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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

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**THE IMPACT OF THE COVID-19 PANDEMIC ON THE OUTCOME OF
MYOCARDIAL INFARCTIONS**

Diploma thesis

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List of Abbreviations

ACE2 – angiotensin converting enzyme 2

ACS – acute coronary syndrome

AMI – acute myocardial infarction

CAD – coronary artery disease

CK-MB – MB part of creatine kinase

COVID-19 – corona virus disease 2019

CPR – cardiopulmonary resuscitation

CRP – C-reactive protein

cTn – cardiac Troponin

DAPT – dual anti platelet therapy

IRB – institutional review board

LDL – low density lipoprotein

LV-EF – Left ventricular ejection fraction

MERS-CoV – middle east respiratory syndrome corona virus

NSTEMI – non-ST-segment elevation myocardial infarction

NT-proBNP – N-terminal pro brain natriuretic peptide

PCI – percutaneous coronary intervention

PCR – polymerase chain reaction

R_0 – basic reproduction number

SARS-CoV-2 – severe acute respiratory syndrome corona virus 2

STEMI – ST-segment elevation myocardial infarction

UFH – unfractionated heparin

VOC – variant of concern

VOI – variant of interest

WHO – world health organization

1. INTRODUCTION

1.1. COVID-19 pandemic

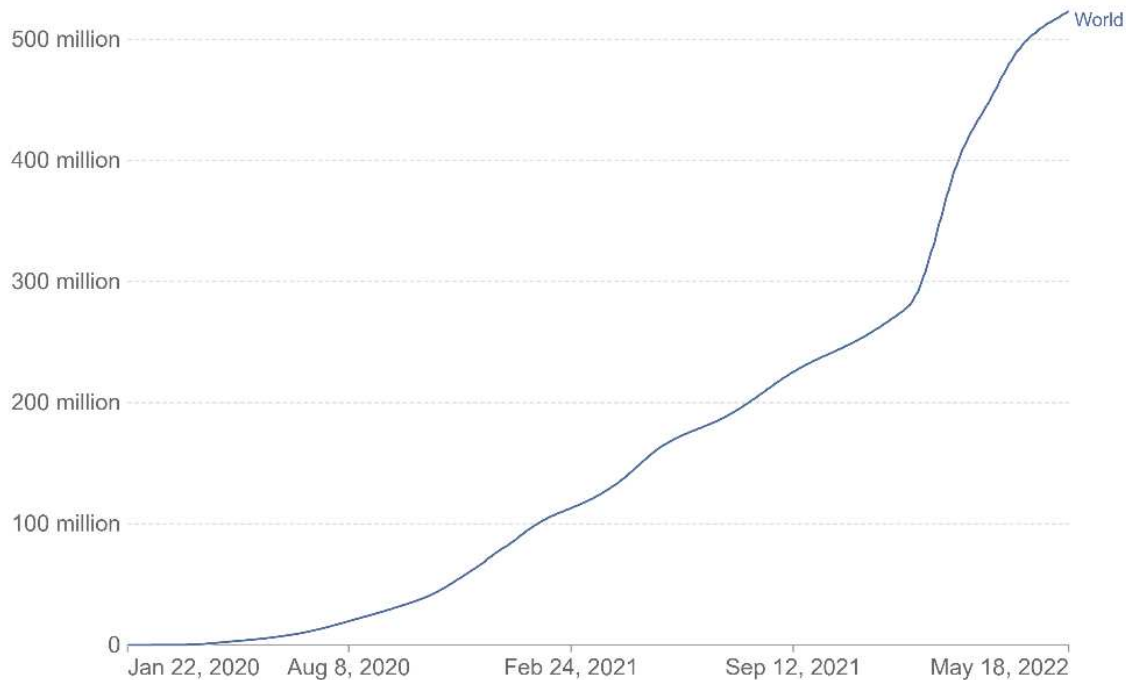
On the 29th of December in 2019 four individuals, who suffered from pneumonia were admitted to the Wuhan hospital. A new variant of the corona virus was isolated in those patients: novel β -genus coronavirus (2019-nCoV) (later referred to as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) (1)). The four patients all were workers at the Huanan Seafood Wholesale Market in Wuhan, China. The pneumonia presented with a strong nonproductive cough. Until January 19th in 2020 198 other cases were identified in Wuhan. Reports of cases in Thailand, Japan, the Republic of Korea, and other parts of China, proved the early spread of the virus (2). Analysis showed a mean incubation period of 5.2 days and a R_0 value of 2.2 (March 2020). The R_0 value gives the mean number of persons one patient can infect. Studies also proved that a person to person spread is possible (3).

Wuhan is seen as the point of origin of the corona virus disease 2019 (COVID-19) pandemic. The decrease in biodiversity is thought to increase the contact between humans and animal reservoirs of viruses because their natural habitat is being destroyed and they are forced to live in proximity to human populations. In Wuhan, bats were the relevant animal. Bats are known to host different kinds of corona viruses, providing a suitable place for the virus to mutate. Different variants of the virus were spreading in different parts of the world. The first case in Italy was reported on the 27th of January, it was a German worker, who was infected by a colleague, who had contact to Wuhan citizens (4).

Until the end of January the virus was reported in 19 countries and the WHO declared the situation as a public health emergency of international concern. The pandemic was declared on the 11th of March 2020, at this point 118.000 infections in 114 countries were counted and 4291 patients have died from the disease (Figure 1.) (5).

Cumulative confirmed COVID-19 cases

Due to limited testing, the number of confirmed cases is lower than the true number of infections.



Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

Figure 1. Cumulative confirmed cases of SARS CoV-2 infections worldwide

COVID-19, corona virus disease 2019; SARS CoV-2, severe acute respiratory syndrome corona virus 2

Source: COVID-19 Data Explorer - Our World in Data [Internet]. Scroll.in. 2021 [cited 2022 May 22]. Available from:

Our World in Data. COVID-19 Data Explorer. Our World in Data [Internet]. 2021 [cited 2022 May 22]. Available from: https://ourworldindata.org/explorers/coronavirus-data-explorer?facet=none&Metric=Confirmed+cases&Interval=Cumulative&Relative+to+Population=false&Color+by+test+positivity=false&country=OWID_WRL~DEU

1.1.1. The SARS-CoV-2 and other corona viruses

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) comes from the family of the *Coronaviridae* and is to 80% related to other corona viruses. It is a RNA virus with a positive sense RNA genome (6).

The virus is mostly transmitted from person to person via respiratory droplets. The virus then gains entrance into the cell via the angiotensin converting enzyme 2 (ACE2), which it binds with its S (spike) protein (6).

The *Coronaviridae* family was responsible for two endemics in the last years, the SARS-CoV-1 endemic in 2003 and the middle east respiratory syndrome corona virus endemic (MERS-CoV) in 2012 (6). The three viruses all mainly target the respiratory system. They all possess a spike protein, which gives the virus its crown-like appearance. Especially the SARS CoV-1 and SARS CoV-2 are genetically quite similar. All three of them are thought to have their origin in bats with possible different species as intermediate carriers, like dromedaries in MERS.

The SARS CoV-1 epidemic resulted in 8,000 infections and 774 deaths in 29 countries, the case fatality rate was 9.6%. The MERS epidemic resulted in 2,519 infections and 866 deaths, which is a case fatality rate of 34.4%. Compared to this, the SARS CoV-2 is much more contagious. This is also proved by the R_0 values: SARS CoV-1 $R_0= 0.58$; MERS $R_0= 0.69$; SARS CoV-2 $R_0=3.1$. (April 2020) (7).

1.1.2. COVID-19

The Corona virus disease 2019 (COVID-19) is primarily a respiratory disease as the virus replicates in the respiratory tract. Patients and especially those with a preexisting chronic disease are prone to develop pneumonia and potentially an acute respiratory distress syndrome (ARDS). The patients usually present with dyspnea, reduced oxygen saturation and elevated inflammation markers (6–8).

COVID-19 is very contagious but less severe in symptoms when compared to the other SARS infections. People older than 50 years are more susceptible to a more severe course of the disease(8). The infection with SARS CoV-2 leads to the release of proinflammatory cytokines like interleukin-6 (and many others) and pneumonia can develop(6).

When the release of inflammatory mediators is very intense, the cytokine storm can lead to an ARDS. This inflammatory reaction is causing different systemic reactions (6–8).

Other organ systems are affected as well. Fever, thrombotic microangiopathy, myocarditis, acute coronary syndrome, lymphocytopenia, general gastrointestinal symptoms, anosmia and ageusia are part of the list of possible symptoms. The symptoms eventually can lead to respiratory and cardiac failure and finally in death. Asymptomatic courses are possible as well and sometimes only anosmia and ageusia are present (6–9).

1.1.3. Chronicles of the pandemic in Germany and Bavaria

The first recorded case of a SARS CoV-2 infection in Germany was on the 27th of January in Bavaria. The first 100 returnees from Wuhan arrive in the following days and are being isolated for 15 days. At the beginning of March, the German government decides to cancel all public events with over 1000 visitors in order to embank the spread of the viral disease in Germany. On the 12th of March Germany decides to focus intensive care capacities on possible COVID-19 infections by recruiting more personnel into hospitals and canceling planned surgeries. Germans visiting Italy, Switzerland or Austria are told to isolate themselves at home for 14 days (10).

On the 16th of March the federal state of Bavaria declares the state of emergency, Bavaria is going to have the most infections in Germany between the 2nd of April and the 21st of October 2020 (11). By now over 6,000 people got infected by SARS CoV-2 in Germany, worldwide more than 180,000 cases are reported (12). Four days later the first lockdown is introduced in Bavaria. From March the 20th until May the 6th, citizens are not allowed to leave their home, apart from valid reasons, including work, important shopping, visits to the doctor and relatives needing care, sporting activities are only allowed alone (11,13).

By the end of March German hospitals secured almost 50% of their capacities for COVID-19 patients, the duty to report free beds is introduced on the 6th of April. Germany continues to expand infection chain tracking system by recruiting more personnel, a digital reporting system for new cases is being developed (10).

On the 22nd of April the Paul-Ehrlich-Institute (Federal Institute for Vaccines and Biomedicines) approved the first clinical trials of a COVID-19 vaccine (10).

The peak of the first COVID-19 wave in Germany was reached at the beginning of April, which allowed the hospitals to continue some elective surgeries in the upcoming time (10,12).

On the 6th of May, Bavaria lifts the curfew but still restricts the get-together of more than two households. In the course of June more and more restrictions get lifted and on the 17th of June the state of emergency in Bavaria is repealed. The German minister of Health appeals to the population to not be afraid of visits to health institutions, the risk of getting infected there does not outweigh the possible health risks of unrecognized and untreated diseases apart from COVID-19. Reports revealed a decrease in visits of 30-50% especially to the department of cardiology and oncology (10,11).

The German government spent 9.5 billion euros on the 4th of June to strengthen the health care system for this and further pandemics. The money is designated to local health

authorities, hospitals, the procurement of protective equipment and the development of a vaccine against SARS CoV-2 (10).

Later on, it is made possible for asymptomatic persons to be tested on SARS CoV-2, as also those without symptoms can spread the virus. For better tracking of the disease spread the Coronavirus warning app is introduced on the 16th of June. Individuals who return from countries with an increased risk of infection are obliged to get a COVID-19 test upon arrival in Germany. At the end of August those people must quarantine themselves regardless of their test result (10).

At the end of the summer the numbers of new infections begin to rise again, and special fever outpatient clinics are introduced to reduce the impact of the pandemic on hospitals and general practitioners (10,12).

With the beginning of the second wave of the COVID-19 pandemic in Germany on the 28th of September 2020 a new political strategy is announced, the so called hot-spot strategy. Considering local infection rates, the local authorities can now react with corresponding restrictions to dampen the spread of new infections. Bavaria approaches the new wave with a “lockdown light” at the beginning of November 2020, which prohibits the meetings of more than two households. Those rules get tightened in December by restricting the number of people, who are allowed being together to merely five. On the 9th of December Bavaria declares the state of emergency again. The leaving of one owns home is now only allowed with an important cause, similar to the curfew in spring 2020. Those rules are going to be intensified in upcoming laws during December (10,11,14).

The government is ordering vaccines against SARS CoV-2 and spends 2.5 billion euros. In the second half of December plans are being made on who to prioritize when the first vaccines are available. The European Medicines Agency approves the vaccine from BioNTech on the 21st of December 2020 and the first vaccination in Germany will be performed on the 26th of December. The second vaccine from Moderna will be approved on the 6th of January 2021. On the 13th of January more than 750,000 people are vaccinated in Germany, in February already 3 million doses were injected, persons in nursing homes are the first to receive the vaccination (10,11,15).

1.1.4. Variants and Evolution of SARS-CoV-2

As an RNA-virus, SARS-CoV2 undergoes frequent mutations, which can lead to a better adaptation to its environment and a more efficient transmission. Especially mutations of the spike protein can make the virus more transmissible, which makes COVID-19 more infectious. As mentioned above the virus uses ACE2 as its receptor to gain access into cells via its spike protein, so a mutated spike protein can result in increased receptor binding affinity. As more people get infected with SARS CoV-2 the immunity in the population rises, which increases the pressure on the virus to adapt to a prepared immune system. One example of those mutations is the D614G amino acid exchange in the spike protein. People infected with this virus have an increased virus load and are more prone to infect persons in their environment (16,17).

The WHO classifies certain variants of SARS CoV-2 as variants of concern (VOC). In comparison to variants of interest (VOI), those VOCs have altered characteristics of transmissibility, virulence or can manipulate countermeasures like tests or vaccines. The first of those VOCs is the B.1.1.7 or alpha variant. The nomenclature is according to the Pangolin classification. The alpha variant was first sequenced in Great Britain (hence the name British variant) in December 2020. 17 amino acids are different in this virus compared to the Wuhan variant. Certain mutations of the spike protein led to false-negative results in PCR tests. It is characterized by a higher reproduction rate, case mortality rate and secondary attack rate. In the first half of 2021 it became predominant in numerous countries including Germany. The B.1.1.7 variant was in charge of 4.4% of new infections in Germany in the third week of 2021. The new infections rose to 9% and 15.4% in the fourth and fifth week respectively (16,17).

At the same time a different variant emerged in South Africa, B.1.351 or beta variant. It possesses nine changes of amino acids, mostly in the spike protein and is able to evade from neutralizing antibodies to some extent. This can lead to a decreased effectivity of possible vaccines or a reduced immunity against this virus when previously infected with an old strain. It is also characterized by an increased transmissibility (16,17).

The gamma variant P.1 emerged in Brazil and became a VOC on the 11th of January in 2021. It is also more transmissible due to mutations of the spike protein (16,18).

In Germany the B.1.1.7 variant was the prominent one at the beginning of 2021, it became responsible for 88% of new cases at the end of March (Figure 2.) (19).

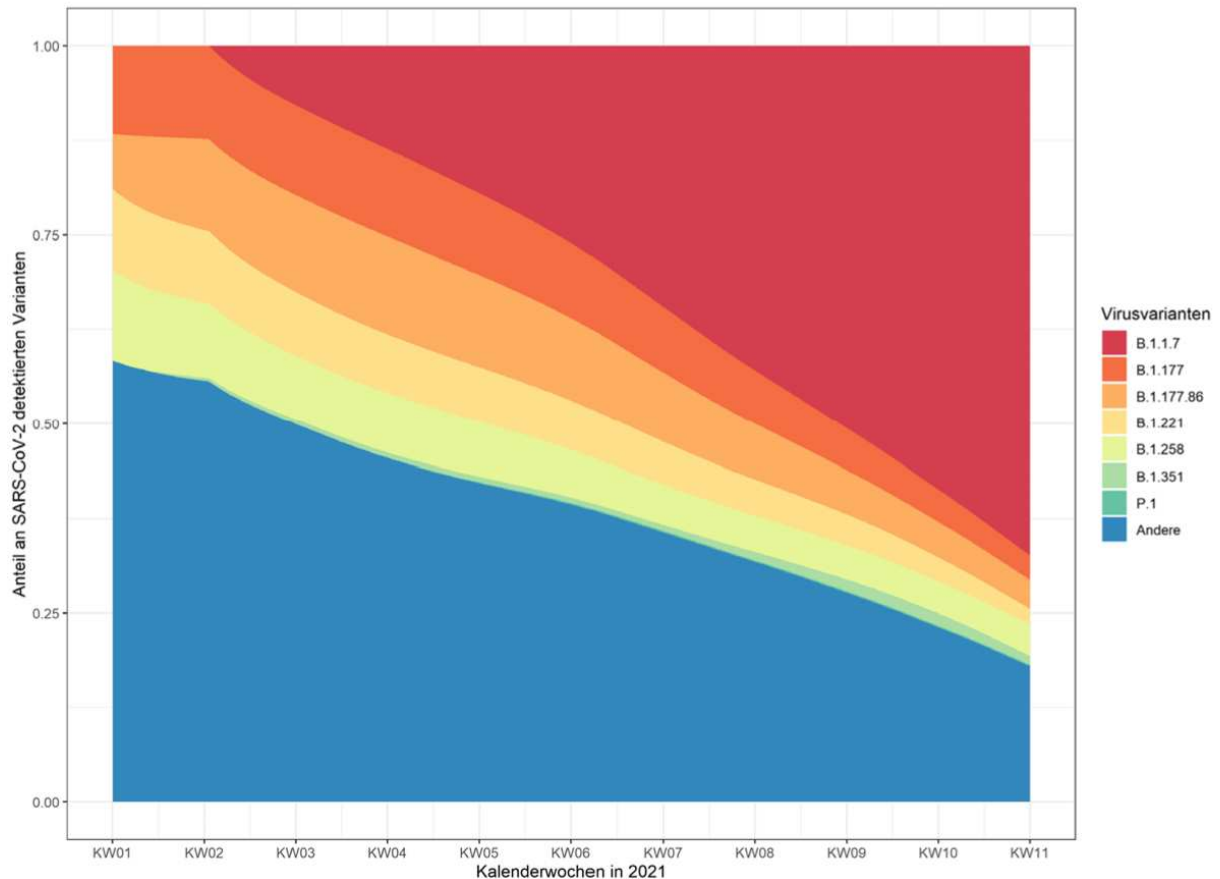


Figure 2. Development of the SARS CoV-2 variants in 2021, x axis - calendar week of 2021, y axis Proportion of SARS CoV-2 detected variants, the variants are color coded on the right Source: RKI Bericht zu Virusvarianten von SARS-CoV-2 in Deutschland (Stand: 07.07.2021) [Internet]. [cited 2022 Jun 17]. Available from:

https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/DESH/Bericht_VOC_2021-03-31.pdf?__blob=publicationFile

1.2. Myocardial infarction

In Germany 1.3% (average from the years 2005, 2007, 2009) of inpatients present due to an acute myocardial infarction (AMI), whereas ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) cases are weighed out. 76% of the cases were older than 60 years and mostly male (67%). Around 11% of the patients died in the hospital after having a myocardial infarction, most of them had a STEMI rather than an NSTEMI. Proportionally more women died from an AMI (20). Coronary artery disease itself is responsible for 13.2% of all deaths, it is the leading cause of death worldwide (21).

Pathologically a myocardial infarction is defined as necrotic death of myocardial cells due to lack of oxygen supply, resulting in ischemia(22) . The first cells begin to die after 20 minutes, and macroscopic changes are present after a few hours. To identify an injury to the myocardium the cardiac enzymes are analyzed, preferably cardiac Troponin (cTn) or the myocyte specific MB-part of the creatine kinase (CK-MB). To exclude chronic elevations of these markers, as present in renal or cardiac failure, an increase or decrease of these values should be measured to manifest the diagnosis. If, however the blood sample was taken late after the symptom onset it is possible that the values of the enzymes are in the plateau phase and no marked increase or decrease can be noted. The values of both enzymes peak after 8-12 h, and cTn can stay elevated up to two weeks (22,23).

Acute Coronary Syndrome (ACS) can be classified into three entities. The STEMI shows ST-segment elevations in the ECG due to occlusion of a coronary artery, the level of cardiac enzymes (most preferably troponin) shows dynamic changes in this case. The NSTEMI does not show constant ST-segment elevations. Other findings, like ST-segment depressions are possible and an increase or decrease in troponin levels is part of the diagnosis. The last entity of the ACS is the unstable angina, where no cell damage occurs and troponin levels are therefore unchanged. All three syndromes share the same clinical symptoms: pain in the chest, with possible radiation to jaw, arm, and neck, dyspnea, palpitations, nausea, and anxiety (22,24)

ECG changes in myocardial infarction are dynamic, that's why more than one, or even continuous ECG monitoring is preferred. ST segment elevations equal or more than 0.1 mV are likely due to a myocardial infarction if found in two contiguous leads. In the leads V2 and V3 deviations must be at least 0.2 mV in men older than 40 years of age, 0.25 mV in men younger than 40 years or at least 0.15 mV in women. ST segment depressions of at least 0.05 mV in two contiguous leads are also suspicious for myocardial infarction, as well as an inverted T wave of at least 0.1mV plus a prominent R wave (or R/S ratio of more than 1). ECG changes on their own are not always diagnostic for myocardial infarction, as ST segment changes can occur in other diseases affecting the heart as well (22).

1.2.1. Pathophysiology

The myocardial infarction is most commonly preceded by atherosclerotic processes in the coronary arteries, also called coronary artery disease. Vessel branching points are predilection sites for the development of atherosclerosis because the non-laminar flow leads to increased oxidative stress, cell turnover and intracellular alterations (21). The vascular adaptation

to turbulent flow leads to an intimal thickening and together with other risk factors, like obesity, diabetes mellitus, smoking, arterial hypertension, increased cholesterol levels, and genetic susceptibility, fibroatheromas can develop. Those fibroatheromas develop due to deposition of lipoproteins (primarily LDL) in the intima, the oxidation of the latter induces an inflammatory response, recruiting inflammatory mediators and macrophages. The lipid particles are phagocytosed by the macrophages, which accumulate as foam-cells in the vessel wall, giving it the appearance of a fatty streak. By apoptotic processes the core of the fibroatheroma becomes necrotic. The core is protected by a fibrous cap of variable thickness. A reduced production of NO can also be advantageous for the formation of atherosclerosis as it leads to a dysfunctional endothelium (21,25,26).

In the case of a stable coronary artery disease (CAD) or stable angina pectoris the plaque is continuously growing in size and eventually leads to stenosis of the coronary arteries. Stable CAD is inducible by stress, such as exercise and leads to a pressure-like pain in the chest that can spread to adjacent regions, like arm, jaw, or neck. In comparison to a myocardial infarction, the stable or unstable angina pectoris is reversible (21,27).

When comparing angina pectoris, NSTEMI and STEMI, only in STEMI the thrombus fully occludes the diameter of the artery, which leads to a transmural infarction of the myocardium. Those occlusive events are mainly due to the rupture of an atherosclerotic plaque. The rupture reveals the lipid-rich core, which is highly thrombogenic (21). In NSTEMI and unstable angina the thrombus does not fully occlude the vessel and is more dynamic compared to a STEMI and therefore the myocardial necrosis is less severe (NSTEMI) or not present at all (unstable angina)(21,24,28)

Inflammatory processes are a key factor regarding plaque rupture. The rupture is initiated by T-lymphocytes, which are recruited by dendritic cells. The T-cells secrete inflammatory cytokines (IFN- γ and TNF- α), which eventually leads to the apoptosis of smooth muscle cells and therefore a reduction in collagen synthesis. Collagen is responsible for the stability of the plaque and its cap. Due to the reduced synthesis and the increased destruction of collagen by matrix metalloproteinases, the plaque eventually ruptures. This is the most common way of plaque rupture, others include plaque erosion, which exposes subendothelial tissue, erosion from calcium nodules and hemorrhage inside the plaque (21).

The occlusion of the artery leads to a lack of oxygen supply to the cardiac muscle and acidosis develops. The damage spreads from the endocardium outwards to the epicardium. The cells begin to swell and intracellular pathways cease as the pH drops and sodium, calcium and

reactive oxygen species accumulate inside the cells. The cardiac myocytes either die because of increased intracellular pressure and rupture or due to apoptosis. The affected tissue loses its contractile abilities after only several minutes. Inflammatory cells begin reparation processes and build up granulation tissue, which transforms into avascular and non-contractile scar tissue after seven days (21,29).

1.2.2. Therapy

The first therapeutic approach is with an antiplatelet therapy using acetylsalicylic acid, which inhibits thromboxane A₂ and therefore the platelet aggregation. Additionally opioids can be given to relieve the pain, which also lowers the sympathetic activity and therefore reduces the cardiac work, even though the development of nausea and vomiting limits its use in the setting of ACS. If the oxygen saturation is below 90%, oxygen supplementation is indicated. Benzodiazepines can be considered if the patient is very anxious. In both, STEMI and NSTEMI patients a therapy with aspirin can be started immediately. Beta blockers are also indicated in stable patients to prevent serious arrhythmias. In STEMI patients a dual anti platelet therapy (DAPT) is recommended after the diagnosis is established. Statins are used in STEMI patients to stabilize the plaque and therefore can also be given immediately (27).

In outpatients, a quick delivery into a PCI center is very important. After the first medical contact, the time until a diagnosis is made should be less than ten minutes. If the first medical contact is at a non-PCI center, a transfer to an appropriate center is advised (27).

A primary PCI is recommended within twelve hours after symptom onset and 120 minutes after the diagnosis of STEMI is confirmed. If those conditions cannot be fulfilled, a fibrinolytic therapy is indicated according to current guidelines. Additionally, if symptoms and ECG changes persist, or complications develop, a primary PCI is still the treatment of choice. When all symptoms and ECG changes have disappeared, it is advised to perform an early PCI within 24 hours. When a fibrinolytic approach was chosen, a rescue PCI is indicated when the lysis was not successful. After a successful lysis a routine PCI is done between two and 24 hours. When performing a PCI the radial artery is the preferred access point and stenting with new drug eluted stents is recommended rather than balloon angioplasty exclusively (27).

If the diagnosis is NSTEMI, PCI is recommended as well. The urgency of the latter is determined by risk stratification, very high-risk patients should undergo the intervention within two hours. Very high-risk patients are hemodynamically instable, have life-threatening arrhythmias or other serious complications. If those conditions are not fulfilled a PCI is

recommended within 24 hours or if the patient is only at low risk, a selective PCI is the way of choice. In NSTEMI patients fondaparinux is used if the time until PCI is delayed and an UFH bolus is given at PCI (24).

In STEMI and NSTEMI patients a dual anti platelet therapy after the intervention is recommended. The DAPT consists out of Aspirin and a P2Y₁₂ inhibitor like prasugrel or ticagrelor, or, if those are contraindicated, clopidogrel. Additional anticoagulation during the PCI is recommended with unfractionated heparin. (24,27).

Although reperfusion is the method of choice, it carries the risk of reperfusion injury. Reperfusion is associated with an increase in endothelial permeability. Endothelial dysfunction is thought to be caused by a decrease in nitric oxide (NO) and an excess of oxygen radicals. Vessels are therefore unable to dilate adequately. The imbalance of NO and superoxide also leads to an inflammatory response with the release of platelet activating factor and tumor necrosis factor, it also increases leukocyte adhesion to the endothelium. White blood cells can obstruct the capillaries and a maldistribution of blood occurs. The inflammatory processes can also affect distant organs and a systemic inflammatory response syndrome, and a multiple organ dysfunction syndrome can develop, increasing mortality (30). Other mechanisms include a sudden restoration of intracellular pH, initiating production of reactive oxygen species and an increase of intracellular Ca²⁺. This is followed by inflammatory processes and cellular damage (31). To prevent such reperfusion injury postconditioning can be used, it includes alternating cycles of reperfusion and ischemia, but it is not fully endorsed in the clinical practice (29).

1.2.3. Myocardial infarctions during the COVID-19 pandemic

A systematic review from 2020 reviewed 27 articles regarding admissions in the emergency department during the newly emerged COVID-19 pandemic. 16 articles focused on patients, who presented with symptoms of acute coronary syndrome. Most of the studies reported a decrease in admissions due to ACS between 40 and 50% when compared to the pre-COVID-19 era. When differentiating between STEMI and NSTEMI, the NSTEMI admissions reduced more. A hypothesis for this could be that NSTEMI symptoms are usually not as severe as those documented in STEMI patients and the affected persons hesitated more to attend medical attention. One explanation for this decrease could be the developing fear in the public of getting infected with SARS-CoV-2, especially in institutions of the health care system. In France, an increase in out hospital cardiac arrest was reported, which could be interpreted as a sign for increased hesitation of visiting the emergency department when experiencing cardiac

symptoms. On the other hand, patients wanted to avoid additional pressure on the health care system, as media reports mentioned overstrained medical institutions. Medical workers were more focused on COVID-19 cases during the pandemic, which could have led to misdiagnosis in some cases. Referring doctors also tried to relieve pressure off the health system and minor cases may not have received as much attention (32).

During the COVID-19 pandemic the number of coronary interventions decreased by 49%. This decline was especially prominent for elective interventions. Still, emergency interventions for STEMI patients have decreased by 33-38%. The decrease in elective PCIs is most probably due to their cancellation to increase the intensive care capacities (33,34).

Data from a hospital in Berlin states not only a decrease in admissions but also a worse outcome and an increased mortality in patients presenting with acute coronary syndrome. To determine the outcome of the disease the left ventricular ejection fraction and NT-proBNP levels were measured. During the COVID-19 era the ejection fraction dropped from 46 to 39% and NT-proBNP levels increased from an average of 8670 to 9935 ng/L. Additionally, the case fatality rate in ACS patients increased by 12.5% compared to the pre COVID-19 time. The worse outcome results from a prolonged time from symptom onset to presentation, so the ischemic time was longer as well (34).

2. OBJECTIVES

2.1. Aims of the study

The aim of this study is to gain more information about morbidity and mortality of myocardial infarctions during the COVID-19 pandemic in the rural region around Coburg, Germany. We want to examine the outcome of myocardial infarctions, that occurred during the first year. This study goes into detail comparing the different waves of the pandemic with each other. We don't focus on the viral disease itself, but on the all-encompassing changes in society and in the health care system.

2.2. Hypothesis

During the COVID-19 pandemic prognostic parameters for myocardial infarctions indicate a decreased outcome.

3. MATERIALS AND METHODS

3.1. Study Design

The study was designed as a retrospective analytical cross-sectional study. The research was performed in the REGIOMED Hospital in Coburg, Bavaria, Germany. The acquired data was anonymized and no conclusions about personal patient information can be drawn. The collected data sets were subdivided into groups and subgroups with regard to the classification of the phases during the COVID-19 pandemic provided by the Robert Koch Institute (35) (Table 1.). The control group is formed from cases in the same time frame from one year earlier.

Table 1. classification of phases during the COVID-19 pandemic in Germany

| Phase | Name | Start | End |
|-------|----------------|------------|------------|
| 1 | First wave | 02.03.2020 | 17.05.2020 |
| 2 | Summer plateau | 18.05.2020 | 27.09.2020 |
| 3 | Second wave | 28.09.2020 | 28.02.2021 |

Data from the Robert Koch Institute

Tolksdorf K, Buda S, Schilling J. Aktualisierung zur „Retrospektiven Phaseneinteilung der COVID-19-Pandemie in Deutschland". Epidemiologisches Bulletin. 2021;37:13–4.

3.2. Data Collection

The required data was acquired by using the clinic's information system *Orbis* powered by Dedalus. The relevant set of patients was gained by using the inbuilt search and filter option.

First, all cases which were coded with the ICD code for acute myocardial infarction (I21.-) and presented in the period between the 2nd of March 2020 and the 28th of February 2021 were collected. Second, all cases with the ICPM code for a percutaneous transluminal intervention of the heart and coronary arteries (8-837) in the same timespan were gathered. The group of patients with the correct ICD code was reduced by filtering only those cases which were admitted to the hospital in Coburg. After merging the two groups based on their case numbers, deleting any duplicates, further filtering out secondary diagnoses and only including the verified diagnosis at discharge, we received the relevant set of patients. This set created our COVID-group.

The procedure was repeated and all patients with the same prerequisites, who presented in the period between 2nd of March 2019 and the 28th of February 2020 created the control group.

3.3. Variables

From the above-mentioned data set we received multiple parameters. We used the sex, age and the date of intervention as standard characteristics. The left ventricular ejection fraction was used to evaluate the cardiac function. Troponin and the MB part of creatine kinase (CK-MB) were used to investigate the myocardial damage and N-terminal pro brain natriuretic peptide (NT-proBNP) to evaluate cardiac insufficiency. Additionally, kidney function and inflammation markers were considered, creatinine and C-reactive protein (CRP) respectively. We also checked if major cardiac events were recorded, as those death, cardiopulmonary resuscitation, life-threatening tachycardias (ventricular tachycardia, ventricular fibrillation) and cardiogenic shock were incorporated.

Table 2. Parameters and units

| parameters | units |
|------------------------------------|--------|
| sex | |
| age | years |
| Date of intervention | |
| Left ventricular ejection fraction | % |
| Troponin | ng/ml |
| CK-MB | μkat/L |
| NT-proBNP | pg/ml |
| Creatinine | μmol/l |
| CRP | mg/l |
| MACE (death, VT, VF, CPR, shock) | |

CK-MB, MB part of creatine kinase; NT-proBNP, N-terminal pro brain natriuretic peptide; CRP, C-reactive protein; VT, ventricular tachycardia; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation

When possible, the first and last measurement of troponin, NT-proBNP, creatinine and CRP was included. The last measurement is going to be marked with a “2” in the following.

3.4. Ethical Approval

The previously prepared research plan was sent to the institutional review board (IRB) of the Medical School Regiomed Coburg. Based on §2 of the statutes of the IRB, there are no objections to the implantation of the research project. The study was performed in accordance with the declaration of Helsinki.

3.5. Statistical Analysis

The statistical analyses were performed using *JASP* (JASP Team (2022). *JASP* (Version0.16.1) [Computer software], Amsterdam, Netherlands).

For the descriptive statistics of continuous variables, the distribution was determined using the Shapiro-Wilk Test. Normally distributed data was then compared with the Student T Test. The data was presented using mean and standard deviation. Non-normally distributed data was compared with the Mann-Whitney-U test. The data was presented using median and interquartile range. Non-continuous data was presented in frequency tables and compared with a Chi-squared test. The significance cut-off was set to a P value of $P < 0.05$.

4. RESULTS

4.1. Year one of the COVID-19 pandemic

In this study 999 cases were included after considering the criteria of data collection listed above in Methods. All patients who received their treatment between the 2nd of March 2020 and the 28th of February 2021 represent the “COVID-group”. Patients, who presented in the same period one year earlier constitute the control group (02.03.2019 – 28.02.2020). In the control group, 534 patients received an intervention after a myocardial infarction, in the COVID group it has been 465. This represents a decrease of 12,92%. The median age in the control group was 70 years and 69 years in the COVID group. There was a significant difference in distribution of sex between both groups. Even though in both groups more males are present, there are proportionally more women in the control group compared to the COVID group (Table 3.) (Male proportion: 66.9% in control group, 74.4% in the COVID group $P=0.009$; $X^2=6.804$).

Table 3. patient characteristics

| | Control group (N=534) | COVID group (N=465) | <i>P</i> |
|----------------|------------------------------|----------------------------|--------------------|
| Age (years) | 70.0 (20) | 69.0 (21) | 0.419* |
| Male sex | 357 (66.9%) | 346 (74.4%) | 0.009 [†] |

*Mann-Whitney U Test

[†] Chi-squared Test

Data is presented as median and interquartile range (in brackets), absolute values, or percentages

When comparing all variables between both groups, we identified three parameters that differed significantly from the pre-COVID time. Table 4 shows the median left ventricular ejection fraction, which is the same in both groups, yet the Mann-Whitney U Test showed a significant difference, as it does not calculate based on the median but with the use of ranks. The mean fraction was therefore 3.4% higher before the pandemic started (mean of control group: 48.5% COVID group: 46.8% $P=0.038$; $W=108213.5$). Additionally, the marker for myocardial damage CK-MB (median COVID group: 0.53 $\mu\text{kat/L}$ control group: 0.45 $\mu\text{kat/L}$

$P=0.004$; $W=104559.5$) and the heart failure enzyme NT-proBNP² (median COVID group: 3281.0 control group: 1536.6 $P=0.028$; $W=6923.0$) were significantly more elevated in the COVID group. But it is worth mentioning that in some cases those parameters were not recorded. 12 records were missing for ejection fraction in the control group and 16 in the COVID group. 73 and 57 records were missing for the CK-MB values in the control and COVID group respectively. 444 and 334 records were missing for NT-proBNP in control and COVID group respectively (Table 4).

No statistically significant differences could be found after comparing the other variables (duration of stay, troponin, the first value of NT-proBNP, creatinine, CRP, and major adverse cardiac events). Nevertheless, troponin was trending to be higher in the COVID group, when measured at first contact, the last measurement was actually lower in the COVID group. CRP values, as well as creatinine values were also increased in the COVID group. Patients of the control group had a shorter duration of stay in the hospital. Major adverse cardiac events were less frequent in the first year of the pandemic (Table 5.) (Figure 3.).

Table 4. significant differences between control and COVID group

| | Control group (N) | COVID group (N) | Control group | COVID group | <i>P</i>* |
|---------------------------------------|------------------------------|----------------------------|----------------------|--------------------|------------------|
| LV-EF (%) | 449 | 522 | 50.0 (20.0) | 50.0 (20.0) | 0.038 |
| CKMB (μ kat/L) | 408 | 461 | 0.45 (0.98) | 0.53 (1.32) | 0.004 |
| NT- proBNP ² (pg/ml) | 131 | 90 | 1536.6 (5336.9) | 3281.0 (8037.5) | 0.028 |

*Mann-Whitney U Test

Data is presented as absolute numbers or median and interquartile range

² last recorded value

LV-EF, left ventricular ejection fraction; CK-MB, MB part of creatine kinase; NT-proBNP, N-terminal pro brain natriuretic peptide

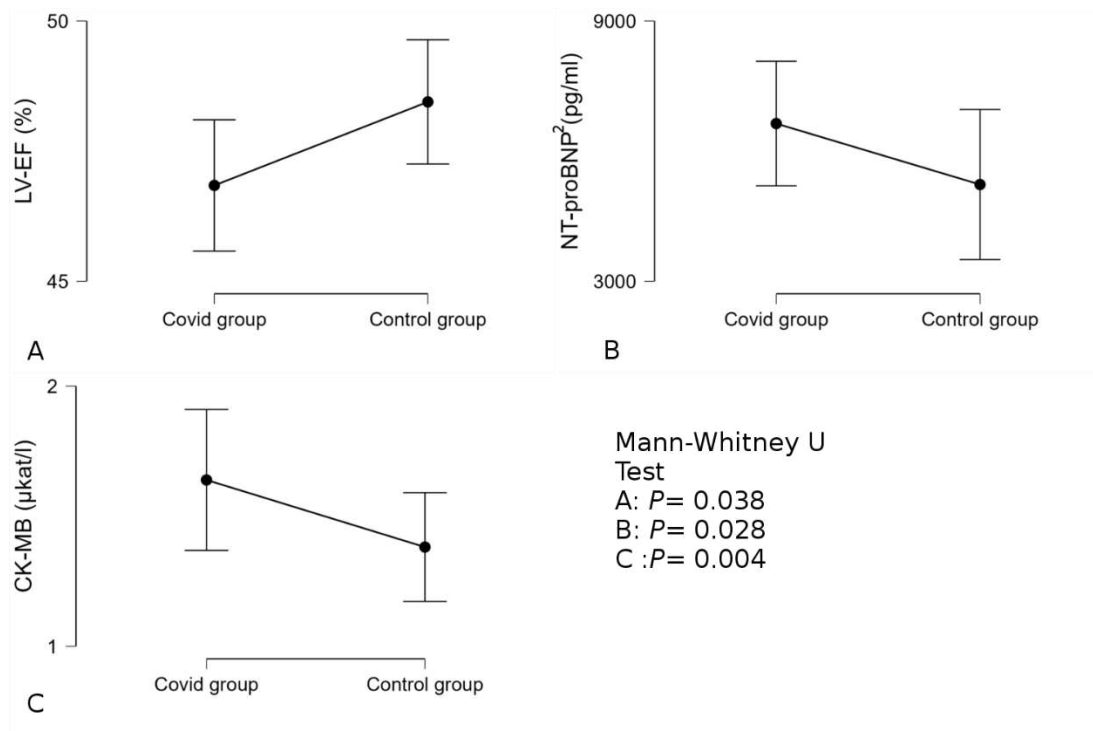


Figure 3. A. Comparison of the left ventricular ejection fraction (LV-EF) between the COVID group (2020/2021) and the control group (2019/2020); B. Comparison of the N-terminal pro brain natriuretic peptide (NT-proBNP²- last measured value) values between the COVID group (2020/2021) and the control group (2019/2020); C. Comparison of the CK-MB values between the COVID group (2020/2021) and the control group (2019/2020)

Table 5. nonsignificant differences between control and COVID group

| | Control group (N) | COVID group (N) | Control group | COVID group | P* |
|----------------------------------|--------------------------|------------------------|----------------------|--------------------|------------|
| Duration of stay (days) | 531 | 461 | 6.0 (5.0) | 6.0 (5.0) | 0.101 |
| Troponin (ng/ml) | 517 | 451 | 0.095 (0.373) | 0.089 (0.384) | 0.929 |
| Troponin ² (ng/ml) | 472 | 422 | 0.544 (1.814) | 0.452 (0.531) | 0.374 |
| NT-proBNP (pg/ml) | 330 | 330 | 1355.0 (3812.9) | 1520.0 (4034.2) | 0.8 |
| Creatinine (µmol/l) | 529 | 454 | 87.52 (35.336) | 97.24 (35.36) | 0.224 |
| Creatinine ² (µmol/l) | 507 | 445 | 87.52 (35.36) | 87.52 (35.36) | 0.895 |
| CRP (mg/l) | 527 | 454 | 4.6 (12.25) | 4.2 (11.51) | 0.116 |
| CRP ² (mg/l) | 501 | 443 | 13.2 (25.2) | 12.5 (23.85) | 0.271 |
| MACE | 534 | 465 | 80 (14.98%) | 67 (14.4%) | 0.789 † |

*Mann-Whitney U Test

† Chi-squared test

² last recorded value

Data is presented as absolute numbers and percent or median and interquartile range

NT-proBNP, N-terminal pro brain natriuretic peptide; CRP, C-reactive Protein; MACE, major adverse cardiac events

4.2. Wave one of the COVID -19 pandemic

We now subdivided these two groups in several subgroups, to record alterations within a smaller timespan. In the following sections the control group always represents the group of patients from the same time frame from one year earlier. The first wave of COVID-19 infections in Germany was dated from the 2nd of March to the 17th of May in 2020. 99 patients received a transluminal intervention after having a myocardial infarction during this time, one year earlier it has been 122. This reflects a decrease of 18.9%. The patients in the pandemic were 3.5 years younger on average. Changes in the sex distribution was not significant, male patients prevailed (68.9% male in control group, 79.8% in wave 1 P=0.066; X²=3.383) (Table 6.).

Table 6. Patient characteristics comparing wave 1 of the pandemic and the according control group

| | Control group (N=122) | Wave 1 (N=99) | <i>P</i> |
|----------------|------------------------------|----------------------|--------------------|
| Age (years) | 71.5 (19.75) | 68.0 (19.0) | 0.283* |
| Male sex | 84 (68.9%) | 79 (79.8%) | 0.066 [†] |

*Student T test

[†] Chi-squared Test

Data is presented as median and interquartile range (in brackets), absolute values, or percentages

From the collected parameters only CK-MB was significantly higher in the COVID group (median control group: 0.48 μ kat/l COVID group: 0.58 μ kat/l $P=0.048$; $W=5511.5$). On the other hand, the last measured CRP-value was significantly higher in the pre-COVID group (median control group: 13.75 m/l COVID group: 9.25 mg/l $P=0.013$; $W=4295.5$). Additionally, the frequency of life-threatening tachycardias was significantly higher in the pre-COVID group (control group: 8.3% COVID group: 1.0% $P=0.014$; $X^2=6.098$).

All other values did not significantly differ between those groups. All results can be seen in table 7. Interestingly the mean last measured value of troponin, the first NT-proBNP value, the last creatinine value and both CRP values were lower in the wave one COVID group. Also, the left ventricular ejection fraction was higher in this group and less major cardiac events occurred (Table 7.).

Table 7. Comparison between wave one of the pandemic and the relevant control group

| | Control group (N) | N COVID group (N) | Control group | COVID group | P* |
|----------------------------------|--------------------------|--------------------------|----------------------|--------------------|--------------------------|
| Duration of stay (days) | 121 | 98 | 6.0 (4.0) | 6.0 (4.0) | 0.087 |
| LV-EF (%) | 119 | 99 | 50.0 (25.0) | 50.0 (20.0) | 0.901 |
| Troponin (ng/ml) | 119 | 96 | 0.081 (0.32) | 0.099 (0.49) | 0.251 |
| Troponin ² (ng/ml) | 108 | 93 | 0.58 (1.47) | 0.46 (1.448) | 0.848 |
| CK-MB (μkat/L) | 104 | 91 | 0.48 (1.02) | 0.58 (1.22) | 0.048 |
| NT-proBNP (pg/ml) | 88 | 70 | 1613.0 (3836.2) | 1273.0 (2689.3) | 0.375 |
| NT-proBNP ² (pg/ml) | 24 | 22 | 2222.0 (5110.0) | 2896.0 (4772.5) | 0.242 |
| Creatinine (μkat/L) | 120 | 97 | 87.52 (37.57) | 87.52 (26.52) | 0.315 |
| Creatinine ² (μkat/L) | 114 | 96 | 87.52 (41.90) | 87.52 (26.52) | 0.478 |
| CRP (mg/l) | 120 | 97 | 4.85 (12.75) | 3.30 (9.60) | 0.077 |
| CRP ² (mg/l) | 112 | 96 | 13.75 (25.15) | 9.25 (14.0) | 0.013 |
| MACE | 121 | 99 | 20 (16.5%) | 9 (9.1%) | 0.105 [†] |
| Tachycardia | 121 | 99 | 10 (8.3%) | 1 (1.0%) | 0.014[†] |

*Mann-Whitney U Test

† Chi-squared test

² last recorded value

Data is presented as absolute numbers and percent or median and interquartile range

LV-EF, left ventricular ejection fraction; CK-MB, MB part of creatine kinase; NT-proBNP, N-terminal pro brain natriuretic peptide; CRP, C-reactive protein; MACE, major adverse cardiac events

4.3. Wave two of the COVID -19 pandemic

In the second wave of the pandemic (28.09.2020 – 28.02.2021) 211 patients got treated in the Coburg Hospital after having a myocardial infarction. The control group includes 172 patients who were treated between the 28th of September 2019 and the 28th of February 2020. The mean age was 69.5 years. Changes in sex distribution were significant, and 73.9% of the

patients were male (64.5% male in control group, 73.9% in wave 2 $P=0.046$; $X^2=3.964$) (Table 8).

Table 8. Patient characteristics comparing wave 2 of the pandemic and the according control group

| | Control group (N=172) | Wave 2 (N=211) | <i>P</i> |
|-------------|-----------------------|----------------|--------------------|
| Age (years) | 69.0 (20.25) | 69.0 (21.5) | 0.434* |
| Male sex | 111 (64.5%) | 156 (73.9%) | 0.046 [†] |

*Mann-Whitney U Test

[†] Chi-squared Test

Data is presented as median and interquartile range (in brackets), absolute values, or percentages

The second wave of the COVID-19 pandemic revealed 5 variables, that were significantly different in the COVID group. The mean ejection fraction dropped to 46.5% which represents a decrease of 7.2% (mean control group: 50.1% wave2: 46.52% $P=0.026$; $W=14693.5$). Yet again the median as shown in table 9 does not show a difference. The median first and last measure of NT-pro BNP also increased significantly by 107.7% and 211.3% respectively (control group: 887.9pg/ml wave2: 1844.0pg/ml $P=0.024$ $W=8992.0$; control group: 1099.0pg/ml wave2: 3421.0pg/ml $P=0.06$; $W=1118.0$). 49 and 77 reports were missing for the first measure and 138 and 150 were missing for the last measure of NT-proBNP (for control and COVID group respectively). Both creatinine values were significantly higher in the COVID group. An increase of 11.1 % and 18.9 % was reported for the first and last value respectively (control group: 87.52 μ mol/l wave2: 97.24 μ mol/l $P=0.009$; $W=20119.5$; control group: 87.52 μ mol/l wave2: 92.38 μ mol/l $P=0.033$; $W=18547.0$).

All other variables that were evaluated from the COVID group of the second wave were higher than in the control group, the only exception was the last recorded CRP-value which was lower. Yet, those results are not statistically significant (Table 10.).

Table 9. Comparison between wave 2 of the pandemic and the relevant control group – significant results

| | Control group (N) | wave 2 (N) | Control group | Wave 2 | <i>P</i> * |
|---------------------------------------|----------------------|------------|---------------------|---------------------|------------|
| LV-EF (%) | 167 | 203 | 50.0 (20.0) | 50.0 (20.0) | 0.026 |
| NT-proBNP (pg/ml) | 95 | 162 | 887.9 (2687.65) | 1844.0 (5018.35) | 0.024 |
| NT- proBNP ² (pg/ml) | 22 | 73 | 1099.0 (4288.45) | 3421.0 (8864.0) | 0.006 |
| Creatinine (μmol/l) | 169 | 206 | 87.52 (26.52) | 97.24 (44.2) | 0.009 |
| Creatinine ² (μmol/l) | 161 | 204 | 87.52 (35.36) | 92.38 (37.57) | 0.033 |

*Mann-Whitney U Test

Data is presented as absolute numbers or median and interquartile range

² last recorded value

LV-EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide

Table 10. Comparison between wave two of the pandemic and the relevant control group – nonsignificant results

| | Control group (N) | wave 2 (N) | Control group | Wave 2 | P* |
|-------------------------------|------------------------------|-------------------|--------------------------|---------------|------------|
| Duration of stay (days) | 172 | 211 | 6.0 (4.0) | 6.0 (4.0) | 0.175 |
| Troponin (ng/ml) | 166 | 205 | 0.082 (0.271) | 0.091 (0.434) | 0.395 |
| Troponin ² (ng/ml) | 155 | 190 | 0.458 (1.927) | 0.419 (1.485) | 0.47 |
| CK-MB (μkat/L) | 154 | 181 | 0.48 (0.865) | 0.48 (1.38) | 0.682 |
| CRP (mg/l) | 169 | 206 | 3.9 (8.3) | 4.8 (13.73) | 0.132 |
| CRP ² (mg/l) | 160 | 202 | 13.35 (25.88) | 14.5 (28.85) | 0.649 |
| MACE | 172 | 211 | 23 (13.4%) | 37 (17.5%) | 0.265 † |

*Mann-Whitney U Test

† Chi-squared test

² last recorded value

Data is presented as absolute numbers and percent or median and interquartile range
CK-MB, MB part of creatine kinase; CRP, C-reactive protein; MACE, major adverse cardiac events

4.4. Wave one of the COVID-19 pandemic compared to wave two

As already mentioned above, 99 patients were representing wave one and 211 patients represent wave 2 of the COVID-19 pandemic. The mean age only differed 1.1 years between both groups. 79.8% were male patients in wave 1 compared to 73.93% in wave 2. Those results are not statistically significant (Table 11.).

Table 11. patient characteristics comparing wave one and two

| | Wave 1 (N=99) | Wave 2 (N=211) | <i>P</i> |
|----------------|---------------|----------------|----------|
| Age (years) | 68.0 (19.0) | 69.0 (21.5) | 0.496* |
| Male sex | 79 (79.8%) | 156 (73.93%) | 0.261 † |

*Mann-Whitney U Test

† Chi-squared Test

Data is presented as median and interquartile range (in brackets), absolute values, or percentages

The patients in wave two had significant higher CRP values (wave1: 3.3mg/l wave2: 4.8mg/l $P=0.045$; $W=8564.0$ and wave1: 9.25mg/l wave2: 14.5mg/l $P=0.009$; $W=7867.0$. First and last measured level respectively). During wave two significantly more patients died after having a myocardial infarction (wave 1 3.0% wave2 9.9% $P=0.033$; $X^2=4.521$). The number of deaths increased by 6.9%. Patients also suffered more often from a life-threatening tachycardia in wave two (wave 1: 1.0%; wave2: 7.6% $P=0.018$; $X^2=5.617$) (Table 12.).

The mean duration of stay was longer in wave two. The left ventricular ejection fraction was reduced in wave two. Both NT-proBNP values and both creatinine values were higher in wave two. In wave 1 both troponin values and CK-MB was increased compared to wave two. There were more major adverse cardiac events in wave two. These results only showed trends and were not statistically significant (Table 13.).

Table 12. Comparison between wave 1 and wave 2 of the pandemic

| | wave 1 (N) | wave 2 (N) | Wave 1 | Wave 2 | P* |
|-------------------------|-------------------|-------------------|---------------|---------------|-----------|
| CRP (mg/l) | 97 | 206 | 3.3 (9.6) | 4.8 (13.73) | 0.045* |
| CRP ² (mg/l) | 96 | 202 | 9.25 (14.0) | 14.5 (28.85) | 0.009* |
| Death | 99 | 211 | 3 (3.0%) | 21 (9.9%) | 0.033 † |
| Tachycardia | 99 | 211 | 1 (1.0%) | 16 (7.6%) | 0.018 † |

*Mann-Whitney U Test

† Chi-squared Test

Data is presented as median and interquartile range (in brackets), absolute values, or percentages

² last recorded value

CRP, C-reactive protein

Table 13. Comparison between wave 1 and wave 2 of the pandemic – nonsignificant values

| | wave1 (N) | wave2 (N) | Wave1 | Wave2 | P* |
|----------------------------------|----------------------|----------------------|-----------------|-----------------|--------------------|
| Duration of stay (days) | 99 | 211 | 6.0 (4.0) | 6.0 (4.0) | 0.701 |
| LV-EF (%) | 99 | 203 | 50.0 (20.0) | 50.0 (20.0) | 0.72 |
| Troponin (ng/ml) | 96 | 205 | 0.1 (0.49) | 0.09 (0.43) | 0.73 |
| Troponin ² (ng/ml) | 93 | 190 | 0.46 (1.45) | 0.42 (1.49) | 0.348 |
| CK-MB (μkat/L) | 91 | 181 | 0.58 (1.22) | 0.48 (1.38) | 0.169 |
| NT-proBNP (pg/ml) | 70 | 162 | 1273.0 (2689.3) | 1884.0 (5018.4) | 0.155 |
| NT-proBNP ² (pg/ml) | 22 | 73 | 2896.0 (4772.5) | 3421.0 (8864.0) | 0.587 |
| Creatinine (μmol/l) | 97 | 206 | 87.52 (26.52) | 97.24 (44.2) | 0.211 |
| Creatinine ² (μmol/l) | 96 | 204 | 87.52 (26.52) | 92.38 (37.57) | 0.384 |
| MACE | 99 | 211 | 9 (9.1%) | 37 (17.5%) | 0.051 [†] |

*Mann-Whitney U Test

[†] Chi-squared test

² last recorded value

Data is presented as absolute numbers and percent or median and interquartile range

LV-EF, left ventricular ejection fraction; CK-MB, MB part of creatine kinase; NT-proBNP, N-terminal pro brain natriuretic peptide; MACE, major adverse cardiac events

5. DISCUSSION

In this study we conducted the impact of the COVID-19 pandemic on the outcome of patients with myocardial infarctions, who did undergo a coronary intervention. The most important finding is that the left ventricular ejection fraction (LV-EF) was significantly lower in patients presenting during the COVID-19 pandemic. The LV-EF is essential for the prognosis after an ischemic cardiac event as it shows the mechanical capabilities of the injured left ventricle, which is responsible for oxygenation of all tissues (27).

We did not conclude whether a time delay was present during the pandemic, but multiple studies recorded a deferral between symptom onset and seeking first medical contact in this period, as presented in the systematic review (32). In myocardial infarction every factor that prolongates the ischemic time will eventually lead to a greater extent of myocardial injury (34). CK-MB is a marker of myocardial injury and stands in proportion with the extent of infarcted tissue (36). CK-MB was significantly elevated in the first year of the pandemic compared to the pre-COVID era, suggesting a correlation to increased infarct size due to hesitation in COVID times. Interestingly, the troponin levels, even though it is the most important ischemia marker, were not significantly higher during the pandemic. Troponin has a long plateau phase, so patients who are presenting later can still have similar values (23).

Also noteworthy is the decline in patients recorded during the pandemic. In Coburg a decrease of 12.9% was recorded during the whole first pandemic year. In the first wave it was even more, 18.8%. This reduction is consistent with the findings from Berlin, where a drop of 47% was noted, but this data includes all cases of acute myocardial infarction not only those who had a PCI as well (34). Interestingly though, no decline in patients during the second wave could be seen in Coburg, actually more patients were treated in this time.

Additionally, patients in the second wave of the pandemic showed a significantly increased serum creatinine level, which itself is associated with an increased mortality in ACS patients (37).

When looking closer into the results it shows that during the second wave of the pandemic patients had a worse outcome. Compared to pre-COVID times the LV-EF was only significantly decreased in the second wave, the same was noted when looking at the creatinine levels. The CK-MB values were higher only in the first wave. When directly comparing the two waves in the first year of the pandemic it shows that proportionally more people died in the second wave and more life-threatening tachycardias were monitored at the same time. The inflammation marker CRP was higher in wave two as well. Another important prognostic factor of myocardial infarctions is the enzyme NT-proBNP. It is released from cardiac myocytes in

times of increased stretch, such as caused by myocardial infarction. The peptide rises in accordance with the size of the ischemic insult and is commonly used as a prognostic factor for mortality and heart failure. In this study a significant increase was measured in the second wave of the COVID-19 pandemic, strengthening the hypothesis of a reduced outcome of myocardial infarctions in this time. Unfortunately, a lot of values were missing, as it was not measured in every patient because it is not a standard lab value. For the first recorded measure, 95 and 162 valid cases were present, and the values showed a significant increase of 74.2% in NT-proBNP levels compared to the control group. This result is even more noteworthy when seen together with the reduced left ventricular ejection fraction, as both parameters stand for the function of the left ventricle (38).

Even though the two distinct waves of the COVID-19 pandemic don't show the exact same results, they do show a significant worse outcome of myocardial infarctions. The pandemic had an integral impact on the society and the health care system all over the world. Limitations to the day-to-day life, problems in the economy and reduced interpersonal interactions had a direct impact on the life and behavior of people. The fear of getting infected was high, especially in persons with higher risk of a serious course of the disease. The group of people with comorbidities, who are more prone to suffer from a myocardial infarction, overlap with the high-risk groups during the COVID-19 pandemic. Hypertension, diabetes mellitus and obesity are all factors that increase the risk of contracting either of the two diseases, previous myocardial infarctions increase the risk of serious complications of a SARS-CoV-2 infection (27,39).

The fear of acquiring COVID-19 was a reason for the delays and hesitation when presenting to a medical institution with a health problem, including symptoms of myocardial infarction. Media and politics played a role in this, as they tried to relieve the health care system and make room for treating severely ill COVID patients. The media presence led to an increased attention toward the virus and many people were aware of it. Unfortunately, that led to a misunderstanding, as people were afraid of acquiring the disease when visiting a hospital. The hospital setting was seen as a high-risk location (40,41). The consequence from this is a worse prognosis for patients with myocardial infarction as this and other studies show. The biomarkers and mechanical capabilities are significantly more critical. Other studies even showed an increase in mortality (34).

In the public and in the hospital setting strict safety regulations were introduced to minimize the risk of the spreading of SARS-CoV-2. Hand hygiene, safety masks, distance,

face shields were used in hospitals as well. All of this should reassure a person in need for urgent medical attention to not stay at home but seek this attention as soon as possible. A study from the US proved that the risk of nosocomial infections regarding the SARS-CoV-2 was very low. This could only be achieved by vigorous testing and strict safety measurements (42).

6. CONCLUSION

From this study we can conclude that the COVID-19 pandemic had a negative impact on the outcome of acute myocardial infarctions. Yet, this result could not be seen in all variables. Most notably is the decrease of the left ventricular ejection fraction as it is an important prognostic factor. The hypothesis that prognostic parameters for myocardial infarction indicate a decreased outcome during the COVID-19 pandemic is true. A probable cause for this outcome is a delay after symptom onset until presentation to medical attention, which is proved by other studies.

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8. SUMMARY

Objectives: The objective of this study was to examine whether the social, political, and medical changes during the corona virus disease 2019 (COVID-19) pandemic had a significant impact on the outcome of myocardial infarctions.

Materials and Methods: The study was designed as a retrospective analytical cross-sectional study. Data was acquired from the REGIOMED hospital in Coburg, Germany. 999 data sets of patients were used. In the time frame from the 2nd of March 2020 and the 28th of February 2021 and the respective period in 2019/2020 all patients with an acute myocardial infarction, who received a percutaneous coronary intervention (PCI) were included into the study. To see which impact the pandemic had on the outcome of the disease the left ventricular ejection fraction (LV-EF), Troponin, MB part of creatine kinase (CK-MB), N-terminal pro brain natriuretic peptide (NT-proBNP), Creatinine, C-reactive protein (CRP) and major adverse cardiac events were compared between the two years. Additionally, the two distinct waves of the pandemic were compared against each other and with the respective periods in the preceding year.

Results: A decrease in admissions was noted during the first year of the COVID-19 pandemic. The statistical analysis showed a significant decrease of the left ventricular ejection fraction ($P=0.038$) in patients presenting during the pandemic, the CK-MB levels were increased ($P=0.004$). An isolated analysis of the first COVID-19 wave showed elevated CK-MB compared to the control group ($P=0.048$). The other variables were not significantly worse. In the second wave the LV-EF was significantly decreased compared to the previous year ($P=0.026$), additionally the creatinine values were increased as well ($P=0.033$; $P=0.009$). Comparing both waves with each other, the second wave showed a worse outcome as more people suffered from life-threatening tachycardias ($P=0.018$) and more people died ($P=0.033$). The two measured CRP-values were significantly increased in the second wave compared to the first one ($P=0.045$; $P=0.009$).

Conclusions: The COVID-19 pandemic did have a negative impact on the outcome of myocardial infarctions. Especially noteworthy is the decreased left ventricular ejection fraction recorded in the whole first year of the pandemic and additionally in the second wave. The ejection fraction is an important prognostic factor. With information from other studies, a probable cause of the worse outcome is a delay in presentation after symptom onset.

9. CROATIAN SUMMARY

Naslov: Utjecaj pandemije corona virus disease 2019 (COVID-19) na ishod infarkta miokarda

Ciljevi: Cilj ove studije bio je ispitati jesu li društvene, političke i medicinske promjene tijekom pandemije COVID-19 imale značajan utjecaj na ishod infarkta miokarda.

Materijali i metode: Studija je zamišljena kao retrospektivna analitička presječna studija. Podaci su dobiveni iz bolnice REGIOMED u Coburgu, Njemačka. Korišteno je 999 skupova podataka o pacijentima. U roku od 2. ožujka 2020. i 28. veljače 2021. i odgovarajućeg razdoblja 2019./2020. U istraživanje su uključeni svi bolesnici s akutnim infarktomiokarda liječeni perkutana koronarna intervencija (PCI). Kako bi se vidjelo kakav je utjecaj pandemije imala na ishod bolesti, uspoređeni su ejekciona frakcija lijeve klijetke (LV-EF), troponin, MB dio kreatin kinaze (CK-MB), N-terminalni natriuretski peptid za mozak (NT-proBNP), kreatinin, C-reaktivni protein (CRP) i veliki štetni srčani događaji između dvije godine. Osim toga, uspoređena su dva različita vala pandemije jedan s drugim i s odgovarajućim razdobljima u prethodnoj godini.

Rezultati: Tijekom prve godine pandemije COVID-19 zabilježen je pad broja prijema. Statistička analiza je pokazala značajno smanjenje istisne frakcije lijeve klijetke ($P=0,038$) u bolesnika koji su se pojavili tijekom pandemije. Zabilježen je značajan porast razine CK-MB ($P=0,004$). Izolirana analiza prvog vala COVID-19 pokazala je povišeni CK-MB u usporedbi s kontrolnom skupinom ($P=0,048$). Ostale varijable nisu bile značajno lošije. U drugom valu LV-EF značajno je smanjen u usporedbi s prethodnom godinom ($P=0,026$), dodatno su povećane i vrijednosti kreatinina ($P=0,033$; $P=0,009$). Uspoređujući oba vala međusobno, drugi val je pokazao lošiji ishod jer je više ljudi patilo od tahikardija ($P=0,018$) opasnih po život, a više ljudi je umrlo. Dvije izmjerene CRP-vrijednosti bile su značajno povećane u drugom valu u odnosu na prvi ($P=0,045$; $P=0,009$).

Zaključci: Pandemija COVID-19 je imala negativan utjecaj na ishod infarkta miokarda. Posebno se ističe smanjena ejekciona frakcija lijeve klijetke zabilježena tijekom cijele prve godine pandemije i dodatno u drugom valu. Izbačena frakcija je važan prognostički čimbenik. Uz informacije iz drugih studija, vjerojatni uzrok goreg ishoda je kašnjenje u prezentaciji nakon pojave simptoma.

10. CURRICULUM VITAE

Personal data

Name: Tom Florian Witthauer

Date of birth: 09.05.1997

Nationality: German

Education

| | |
|----------------------|--|
| Since September 2016 | Medical studies at the University of Split School of Medicine / Medical School Regiomed Coburg |
| June 2015 | A-levels average grade 2,3 |
| 2007 – 2015 | Frankenwald-Gymnasium Kronach (high school) Science and technology branch |
| 2003 – 2007 | Volksschule Weißenbrunn (elementary school) |

Work and internships

| | |
|---------------------------|--|
| Winter 2020 and 2021 | Covid-19 vaccination centre Kronach |
| April – June 2016 | Internship HELIOS hospital „Frankenwaldklinik“ Kronach (Trauma surgery and emergency department) |
| October – December 2015 | Nursing internship HELIOS hospital „Frankenwaldklinik“ Kronach |
| September 2015, July 2021 | Internship general practice Dr. Witthauer Weißenbrunn |

Others

English B2+/C1, French B1+

Volunteering in the Bavarian Red Cross