms after the J-point in two anatomically consecutive leads
ST-abnormality	≥1mm elevation of ST segment measured at the J-point in any two anatomically consecutive leads or ≥1mm ST-depression 60 ms after the J-point in two anatomically consecutive leads
T-wave inversion	Negative T-wave in >1mm in any lead except for aVR or V1
Electrical axis	Normal electrical axis from -30° to 90°, <-30° = left axis deviation >90° = Right axis deviation.
PQ-interval	The PQ interval is the time from the onset of the P wave to the start of the QRS complex
QRS-duration	Duration from start of Q or R-wave to end of S-wave

Abnormal ECG	Any of HR ≤50 BPM or QRS ≥ 120 ms or QTc ≥ 500 ms or abnormal QRS-axis or abnormal QRS morphology or low QRS amplitude or Q-wave pathology or ST-elevation or ST-depression ≥1 mm in two continuous leads or abnormal T-wave inversion or non-sinus rhythm or AV-block>2.

Results

Among the 238 patients included in this study we found that 100 patients were in need of ICU treatment, died in-hospital or within two weeks of discharge, this group is referred to as ICU/death. 138 patients survived without need of ICU treatment, referred to as not ICU/death. Seventy-two patients were admitted to ICU and a total of 43 patients died, of which 28 patients never received ICU care. Of all 439 patients available for this study, 34 patients were excluded since they did need in-hospital care and 167 patients due to lack of without ECG examination within 24 h from admission.

Mean age in our study was 61 years, ranging ±16 (95% CI) and 74% (175) of patients in the study population were of male sex, the mean BMI of the cohort was 28 ± 6.1 kg/m^2. Hypertension was the most common comorbidity present in 45% of patients, followed by diabetes (23% of all patients), atrial fibrillation (14% of all patients), stroke (14% of all patients) and ischemic heart disease (12% of all patients). Prevalence of previous HF with or without preserved ejection fraction, and previous venous thromboembolism (VTE) was relatively uncommon in this patient material (9%, 2% and 5% respectively). Most frequent medication before Covid-19 were statins and Beta-blockers (28% vs 25%), followed by ACE-inhibitors (21% of all patients). Calcium antagonist, ARB, diuretics, aspirin and NOAC were also relatively common in the study population (19%, 13%, 12% 11% and 11%).

In this study males had a significantly increased risk of ICU/death (81% vs 68%, *p*-value 0.026) and a higher BMI was associated with an increased risk of ICU/death (29 vs 27, *p*-value 0.04). Age did not differ between the two groups. Overall, in medical history we find no significant differences between ICU/death patients and not ICU/death patients (table 2). Regarding previous medication we found that Beta-blockers were significantly more common

in the ICU/death group compared to the not ICU/death group (34% vs 20%, *p*-value <0.01), as well as warfarin (5% vs 0.7%, *p*-value 0.04).

Table 2. Baseline characteristics - Presenting characteristics, previous medication and medical conditions of interest with distribution among groups calculated for significance using Chi-square test and student's T-test.

Variable	Total N = 238	ICU/death N=100	Not ICU/death N = 138	*p*-value
Age, years	61±16	62±15	61±17	0.87
Male sex, % n/N	74% (175)	81% (81)	68% (94)	**0.026**
Body Mass Index	28 ± 6.1	29 ± 7.0	27 ± 5.1	**0.041**
Previous medical history, % (n/N)				
Ischemic heart disease	12% (28)	15% (15)	9.4% (13)	0.19
HFrEF*	2% (5)	2% (2)	2% (3)	0.93
HFpEF**	9% (21)	11% (11)	7% (10)	0.31
Atrial fibrillation	14% (33)	16% (16)	12% (17)	0.42
Stroke	14% (32)	15% (15)	12% (17)	0.56
Venous thromboembolism	5% (12)	5% (5)	5% (7)	0.98
Hypertension	45% (108)	51% (51)	41% (57)	0.14
Regular medication				
Diabetes	23% (54)	25% (25)	21% (29)	0.47
Beta-blocker	25% (60)	34% (34)	20% (27)	**0.014**
Aspirin	11% (27)	13% (13)	10% (14)	0.46
NOAC†	11% (27)	12% (12)	11% (15)	0.77
Warfarin	3% (6)	5% (5)	1% (1)	**0.035**
ACE††	21% (49)	24% (24)	19% (26)	0.39
ARB§	13% (30)	12% (12)	13% (18)	0.86
Calcium antagonist	19% (44)	20% (20)	17% (24)	0.56
Statins	28% (65)	34% (34)	23% (32)	0.076
P2Y12-inhibitor	6% (15)	8% (8)	5% (7)	0.34
Mineralocorticoid receptor antagonist	3% (6)	3% (3)	2% (3)	0.67
Diuretics	12% (29)	16% (16)	9% (13)	0.11

*Heart failure reduced ejection fraction; ** Heart failure preserved ejection fraction; †Novel Oral Anticoagulants; ††Angiotensin Converting Enzyme Inhibitors; §Angiotensin Receptor Blockers

In table 3 we present signs and symptoms at the emergency department. The most frequent symptoms were cough (79%), dyspnea (69%), fever (60%) and pulmonary rales (43%). Sore throat, diarrhea and chest pain were also relatively common (14%, 14% and 11%). Anosmia presented as loss of smell and/or taste were seen in 7.6% vs 7.1% of all patients. Regarding clinical parameters these patients had a mean saturation level of 91% varying from 85-94%, respiratory rate with mean of 27 ± 8.2 and 71% of patients received additional oxygen. Mean

heart rate at the emergency department was 98 ± 21 mmHg and mean systolic blood pressure was 130 ± 21 mmHg over 77 ± 14 mmHg. CRP levels were often elevated, mean value 93 mg/L, ranging between 43 mg/L and 160 mg/L. Mean creatinine level in the overall study population was 100 ± 71 μmol/L, TNT 14 ng/L ranging between 7.9-29 ng/L, and NT-pro-BNP (first value) of 390 ng/L with range of 130-790 ng/L. The CT value is calculated as the number of polymerase chain reaction (PCR) cycles needed before concentration of DNA reaches threshold level using reverse transcription real-time PCR, hence a lower CT value corresponds to a higher concentration of viral RNA in an exponential manner. In our data the mean CT-value was shown as 27 ± 5.7 cycles.

In the first segment of table 3, we found that dyspnea was significantly more prevalent in the ICU/death group, compared to the not ICU/death group (80% vs 61%, *p*-value 0.002) as well as chest pain (15% vs 5%, *p*-value 0.013) and pulmonary rales (52% vs 37%, *p*-value 0.03). Furthermore, three clinical parameters differed significantly between ICU/death group and not ICU/death group, all with *p*-values <0.001; mean saturation on air (85% vs 93%), need of supplementary oxygen (89% vs 57%) and respiratory rate (30 breaths/min vs 24 breaths/min). Differences between the two groups regarding blood pressure and heart rate were not significantly different butt noted as a trend. Troponin T (TNT) (16 vs 9, *p*-value 0.005), C-reactive protein (CRP) (135 vs 75, *p*-value <0.001) and creatinine (115 vs 91, *p*-value 0.019), all laboratory values that were significantly higher in the ICU/death group compared to not ICU/death group at admission. SARS-CoV-2 CT-value were significantly lower in the ICU/death group compared to the not ICU/death group (26 vs 28, *p*-value 0.022), CT-value, as previously described, a way to measure concentration of viral RNA present in a nose swab.

Table 3. Presenting symptoms and signs. Clinical measurements and observations at admission to hospital in correlations to distribution in groups. Significance was calculated using Chi-square, Mann-Whitney U-test and student's t-test.

Variable	Total N = 238	ICU/death N = 100	Not ICU/death N = 138	*p*-value

Symptoms at admission, % (n/N)				
Fever	60% (138)	63% (63)	57% (76)	0.32
Cough	79% (188)	84% (84)	75% (104)	0.11
Dyspnea	69% (164)	80% (80)	61% (84)	**0.002**
Sore throat	14% (33)	17% (17)	12% (16)	0.23
Nasal congestion	3% (7)	1% (1)	4.4% (6)	0.13
Loss of smell	7.6% (18)	5% (5)	9.4% (13)	0.20
Loss of taste	7.1% (17)	5% (5)	8.7% (12)	0.28
Abdominal pain	3.4% (8)	2% (2)	4.3% (6)	0.32
Chest pain	11% (26)	5% (5)	15% (21)	**0.013**
Diarrhea	14% (33)	17% (17)	12% (16)	0.23
Pulmonary rales	43% (90)	52% (52)	37% (44)	**0.03**
Clinical parameters at admission				
Saturation before O2 treatment	91 (85-94)	85 (76-91)	93 (90-96)	**<0.001**
Need of supplementary O2	71%	89% (89)	57%	**<0.001**
Respiratory rate, BrPM*	27 ± 8.2	30 ± 8	24 ± 7.7	**<0.001**
Systolic blood pressure, mmHg	130 ± 21	130 ± 24	130 ± 19	0.24
Diastolic blood pressure, mmHg	77 ± 14	76.51 ± 14	78 ± 14	0.61
Heart rate, BPM**	98 ± 21	100 ± 23	96 ± 20	0.16
Lab parameters at admission				
SARS CoV2 first CT-value†	27 ± 5.7	26 ± 6.3	28 ± 5.1	**0.022**
Creatinine	100 ± 71	115 ± 89	91 ± 51	**0.019**
C-Reactive Protein	93 (44-160)	135 (78–210)	75 (31-110)	**<0.001**
TNT†† First value	14 (7.9-29)	16 (9.0–34)	9.4 (6.0-17)	**0.005**
NT-proBNP§ First value	390 (140-900)	360 (130–750)	470 (180-1500)	0.39

Breaths per minute; **Beats per minute; †Cycle Threshold value; ††Highly Sensitive Cardiac Troponin T; §N-terminal prohormone of brain natriuretic peptide, O2 = Oxygen.

When analyzing ECGs at admission, we found that 89% of patients had sinus rhythm at emergency department and normal QRS morphology was shown in 89% of patients (table 4). Normal AV conduction was recorded in 87% of all patients and Q-wave pathology was present in 16 patients. AF were recorded in 9.7% of all patients and long QTc was shown in seven cases. Right and left bundle branch block (R/LBBB) was found in 5.9% vs 2.5% of all patients, respectively. ST-elevations and depressions had a prevalence of 5% vs 4.2% in all patients. Negative T-wave was the most frequent alteration in ECG readings and occurred in 24% of all patients. Mean of electrical axis was 21 degrees ranging 13 and 25 degrees.

In the data presented in table 4 we did not find any specific ECG alterations that differed significantly between ICU/death group and not ICU/death group. Atrial fibrillation was slightly more common in ICU/death group, 12% versus 8% in not ICU/death patient group. Atrial flutter was only present in one patient in the ICU/death group and none of the not ICU/death patients. Negative T-wave was the most frequent alteration in ECG readings and occurred in 29% of patients in the ICU/death group and 21% of the patients in the not ICU/death group though the difference was not statistically significant (*p*-value 0.16) Mean electrical axis was 15.5 degrees in the ICU/death group compared to 27 degrees in the not ICU/death group, again the difference was not statistically significant (p-value 0.28).

Table 4. ECG at admission to Sahlgrenska university hospital. Differences between patients in need of ICU care or died and patients that survived without ICU care were calculated using Mann-Whitney U-test and Chi-square test.

Variable	Total N = 238	ICU/death N = 100	Not ICU/death N = 138	*p*-value
Sinus rhythm, % (n/N)	89% (212)	88% (88)	90% (124)	0.65
Atrial fibrillation	9.7% (23)	12% (12)	8% (11)	0.30
Atrial flutter	0.4% (1)	0% (0)	0.7% (1)	0.39
Other rhythm	0.4% (1)	0% (0)	0.7% (1)	0.39
Long QTc	2.9% (7)	4% (4)	2.2% (3)	0.41
QTc>500ms	0.4% (1)	1% (1)	0% (0)	0.24
Normal AV-conduction	87% (206)	85% (85)	88% (121)	0.55
Q-wave pathology	6.7% (16)	8% (8)	5.8% (8)	0.51
Normal QRS morphology	89% (211)	89% (89)	88% (122)	0.89
RBBB	5.9% (14)	6% (6)	5.8% (8)	0.95
LBBB	2.5% (6)	2% (2)	2.9% (4)	0.66
Other QRS morphology	2.5% (6)	3% (3)	2.2% (3)	0.69
Low QRS amplitude	7.1% (17)	8% (8)	6.5% (9)	0.66
ST elevation	5% (12)	6% (6)	4.3% (6)	0.57
ST elevation, reciprocal changes	0% (0)	0% (0)	0% (0)	N/A
ST depression	4.2% (10)	3%	5.1% (7)	0.43
Negative T-wave	24% (58)	29%	21% (29)	0.16
Electrical axis, degrees	21 (13-25)	16 (6.2-25)	27 (13-30)	0.28
PQ-interval, milliseconds	150 (149-157)	150 (146-158)	152 (149-159)	0.69
QRS-duration, milliseconds	92 (93.5-97.78)	95 (93.35-100.09)	90 (92-98)	0.16

QTc time, milliseconds	281 (284-301)	279 (278-310)	283 (281-302)	0.72

AV = atrioventricular; RBBB = right bundle branch block; LBBB = left bundle branch block; N/A = not applicable

In table 5 a number of recorded ECG abnormalities was selected and analyzed with logistic regression to investigate weather there was an elevated risk of severe Covid-19. "Abnormal ECG" includes any type of abnormality on examination and was shown to be associated with a higher risk of ICU/death (OR 2.1, 95% CI 1.2 – 3.6, *p*-value 0.007). No single specific ECG alteration showed a significantly increased risk of ICU/death in this study.

Table 5. Admission ECG and risk of ICU/death. Odds ratio was calculated using logistic regression analysis on binary data using SPSS.

Variable	Odds Ratio	95% CI	*p*-value
Abnormal ECG	2.1	1.2-3.6	**0.007**
Abnormal Rhythm	1.2	0.53-2.7	0.65
ST-abnormality	1.0	0.42-2.6	0.94
ST-elevation	1.4	0.44-4.49	0.57
ST-depression	0.58	0.15-2.3	0.44
Q-wave-pathology	1.4	0.51-3.9	0.51
Long QTc	1.9	0.41-8.6	0.42

ECG = Electrocardiography.

In table 6 clinical symptoms and lab-values were examined using logistic regression to find predictive variables of severe Covid-19. We found that male sex, dyspnea, pulmonary rales and CRP (OR 1.01 for every unit of CRP elevation) at admission showed a significantly increased risk of ICU/death (table 6). Dyspnea had the highest odds ratio of 2.6, followed by male sex (OR 2.0) and pulmonary rales (OR 1.8). High saturation with no added oxygen (OR 0.84 per percent higher saturation) and high first SARS-CoV2 CT-value (OR 0.94 per every higher number of PCR cycles) was associated with lower risk of ICU/death.

Table 6. Clinical predictors of ICU/death – Characteristics, administered treatments, observations and lab values calculated for increased risk of treatment in ICU or with fatal outcome using logistic regression.

Variable	Odds Ratio	95% CI	*p*-value
Male sex	2.0	1.1-3.7	**0.028**
Dyspnea	2.6	1.4-4.7	**0.002**
Pulmonary rales	1.8	1.1-3.2	**0.031**
Saturation no O_2 added	0.84	0.80-0.89	**<0.001**
First CT-value	0.94	0.89-0.99	**0.024**
CRP	1.010	1.006-1.014	**<0.001**

CT-value = cycle threshold-value; CRP = C-reactive protein

At last, we analyzed in-hospital complications with correlation to ICU care or death using logistical regression (table 7). Respiratory support had the highest prevalence and was administered to 35% of all patients via nasal high flow oxygenation and 27%, and through invasive ventilation. 7.1% of all patients received dialysis and 1 (0.4%) patient was administered extracorporeal oxygenation. AF as a complication during Covid-19 infection was shown in 15% of all patients, 8 patients (3.4%) suffered PE and 4 patients (1.7%) had an AMI.

Sustained VT, asystole >10 seconds (documented cardiac event with loss of ventricular contractions and electrical activity above 10 seconds), atrial fibrillation, nasal high flow oxygen, need of invasive ventilation and kidney dysfunction leading to dialysis were all significantly more common in the ICU/death group compared to the not ICU/death group (table 7). Sustained VT and asystole >10 seconds was only seen in the ICU/death group (3 patients and 5 patients, respectively). AMI, ischemic stroke, cerebral hemorrhage and PE showed no significant difference between the groups but are very few and occurred predominantly in the ICU/death group (3% vs 0.7%, 1% vs 0%, and 5% vs 2% respectively).

Table 7. In-hospital complications of Covid-19 patients Incidence of administered treatment and complications during hospitalization comparing patients that died or were in need of ICU care to patients that survived without ICU care. Differences were calculated using logistic regression for statistical significance.

Variable	Total N = 238	ICU/ death N = 100	Not ICU/death N = 138	*p*-value
Need of assisted breathing				
Nasal high flow oxygen	35% (84)	74% (74)	7.2% (10)	**<0.001**
Invasive ventilation	27% (63)	62% (62)	0.7% (1)	**<0.001**
Need of dialysis	7.1% (17)	17% (17)	0% (0)	**<0.001**
Need of ECMO	0.4% (1)	1% (1)	0% (0)	0.24
Acute myocardial infarction	1.7% (4)	3% (3)	0.7% (1)	0.19
Ischemic stroke	0.4% (1)	1% (1)	0% (0)	0.24
Cerebral hemorrhage	0.4% (1)	1% (1)	0% (0)	0.24
Pulmonary embolism	3.4% (8)	5% (5)	2.2% (3)	0.23
Atrial fibrillation/ flutter	15% (36)	27% (27)	6.5% (9)	**<0.001**
Any VT	0.4% (1)	1% (1)	0% (0)	0.24
Sustained VT	1.3% (3)	3% (3)	0% (0)	**0.041**
Asystole > 10 seconds	2.1% (5)	5% (5)	0% (0)	**0.008**

ECMO = Extracorporeal Membrane Oxygenation; VT = Ventricular Tachycardia

Discussion

Cardiovascular burden

In this study, no significant correlation was established between severity of Covid-19 and pre-existing CVD. It is hard to interpret the higher frequency of beta-blockers and warfarin in the ICU/death group, maybe these correlations are falsely positive due to lack of correction for multiple testing. Anyway, since no correlation to a more severe disease were detected for pre-existing CVD, nor for any of the other drugs commonly used in CVD patients, such as NOAC, Aspirin, ACE2 inhibitors, ARB blockers, diuretics, the increased risk of severe disease seen in patients using beta blockers and Warfarin cannot be interpreted as an indication of increased risk of severe disease in CVD patients in this study. The higher frequency of sustained VT, asystole >10 seconds or atrial fibrillation in the ICU/death group is probably explained by disease severity but could also indicate a higher pre-existing CV burden. In our study, elevation of cardiac enzymes (TNT/TNI) circulating in plasma was more common in severe disease, as seen in a previous study by Hendren *et al.* Elevation of troponins can be due to CV stress associated with infection, high cytokine levels or direct viral infection of cardiomyocytes among several other pathological conditions during infection (14, 16, 20, 21). Wang *et. al* showed that severe disease was correlated to elevation of heart rate and atrial fibrillation as to severity of disease, we found a similar trend, although not significant (29).

Previous studies have found correlation between comorbidities and severity in Covid-19 disease (12, 13, 24, 32). Our lack of correlation between severity of Covid-19 and prior CV burden could be due to our small sample size. Also, all patients in our study had a disease severe enough to need in-hospital care, leading to a biased selection of patients not including patients with mild symptoms. Also, the algorithm for patient selection in our study might

affect the outcome of the study. Since all patients, 167 patients without ECG, corresponding to 70% of the study were excluded from this study. Usually, patients with previous cardiac disease, as well as older patients more often undergo ECG at emergency department, hence, this leads to a study population of older and sicker patients. There was a non-significant trend in our material of a higher prevalence of previous hypertension, ischemic heart disease, atrial fibrillation and stroke in the ICU/death group compared to the not ICU/death group which would be in concordance with previous findings (13, 19, 24, 32). Further, there was no significant difference in use of Angiotensin Converting Enzyme Inhibitors (ACE-inh.) and Angiotensin Receptor Blockers (ARB-bl.). This indicates no adverse effect on medication of RAAS in patients with Covid-19, as seen in previous studies (14, 24).

NT-proBNP is often elevated in patients with HF, reported as a CV complication in Covid-19 and a comorbidity with increased risk of severe disease (16, 29). A study by Wang et. al. showed significant elevation of NT-pro BNP in critically ill patients, this correlation could not be confirmed in our study (29). No conclusions regarding NT-proBNP and severity in Covid-19 can be drawn as of our results.

Extra-cardiovascular burden

Regarding extra-CVD burden, symptoms and clinical parameters on admission showed that patients with impaired lung function were more likely to need ICU treatment or die; mean saturation was 93% in not ICU/death group and 85% in the ICU/death group (table 3), and low saturation showed an increased risk of ICU care or death (OR 0.85 per cent higher saturation, table 6). Pulmonary rales, chest pain, need of supplementary oxygen and high respiratory rate were also significantly more frequent in the ICU/death group (table 3). Dyspnea at admission had a significant increased risk of ICU care or death (OR 2.1), as well

as pulmonary rales (OR 1.8). This is expected since lung engagement is a hallmark of severe Covid-19 (4, 15), and need of assisted ventilation is often a reason for admission to ICU care. CRP at admission was significantly higher in the ICU/death group. Likewise, every unit in CRP results in increased risk of severe disease (OR 1.01 *p*-value<0.001), which is in concordance with previous studies (4, 15). Increase levels of CRP can be interpreted as a sign of CRS and systemic inflammation that has previously been described in severe Covid-19 (4, 15, 16).

SARS-CoV-2 first CT-value is an inverted measure of viral genome load in a logarithmic scale. In this study OR for SARS-CoV-2 first CT-value was 0.94 indicating that every unit of decrease in first CT-value implies an increased risk of severe covid-19 due a doubled concentration of virus RNA in nose swabs. An increase in levels of CRP can be interpreted as an indicator of systemic inflammation that has been correlated to severe Covid-19 before (4, 15, 20). Further, male sex had an increased risk of severe disease which is in line with previous findings (13, 19, 32).

ECG in Covid-19

The main finding in this study regarding ECG was that no specific ECG-abnormality showed an increased risk of ICU treatment or death for patients with Covid-19. However, any ECG-abnormality at admission was associated with a higher risk of ICU treatment or in-hospital death.

In this study we did not have ECG-recordings prior to Covid-19 to compare ECGs during Covid-19 to, therefore the ECG alteration might have occurred before the infection. In this analysis abnormal ECG was shown predictive of adverse outcome indicating that any kind of

cardiac engagement resulting in ECG alterations affects severity of Covid-19, as seen in previous studies (14, 21, 29). This finding might also be interpreted as an increased risk of severe disease in patients with precious cardiac disease resulting in alterations of the ECG. Hence, since we cannot tell if the ECG alteration is new and thereby a complication to Covid-19, both theories are plausible.

No specific change was significantly more common in the ICU/death group compared to the not ICU/death group. Patients with cardiac involvement in SARS-CoV-2 infection have proven a rather small proportion of Covid-19 patients, as concluded by several previous studies (2, 12, 14, 20). Still, there are many cardiac events shown associated with SARS-CoV-2 infection (14, 19, 34-36), but at low frequencies. Specific ECG alterations are probably directly linked to specific cardiac complications, as ST elevations are linked to coronary occlusion, which has not been taken into consideration in this study due to very low frequencies of these events. It is highly likely that several specific ECG alterations are predictive of adverse outcome in Covid-19 as seen in a previous study conducted by Wang *et. al*. (29) even though not detected in this study, which is probably due to a small study population. To find specific ECG alterations correlated to in-hospital CV complications of Covid-19, a larger sample population or alteration in study design would be needed.

In this study, negative T-wave was the most recurring ECG alteration with a higher prevalence in ICU/death group although not significant (29% vs 21%, *p*-value 0.16). Since T-wave alteration is normally occurring in patients with previous cardiac events such as AMI (37), the presence of negative T-waves most likely represents patients with previous cardiac morbidity rather than actual CV complications of Covid-19. However, a small number of T-wave alterations might be linked to ongoing cardiac complications such as ACS. A study by

Kathy *et al.* reported that an abnormal T-wave on ECG was connected to increased risk of a cardiac event within 30 days, although Covid-19 was not considered in that study. But since Covid-19 has effect on rupture of vascular plaques through inflammation (4, 16) and this is the proposed genesis of T-wave alterations with increased risk of cardiac events (37), it is possible that a portion of the T-wave alterations seen in this study are linked to an increased risk of future cardiac events.

Electrical axis is a measure of direction of electric conduction in heart musculature and increased conduction towards the left side is typically seen as a remodulation occurring due to hypertension (20). In our study, the mean electrical axis was altered to the left in the ICU/death group compared to not ICU/death, even though not significant (16 degrees vs 27 degrees, *p*-value 0.26). This might indicate that more patients have alterations to heart structure in the ICU/death group compared to not ICU/death.

In-hospital complications

Considering in-hospital cardiac complications, AF and sustained VT were significantly more common in the ICU/death group compared to the not ICU/death group (tab. 7). A study by Bergamaschi *et.al.* reported higher incidence of cardiac events in patients with in-hospital onset of AF (21), as seen in our study. A known bias is that when new arrhythmic events occur it usually leads to an upregulation of care. All patients admitted to in-hospital care were not continuously monitored, whereas patients at ICU are always monitored, leading to a bias in detection of cardiac complications in ICU patients. Sustained VT and asystole >10 s are serious complications indicating need of telemetric registration of cardiac function, this might in part explain the lack of prevalence in not ICU/death group. AMI, ischemic stroke, cerebral hemorrhage and PE were all more commonly found in the ICU/death group compared to the

not ICU/death group in our study, although the differences were not statistically significant. These are all associated with increased risk of severe disease in a previous review by Eastin *et.al* addressing comorbidities associated with Covid-19 (31). Probably, our sample size is too small to reveal this connection. In-hospital complications often correlate to upregulation in intensity of care. In our study this is seen with high flow oxygen as a precursor step to invasive ventilation, both significantly more commonly for patients in the ICU/death group (table 7). Need of dialysis was also significantly more common in the ICU/death group, often correlated to advanced disease with multiorgan failure. Kidney failure can be a result of several conditions leading towards dysfunction: multi-organ dysfunction syndrome, hypotension in correlation to sepsis or loss of vascular tension in CRS, loss of cardiac function due to ACS, or blockade of glomeruli due to rhabdomyolysis seen in long ICU admissions (4, 14, 16, 34).

Some of the patients in this study died without receiving ICU care. Clinicians can decide to refrain from invasive respiration when patients have many comorbidities and are of advanced age, since these patients are unlikely to benefit from ICU treatment.

Limitations and benefits

This study has several limitations. First, because data was collected retrospectively, we could not obtain any information that was not already in the patient's medical charts. Second, only patients with Covid-19 admitted to in-hospital care were included, and therefore, no conclusions regarding the total span of patients with Covid-19 can be drawn from this material. Third, patients had to have an available admission ECG to be included in the study, which is more frequently done in patients with previous CV disease, which may have led to a biased selection of older patients with more comorbidities. There were 167 patients without ECG at admission who were excluded from this study, which corresponds to 38% of all patients available for this study. Fourth, we did not do any correction for multiple testing which might lead to falsely significant differences. As strengths of this study, this is to our knowledge the only study of patients at Sahlgrenska hospital during treatment of Covid-19 evaluating ECG patterns. We have systematically gathered patient information of medical history, presenting signs and symptoms, medication, in-hospital complications, lab-values as well as clinical outcome of a unique set of Covid-19 patients.

Conclusions and implications

The only correlations to CVD seen in this study is that abnormal ECG rhythms at admission were more common in patients with severe disease and that patients who developed AF during hospitalization have increased risk of ICU treatment or death. No specific ECG alteration at admission correlated to severity of Covid-19 in the presented analysis. No conclusion can be drawn regarding CV complications in this study, probably due to low frequencies of CV complications reported in Covid-19 patients, and a small study population. Regarding symptoms and lab, we found several parameters more common in severe Covid-19: increased CRP, as a marker of inflammation, high viral load, elevated TNT and signs of kidney failure. The most prominent predictors of need of ICU treatment or death are symptoms of respiratory failure such as pulmonary rales, dyspnea, elevated respiratory rate, low saturation and need of additional oxygen. Age is likely an important factor of clinical severity in patients with Covid-19, although not shown in this study. More studies will be needed to fully understand mechanisms of infection, complications and risk factors in Covid-19.

Populärvetenskaplig sammanfattning

Titel: EKG-MÖNSTER, KARDIOVASKULÄRA KOMPLIKATIONER OCH KLINISKT UTFALL HOS COVID-19 PATIENTER PÅ SAHLGRENSKA UNIVERSITETSSJUKHUSET

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Under slutet av 2019 började ett nytt virus, som kallas severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infektera människor på den asiatiska kontinenten. Inom kort spred sig viruset till flera andra kontinenter och i mars 2020 deklarerade världshälsoorganisationen (WHO) sjukdomen som en pandemi.

Vid smitta av viruset drabbas människor av den infektion vi nu kallar corona virus disease 2019, eller Covid-19. Covid-19 ger allt från inga, eller några få symptom, till svår sjukdom där man behöver vård på sjukhus. Covid-19 kan i de allvarligaste fallen även vara dödlig. De flesta får lindriga symtom av sjukdomen men eftersom väldigt många smittas är det fortfarande många som blir svårt sjuka. Infektionen av viruset sitter i början i de övre delarna av luftvägarna, dvs svalget och näsan, men kan vid svårare sjukdom även sprida sig till lungor och andra organ i kroppen.

Ett av de organ man har sett blivit påverkat av infektionen är hjärtat. Covid-19 kan då medföra ett flertal olika hjärtsjukdomar såsom inflammation i hjärtmuskulaturen eller hjärtinfarkt. Man tror att detta primärt beror på två anledningar: Ett, att inflammationen som skapas under infektionen leder till påverkan på kroppens kärl som blir retade vilket kan leda till påverkan och sjukdom i hjärtat. Två, att viruset potentiellt kan ta sig in i hjärtats celler och skapa inflammation direkt i hjärtat vilket kan påverka dess normala funktion, och leda till hjärtrytmrubbningar och i värsta fall får hjärtat en sämre pumpfunktion. Man vet att immunceller som infekterats av viruset kan ta sig in i hjärtat, men även hjärtats egna celler

kan bli infekterade av viruset. Under virusets angrepp på kroppen påverkas även immunsystemets förmåga att kommunicera med sig själv. Detta gör viruset för att inte bli upptäckt, och leder hos de sjukaste patienterna till en ökning av inflammationen i kroppen som kan bli mycket farlig och potentiellt livshotande. Flera underliggande sjukdomar, såsom högt blodtryck, diabetes, hög kroppsvikt jämfört med kroppsyta (BMI) och höga blodfetter, har hittills rapporterats öka risken att bli svårt sjuk i Covid-19.

I den här studien letade vi efter hjärtpåverkan av Covid-19 genom att granska undersökningar med EKG och laboratorieprover tagna under infektionen. Genom att analysera medicinska journaler försökte vi klargöra hur underliggande hjärtsjukdomar och andra läkemedelsbehandlingar påverkade huruvida man behövde intensivvård eller inte, samt om man överlevde sjukdomen. I resultaten framkom att när symptom från lungorna var tydliga var det större risk för svår sjukdom, men inga tidigare hjärtsjukdomar visade sig vanligare vid svår sjukdom. Om patienten var överviktig eller av manligt kön ökade sannolikheten för att bli svårt sjuk. Likaså blev sjukdomen svårare om blodprover visade att man hade mycket virus eller kraftig inflammation i kroppen, eller vid tecken på att flera organ var infekterade. Vi hittade inga specifika förändringar på EKG som kunde förutsäga allvarlig Covid-19 men om någon typ av EKG-förändring överhuvudtaget förelåg talade detta för en allvarligare form av Covid-19, med högre risk för intensivvård eller död.

Utifrån våra resultatet drar vi slutsatsen att hjärtpåverkan vid Covid-19 är ovanligt och för att tydligt kunna säga om underliggande hjärtsjukdom eller specifika förändringar på hjärtat kan förekomma vid Covid-19 behöver man undersöka fler patienter.

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