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**UNIVERSITY OF SPLIT
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**EVALUATION OF CARDIAC DEVICE IMPLANTATION IN THE ELDERLY:
IMPACT OF COVID-19**

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LIST OF ABBREVIATIONS

ACE-2 - angiotensin-converting enzyme-2

AF – atrial fibrillation

ARDS - acute respiratory distress syndrome

AV node – atrioventricular node

AVB - atrioventricular block

BMI – body mass index

CIED - cardiac implantable electronic devices

COVID-19 - corona virus disease-19

CRP - c-reactive protein

CRT – cardiac resynchronization therapy

ECG – electrocardiogram

EF – ejection fraction

ESC - european society of cardiology

HCoV – human corona virus

ICD – implantable cardioverter defibrillator

ILR – implantable loop recorder

(L)BBB – (left)bundle branch block

LDH – lactate dehydrogenase

MERS-CoV - middle east respiratory syndrome coronavirus

NT-proBNP - n-terminal prohormone of brain natriuretic peptide

NYHA - new york heart association

PCR - polymerase chain reaction

PIMS-TSS - paediatric inflammatory multisystem syndrome-toxic shock syndrome

RBD - receptor binding domain

SARS-CoV - severe acute respiratory syndrome coronavirus

SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

VF – ventricular fibrillation

VT – ventricular tachycardia

WHO – world health organization

1. INTRODUCTION

1.1. Coronavirus

Coronaviruses are a group of related enveloped, positive-sense, single-stranded RNA viruses of the family Coronaviridae, infecting both, animals and humans. The name derives from its characteristic, crown-shaped appearance when observed under the Transmission Electron Microscope (Latin "*corona*": wreath, crown).

Coronaviruses divide into four genera, based on their genomic structure: α , β , γ , and δ . The subgroups α and β exclusively affect mammals and lead to gastroenteritis in animals and respiratory illness in humans (1).

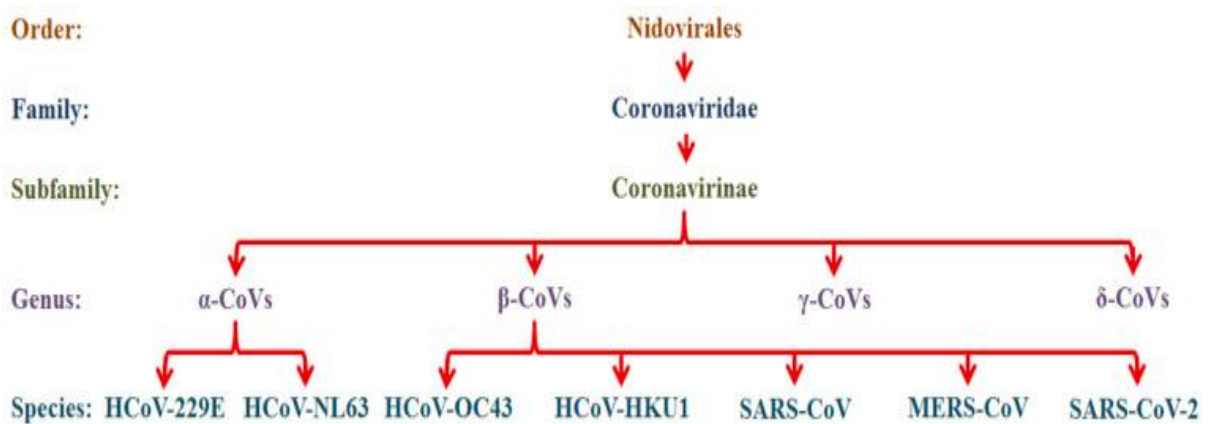


Figure 1. Virus classification (2)

Seven different Coronavirus strains are known to infect humans (3). These include: HCoV-229E (229E) and HCoV-NL63 (NL63) from the α genus and HCoV-OC43 (OC43), HCoV-HKU1 (HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East respiratory syndrome coronavirus (MERS-CoV) from the β genus.

Evidently, four strains; NL63, 229E, HKU1, and OC43 are well adapted to humans, and circulate in the human population, causing only mild symptoms like a common cold in immunocompetent adults (4). On the other hand, SARS-CoV, MERS-CoV and SARS-CoV-2 are found to be zoonotic strains and can take a severe course, causing pneumonia and even lead to death. They can be transmitted from animal to animal (veterinary infectious diseases), animal to human (zoonotic) and human to human (anthroponosis) (2)(5).

SARS-CoV was the causal agent of the severe acute respiratory syndrome outbreaks in 2002 and 2003 in Guangdong Province, China (6). The causative pathogen for the middle east respiratory syndrome, MERS-CoV, infected the first human in Jeddah, Saudi Arabia in 2012 and had a mortality rate of 35% reported the WHO (7). SARS-CoV-2 causes the ongoing pandemic of corona virus disease-19 (COVID-19).

1.1.1. Transmission

Bats are thought to be a natural reservoir for SARS-CoV-2, since it shares a 96.2% homology with a sequence of a strain of coronavirus (RaTG13) previously identified from a horseshoe bat sample (*Rhinolophus* species). But it has been suggested that humans became infected with SARS-CoV-2 via an intermediate host, such as the pangolin at the Huanan seafood market in the Hubei province, China (8). Current evidence suggests that the virus spreads mainly between people via respiratory droplets in face-to-face contact within 6 feet distance. The virus can be transmitted from an infected person's mouth or nose in small droplets when they cough, sneeze, speak, sing or breathe. The virus can also spread via aerosols, much smaller particles, which can float in the air if the environment has the right humidity and temperature, especially in closed rooms. Transmission can also occur with contact to contaminated surfaces: It was shown that the virus can remain capable of replication for up to 96 hours on banknotes at 4 °C, at room temperature the virus was stable for only 8 hours and at 37 °C for only 4 hours (9).

Xi He *et al.* observed the highest viral load and infectivity at the time of symptom onset and implied that infectiousness peaked on or even before symptom onset (10). The incubation period indicates the time from infection to onset of disease. In a study from 2020 with 425 patients the mean incubation period was calculated to be 5.2 days (95% confidence interval [CI], 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days (11). It is possible that the new virus variants alpha and delta have an incubation period about 1.5-2 days shorter than the so-called wild type, i.e., the viruses that circulated in 2020 (12).

1.1.2. Pathogenesis and clinical picture of COVID-19

The membrane of SARS-CoV-2 is covered with spike proteins on which the receptor binding domain (RBD) is found. Entry into human target cells is mediated by the surface receptor angiotensin-converting enzyme-2 (ACE-2), which is found dominantly in the type II pneumocytes in the lungs, but also in the heart, kidney, gastrointestinal tract and blood vessels, unusual for a human respiratory virus. After successful ACE-2 binding, the cleavage of the viral spike protein by proteases like transmembrane serine protease 2 (TMPRSS2), Cathepsin B or L (CTS-B or L), or FURIN is considered as the essential step to effectuate virus infection (13). SARS-CoV-2 replicates in these target cells and mature virions are released to invade adjacent cells. Infected epithelial cells in the respiratory tract are expelled via droplets to infect new hosts.

The invasion of the virus leads to an inflammatory response mediated by cytokines, resulting in inflammatory changes including edema, degeneration and necrotic changes. In advanced disease, accumulation of oxygen free radicals and lactic acid, changes in intracellular pH and electrolyte imbalance cause further cellular damage (14).

COVID-19 varies in clinical manifestations and can be categorized into three stages: mild, severe and critical. In the mild stage of infection, pneumonia is usually absent or mild, most frequently reported with symptoms of upper respiratory infection, marked by febrile illness with dry cough, malaise and myalgia (15). In severe cases, dyspnea, productive cough and hypoxia lead to a respiratory rate more than 30/minute and lung infiltrates >50%. These symptoms develop within 24–48 h after initial symptom onset. Finally, the critical stage comprises severe pneumonia, respiratory failure, ARDS (Acute Respiratory Distress Syndrome), septic shock and/or multiple organ failure.

In a descriptive analysis of 44 672 patients with COVID-19 in China, 81% of patients had mild manifestations, 14% had severe manifestations and 5% had critical manifestations (16).

COVID-19 can manifest in a variety of ways and not only in the lung, but also in other organ systems. The sites of manifestation depends, among other things, on the density of ACE-2 receptors in the tissues that allow the virus to enter the cell. Neurological symptoms include headache, olfactory and gustatory disturbances, dizziness and confusion. SARS-CoV-2 infection may also be associated with gastrointestinal symptoms (nausea, loss of appetite, vomiting, abdominal pain, diarrhea) and liver dysfunction (17). Cardiac involvement was

demonstrated by elevated cardiac enzymes and troponin in a proportion of patients, including children and even those with mild or moderate disease. Particularly in severe respiratory infections, a number of patients experience cardiovascular disease, including myocardial injury, myocarditis, acute myocardial infarction, heart failure and arrhythmias (18, 19). In severe COVID-19 courses, pathologically increased coagulation is associated with an increased risk of thromboembolism, including in the lower extremities, pulmonary artery and cerebrovascular embolism with possible sequelae (20, 21).

In rare cases, children develop a clinical picture that the ECDC (European Centre for Disease Prevention and Control) calls "paediatric inflammatory multisystem syndrome"(PIMS) in combination with "toxic shock syndrome" (TSS). PIMS-TSS bears similarities to the Kawasaki syndrome observed in children in association with other infectious diseases, although children affected by PIMS are usually older. The majority of children require intensive care even though the clinical picture is usually well treatable (22).

First indications for long-term health consequences of SARS-CoV-2 infection (long COVID) have been found in mid-2020. To date, no single clinical picture can be delineated and the underlying mechanisms are not yet clear. A wide variety of symptoms have been reported, which may persist for weeks and months, recur in phases, or be new. Commonly reported complaints include fatigue, exhaustion and reduced exercise capacity, shortness of breath, concentration and memory problems, sleep disturbances, muscle weakness, and psychological problems such as depressive symptoms and anxiety (23, 24).

1.1.3. Diagnostic

Virological diagnostics is the mainstay of SARS-CoV-2 infection detection; to confirm the diagnosis of infection, reverse transcription polymerase chain reaction (RT-PCR) test from a naso-/oropharyngeal swab or sputum is needed.

Moreover, antigen (rapid) test formats are based on the detection of viral protein in respiratory sample materials. Currently, fluorescence- or chemiluminescence-based tests, which require an evaluation device, as well as lateral-flow tests for immediate visual evaluation on site are available in the point-of-care format (rapid tests in the narrower sense). Antigen tests can be a useful addition to PCR test capacities where an initial, preliminary decision on the possible presence of a transmission-relevant infection in a person is to be made quickly in the

acute phase of infection (25). But the analytic sensitivity is inferior to the gold standard of PCR tests.

1.1.4. Treatment

Management is mainly based on preventive measures such as hand hygiene, face masks and personal protective equipment, education, social distancing, isolation of infected individuals and vaccination.

Only a few COVID-19 cases are severe and need therapy which focuses on optimal supportive measures according to the severity of the clinical picture (e.g., oxygen administration, balancing of fluid balance, and, if necessary, antibiotic administration for the treatment of bacterial superinfections) as well as monitoring of relevant underlying diseases and adjustment of their treatment if required. Patients with risk predictors for a severe course, such as age >50 years, male sex, persistent fever and dyspnoea, pronounced lymphocytopenia and elevation of biomarkers such as D-dimer, LDH and troponin should be closely monitored in particular and, if necessary, admitted to inpatient care at an early stage. The risk of a severe COVID-19 course increases with pre-existing conditions, e.g. obesity with BMI >35, cardiovascular diseases, diabetes mellitus, chronic lung/liver/kidney diseases, stem cell or organ transplantation and other forms of immunosuppression (e.g. tumour patients, HIV-infected patients with compromised immune systems, iatrogenic immunosuppression) (26).

Many different specific therapeutic approaches (directly antivirally effective, immunomodulatory effective) were and are being investigated in studies during the COVID-19 pandemic. With the now improved evidence base for many of the investigated substances, it has already been possible to formulate evidence-based therapy recommendations worldwide. The correct assignment of the recommended substances to the respective disease phase is essential. However, it should also be noted, that most substances are used off-label since they are not yet approved. For patients at risk for a severe course of COVID-19, monoclonal antibodies against the spike protein of SARS-CoV-2 are available in the early phase of infection. The combination of the monoclonal antibodies casirivimab and imdevimab (REGN-COV2) was approved in the European Union on 12 November 2021 for early antiviral therapy and prophylaxis in high-risk groups. Evidence from studies to date indicates that their use in the early phase of infection (within the first 3 days and up to a maximum of 7 days after symptom onset) can favourably influence the further course of infection (27).

1.1.4. COVID-19 pandemic

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the pandemic of corona virus disease 2019 (COVID-19) was first described in Wuhan, China in December 2019, in patients complaining about flulike symptoms (28). The virus spread, affecting not only China but is now present on every continent in at least 227 countries (29) (16 March, 2022), which led the World Health Organization (WHO) to declare the COVID-19 outbreak a global pandemic on 11 March 2020. As of 24 March 2022, the pandemic had caused more than 472 million confirmed cases and 6 million deaths (1.3%)(30). In comparison, the SARS pandemic in 2002, caused 8096 infections of which 774 people died (9.6%) and the 2012 MERS pandemic infected 2494 people causing 858 deaths (34.4%). The much larger number of people infected with SARS-CoV-2, and the rate at which the virus is spreading, raised red epidemiologic flags, although MERS and SARS had higher mortalities (4).

The first SARS-CoV-2 case in Germany was diagnosed on 27 January 2020 and from 13 March 2020 on, German states commanded the closure of schools and kindergartens. On 25 March 2020, the federal parliament declared an "epidemic situation of national significance". Curfews and contact restrictions were imposed by march 22nd until may 6th. A so called "lockdown light" was implemented in Bavaria from November 2nd – December 9th 2020, allowing a maximum of 5 persons of two households to meet privately or in public. The declaration of a state of emergency on 9 December 2020 prolonged the contact restriction until 10 January 2021, while further restrictive measures such as leaving one's own home only for valid reasons, including the pursuit of professional or official activities and doctor's appointments were imposed.

Substantial changes in health care systems had to be made in all countries due to the impact of COVID-19; intensive and intermediate care units carry the greatest burden, which is why several hospital wards have also been converted to COVID units, to handle the growing wave of the disease and isolate the infected patients as good as possible.

Priority setting measures and resource distribution, such as redirecting personal and hospital beds for patients with COVID-19 and the postponement of non-emergent elective hospital treatments, were implemented as recommended in Bavaria on November 3, 2020 in the Corona Pandemic Emergency Plan: "Notfallplan Corona-Pandemie: Allgemeinverfügung zur Bewältigung erheblicher Patientenzahlen in Krankenhäusern zum Vollzug des Infektionsschutzgesetzes (IfSG) und des Bayerischen Krankenhausgesetzes (BayKrG)" (31).

Electrophysiology and cardiology units have not been spared from these changes. In the perspective of risking hospital contamination, a substantial decline in the recorded emergency visits, hospital admissions and interventional treatments for heart failure and cardiac arrhythmias has been reported (32, 33). Therefore, the impact of the COVID-19 pandemic on the implantation of cardiac devices was investigated.

1.1.5. Impact of the pandemic on the elderly population

Older people aged 70 and over, men more than women and of these, especially those who are 80 years old and/or have pre-existing medical conditions are considered to be the main risk groups for COVID-19 disease with severe or fatal course of disease. Because vaccinations and effective drug treatments for COVID-19 were not available during the initial phase of the pandemic, nonpharmaceutical interventions were needed to contain the spread of SARS-CoV-2 infection and avoid overburdening health care systems. In addition, to protect the elderly population, recommendations have been made in Germany and other countries on visiting and contact restrictions for residents of long-term care facilities. Furthermore, maintaining outpatient medical care as well as nursing care in the home environment and in long-term inpatient care was more difficult during the pandemic.

Consequently, a trend to delayed presentation and management of acute medical issues other than COVID, including acute coronary syndromes and stroke are medical issues of concern in the elderly. Physical inactivity over months can lead to immune system dysfunction, which could increase infection susceptibility and exacerbate the pathophysiology of chronic conditions like cardiovascular disease that are common among older adults (34). To shed further light on the indirect effects of the pandemic on physical health in the older population, cardiac device implantations in the elderly was investigated.

1.2. Cardiac Devices

1.2.1. Origins

First evident thoughts on the bio-electrical nature of the heart were found around the 1640s. Experiments that apply electrical current through the heart followed in the 1770s by Squires whose patient was a girl and by the Danish physician Nickolev Abildgaard who defibrillated a hen. Rudolph Albert von Kollicker proofed that the frog's heart produces a definite electric current with each beat. 1882, Hugo Von Ziemssen stimulated directly the Ventricle of a woman's heart with electrical current and could change her heart rate at will. Increasing knowledge in the physiology of the heart and advances in electrical technology made a battery-operated pacemaker possible in 1957 and even implantable in 1958 by Senning and Elmqvist (35).

Over the last sixty years, electro therapy evolved tremendously so that cardiac implantable electronic devices (CIED) are now a mainstay of cardiac therapy, underlined by the number of implantations: more than 75,000 pacing modalities (including biventricular systems) and approximately 29,000 ICD/CRT-D systems are newly implanted annually in Germany, in addition to replacement and revision surgeries (36). Not only bradycardic and tachycardic arrhythmias can be treated or influenced by electrical stimulation, but also heart failure, various infiltrative and inflammatory diseases of the heart, as well as different cardiomyopathies and accompanying extracardiac changes such as central sleep apnea (37).

In the case of bradycardic irregularities, pacemaker devices use electrical impulses to stimulate rhythmic myocardial contraction. Tachycardic arrhythmias, on the other hand, can be converted to a normal rhythm by overstimulation/defibrillation with an implantable cardioverter defibrillator (ICD). New pacemakers allow resynchronization (cardiac resynchronization therapy, CRT) of cardiac contraction in cases of heart failure and proven asynchrony of ventricular activation (left bundle branch block).

1.2.2. Pacemaker

The construction of a pacemaker consists of an aggregate (pulse generator, battery-powered) and electrodes/probes, which link the aggregate to the myocardium. The electrode transmits electrical impulses to the heart and signals from the heart (patients ECG) back to the pulse generator. This controls the output of the pacemaker to either initiate or suppress an electrical impulse.

A five-digit letter code, the NBG coding system, has been developed by the North American Society for Pacing and Electrophysiology (NASPE) and British Pacing and Electrophysiology Group (BPEG) to describe the function of antibradycardic pacemakers. Additionally, pacemakers can be distinguished by the number of electrodes present. Single-chamber pacemakers have one electrode placed in either the right atrium or the right ventricle. Dual-chamber pacemakers have 2 electrodes - one located in the right atrium and one in the ventricle, while three-chamber pacemakers also have a probe that can stimulate the left ventricle. The NBG code has five positions that denote pacemaker function; however, the last position is rarely used and is not included in Table 2. “Sensing” refers to the detection of spontaneous cardiac depolarizations. The response of a “sensed” event is either a “triggered” pacing stimulus or an “inhibited” pacing stimulus. Rate-adaptive pacing allows to increase heart rate according to metabolic needs during physical or emotional activity. Rate responsive pacemakers control heart rate by sensing extracardiac signals such as minute ventilation, oxygen saturation or body motion (38).

Table 1. NBG code (39)

I	II	III	IV
Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate adaptive
O = none	O = none	O = none	O = none
A = atrium	A = atrium	I = Inhibited	R = rate adaptive
V = ventricle	V = ventricle	T = Triggered	
D = dual	D = dual	D = dual	

1.2.2.1. Indication

The European Society of Cardiology guideline subdivides bradycardias into persistent and intermittent bradycardias, further subdivided into ECG-documented and suspected, i.e. non-ECG-documented. In terms of etiology, persistent bradycardia has an intrinsic (organic) dysfunction of the sinus or AV node, while extrinsic factors (e.g., vagus stimulation) may also be a cause for intermittent bradycardias. The clinical presentation of the patient is the most important decision criterion for the implantation of a permanent pacemaker. Persistent and intermittent bradycardia differ in their predominant symptomatology: While in persistent bradycardia rather unspecific symptoms such as easy fatigue, reduced physical capacity, cognitive disturbances or dizziness are observed, in intermittent high-grade bradycardia typically presyncope or syncope occurs.

The guideline emphasizes the necessary diagnostics for the differentiated forms of bradycardia:

- For the evaluation of patients with suspected or documented bradycardia, a careful history and physical examination are essential.
- The diagnosis of persistent bradycardia can usually be made on the basis of a resting 12-lead ECG.
- ECG documentation should also be sought for intermittent bradycardia. If necessary, a long-term ECG, the use of an event recorder (up to 30 days) or the implantation of a loop recorder may be required.
- In cases of suspected bradycardia (without ECG documentation of arrhythmia), the results of provocative tests (invasive electrophysiological examination, tilt table examination) may support the diagnosis in individual cases.
- There is no defined lower limit for the heart rate below which pacemaker therapy is indicated. Therefore, from the point of view of the guideline, the correlation between symptoms and bradycardia detected by ECG is essential for the decision on pacemaker therapy (40).

According to the 2021 ESC (European Society of Cardiology) guidelines, following conditions have indications for a cardiac pacing device (40):

- Sinus node dysfunction including bradycardia–tachycardia form
 - Chronotropic incompetence and clear symptoms during exercise, DDD with rate-responsive pacing should be considered
 - In pacing with syncope, cardiac pacing may be considered to reduce recurrent syncope when asymptomatic pauses >6 s due to sinus arrest is documented.
- Atrioventricular block (AVB)
 - Pacing is indicated in patients in sinus rhythm with permanent or paroxysmal third- or second-degree type 2, infranodal 2:1, or high-degree atrioventricular block, irrespective of syndromes
 - Pacing is indicated in patients with atrial arrhythmia and permanent or paroxysmal third-or high-degree AVB irrespective of symptoms
 - In patients with permanent atrial fibrillation in need of a pacemaker, ventricular pacing with rate response function is recommended
 - Pacing should be considered in patients with second-degree type 1 AVB that causes symptoms or is found to be located at intra-or infra-His levels at electrophysiology study
- Bundle branch block (BBB)
 - Pacing is indicated in patients with alternating BBB with or without symptoms
 - In patients with unexplained syncope and bifascicular block, a pacemaker is indicated in the presence of either a baseline His–ventricular interval of ≥ 70 ms, second-or third-degree intra-or infra-Hisian block during incremental atrial pacing, or an abnormal response to pharmacological challenge.
- Unexplained syncope
- Reflex syncope
 - Dual-chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged >40 years, with severe, unpredictable, recurrent syncope who have:

- Spontaneous documented symptomatic asystolic pauses >3 s or asymptomatic pauses >6 s due to sinus arrest or AVB
- Cardioinhibitory carotid sinus syndrome
- Asystolic syncope during tilt test

1.2.3. Implantable Cardioverter-Defibrillator (ICD)

High-frequency and life-threatening arrhythmias of the ventricles (ventricular tachycardia, ventricular flutter, ventricular fibrillation) cannot be treated with a pacemaker. In such cases, an implantable cardioverter-defibrillator is used, which usually also provides all the functions of a pacemaker. Similar to a Pacemaker, ICDs are composed of a generator, which is placed under the left clavicle beneath the pectoralis muscle, and up to three wires that reach through veins the heart chambers. A more recent development is the subcutaneous ICD (S-ICD), which is implanted completely under the skin, so that the leads do not run inside veins which can minimize infections and in grow into the heart.

1.2.3.1. Indication

Implantation is indicated in two different forms of sudden cardiac death prevention: When an ICD is used in high-risk patients for a sudden cardiac death without a previous life-threatening arrhythmia episode it is referred to as primary prevention. On the other hand, if an ICD is used after a so-called index event, i.e., a tachycardia-induced circulatory arrest or ventricular fibrillation has occurred, this is called secondary prevention (41).

Following are ICD therapy indications given by the ESC guidelines in 2015 (42):

- Secondary prevention in ventricular fibrillation or ventricular tachycardia with clinical symptoms
- Secondary prevention in long QT syndrome
- Secondary prevention after syncope
- Secondary prevention in persistent ventricular tachycardia (not treatable)
- Primary prevention in patients with ventricular dysfunction (left ventricular ejection fraction $\leq 35\%$ after ≥ 3 months of optimal medical therapy)

- Dilated cardiomyopathy and
 - hemodynamically not tolerated VT/VF
 - or symptomatic heart failure and ejection fraction $\leq 35\%$
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy and sustained ventricular arrhythmia with haemodynamic instability
- Chagas cardiomyopathy and left ventricular EF $< 40\%$
- Light-chain amyloidosis or hereditary transthyretin associated cardiac amyloidosis and ventricular arrhythmia with haemodynamic instability
- Short QT syndrome
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Torsade de pointes tachycardia ("short-coupled")

1.2.4. Cardiac Resynchronization Therapy (CRT)

In patients with systolic heart failure. i.e., impaired pump function of the heart in which ventricles or different wall sections of the ventricles no longer work synchronously, cardiac resynchronization therapy (CRT) can be used. CRT, also known as biventricular pacing has shown a significant mortality benefit in patient groups with reduced left ventricular ejection fraction (43). In addition to a right ventricular probe, a left ventricular lead is placed through the coronary sinus to the left ventricle that enables synchronization. Through a biventricular stimulation, the CRT system restores synchronous activity of both chambers of the heart with the aim of improving pumping function. Cardiac resynchronization therapy is applied either by a special pacemaker (CRT-P) or in combination with an implantable defibrillator (CRT-D).

1.2.4.1. Indication

The following are 2021 Guideline indications for CRT from the European Society of Cardiology (ESC) and the European Heart Rhythm Association (EHRA) (40):

- CRT is recommended for symptomatic patients with heart failure (HF) in sinus rhythm with LV ejection fraction (LVEF) $\leq 35\%$, QRS duration ≥ 150 ms, and left bundle branch block (LBBB) QRS morphology.
- CRT should be considered for symptomatic patients with HF in sinus rhythm with LVEF $\leq 35\%$, QRS duration 130-149 ms, and LBBB QRS morphology.
- CRT should be considered for patients with HF in sinus rhythm with LVEF $\leq 35\%$, QRS duration ≥ 150 ms, and non-LBBB QRS morphology.
- CRT should be considered for patients with HF and LVEF $\leq 35\%$ in NYHA class III or IV if they are in atrial fibrillation (AF) and have intrinsic QRS ≥ 130 ms, provided a strategy to ensure biventricular capture is in place. AV junction ablation should be added in the case of incomplete biventricular pacing (<90-95%) due to conducted AF.

1.2.5. Implantable event recorder

An implantable event recorder or loop recorder (ILR) is a device used to diagnose previously unrecognized cardiac arrhythmias that cannot be detected by a long-term ECG due to their rareness (less than once per month). An implantable event recorder is placed beneath the skin next to the sternum at the level of the second to third rib and has a battery life of about 3 to 6 years.

1.2.5.1. Indication

An Implantable Loop Recorder should be considered in following scenarios (44):

- An ILR is indicated in recurrent syncopes of uncertain origin
- ILR should be considered in reflex syncope with frequent or severe syncopal episodes
- In patients in whom epilepsy was suspected but the treatment has proven ineffective
- Or may be considered in unexplained falls
- If a paroxysmal atrioventricular (AV) block is likely in patients with bundle branch block despite negative complete EPS

2. OBJECTIVES

The aim of this study was to determine the impact of the COVID-19 pandemic on the implantation rates and types of Cardiac Implantable Electronic Devices (CIEDs) in the elderly population in Coburg before the SARS-CoV-2 outbreak and during the first corona pandemic year. Moreover, we will compare various variables of CIED patients before and during the COVID-19 pandemic to deduce further consequences of the ongoing pandemic. Comparison will be in respect to age, gender, BMI, length of hospital stay and clinical parameters at admission such as heart enzymes and inflammatory parameters.

Hypothesis:

- 1) The COVID-19 pandemic has a significant impact on reducing the implantation rate of cardiac implantable electronic devices (CIEDs) in the elderly.
- 2) Patients during the pandemic have a longer hospital stay.
- 3) Patients during the pandemic have higher clinical parameters at admission.
- 4) Patients are older and have a higher BMI during the Covid-19 pandemic.

3. METHODS

3.1. Study design

This single-center study was conducted as a retrospective observational study at the department of cardiology of the hospital Coburg. The ethical approval for this study was obtained by the institutional review board (IRB) of the Medical School Regiomed Coburg on 18 March 2022. The study was performed in accordance with the declaration of Helsinki.

3.2. Participants

For the purpose of this study, we collected data of 530 patients of the hospital Coburg. The inclusion criterium was the de novo implantation of a CIED from March 1st 2019 – February 28th 2021. The exclusion criteria were age under 70 years and missing or incomplete data, which led to the exclusion of 202 patients. A total of 328 patients were finally included in the study. Two groups were formed according to the date of CIED implantation. The control group A contains collected data from 170 patients of the pre COVID-19 year March 1st 2019 – February 28th 2020 whereas the experimental group B includes 158 implantations during the first corona pandemic year from March 1st 2020 until February 28th 2021.

3.3. Variables and data sources

The medical data from the eligible patients were retrieved from the hospital data base. Laboratory parameters refer to the first blood testing, usually at admission. Following data of interest were collected if available:

- 1) Age
- 2) Gender
- 3) type of CIED implanted
- 4) duration of hospital stay
- 5) BMI
- 6) Troponin T
- 7) NT-proBNP
- 8) CRP

3.3.1. Classification of CIED

A CIED is categorized as either a pacemaker, Implantable Cardioverter-Defibrillator (ICD) or a loop recorder. Biventricular pacemakers or defibrillators are classified as Cardiac Resynchronization Therapy (CRT).

3.3.2. Calculation of BMI

The Body Mass Index (BMI) is calculated from the quotient of body weight in kilogram and height in meter squared (kg/m^2). BMI classifications are underweight (under $18.5 \text{ kg}/\text{m}^2$), normal weight (18.5 to 24.9), overweight (25 to 29.9), and obese (30 or more).

3.4. Description

A comparison between the two timespans (March 1st 2019 – Feb 28th 2020, March 1st 2020 - Feb 28th 2021) and therefore between the groups A and B was made regarding the number and also the types of cardiac device implantations. Additionally, we compared parameters listed in 3.3. between the patients of Group A and B.

3.5. Statistical methods

Microsoft Excel, version 2016 and JASP Team (2022), version 0.16.2 (University of Amsterdam, Amsterdam, Netherlands) were used for statistical analysis. The normality of the distribution of numerical data was determined using the Shapiro-Wilk test. The Mann-Whitney U test was used for data with a deviation of normality, which is reported with medians. The Interquartile range (IQR) will be used to present variability. Categorical variables will be expressed as numbers and percentages and compared by the chi-squared test. Statistical significance of this study was defined as $P < 0.05$.

4. RESULTS

During the year before the COVID-19 pandemic restrictions started in Germany (1 March 2019 - 28 February 2020) there were 170 CIED implantations (group A), whereas during the first pandemic year (1 March 2020-28 February 2021) there were 158 implantations (group B), which means a decrease of ~7.1%. A comparison of cardiac device implantations is presented in Table 2 and Figure 2.

Out of 170 CIEDs in group A, there were 115 pacemakers, 13 ICDs, 21 CRTs and 21 Loop recorders. Group B on the other hand received 117 pacemakers, 10 ICDs, 14 CRTs and 17 Loop recorders. Conspicuous is the increased count of pacemakers in group B (+1.739%), despite a decreased total count of CIEDs (-7.058%). Striking on the other hand is the drastic decline in CRT implantations from 21 to 14 (-33.333%) during the pandemic. Using the chi-squared test, no statistically significant difference between the cardiac device implantations could be detected ($P=0.616$).

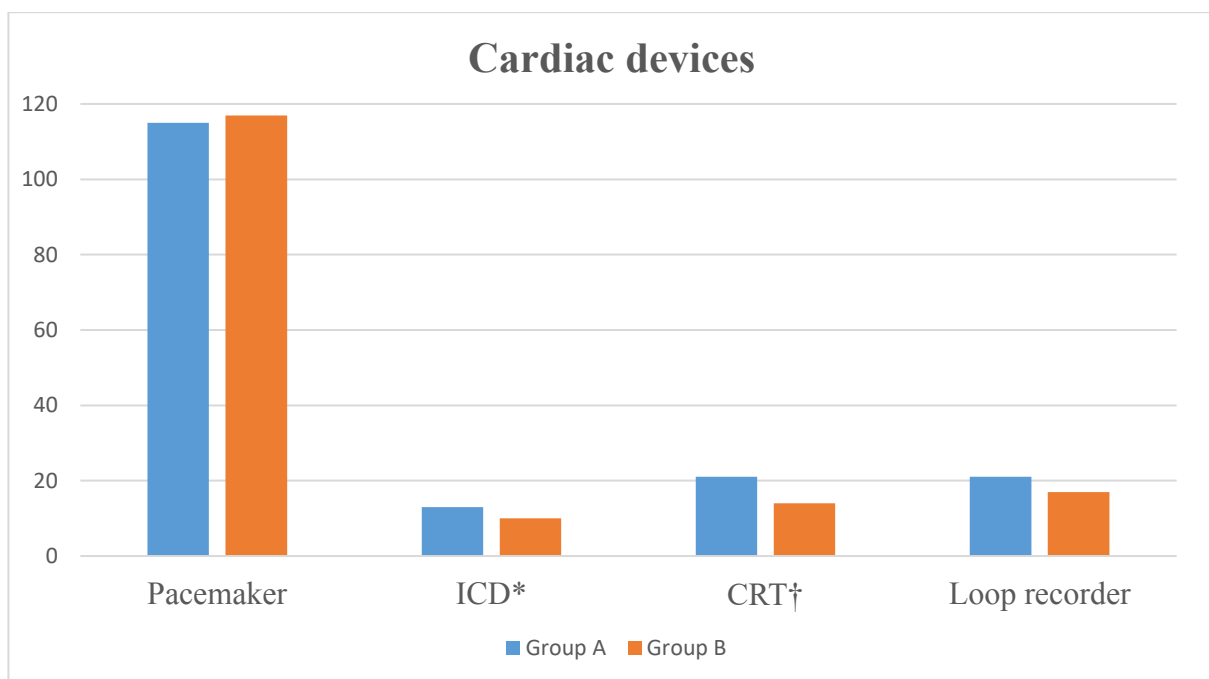


Figure 2. Cardiac devices
 *Implantable cardioverter defibrillator
 †Cardiac resynchronization therapy

Table 2. Comparison of CIED implantations

		Group			
Cardiac device		A	B	Total	Change from A to B
Pacemaker	Count	115	117	232	+1.74%
	% within row	49.57%	50.43%	100%	
	% within column	67.65%	74.05%	70.73%	
ICD*	Count	13	10	23	-23.08%
	% within row	56.52%	43.48%	100%	
	% within column	7.65%	6.33 %	7.01%	
CRT†	Count	21	14	35	-33.33%
	% within row	60 %	40 %	100 %	
	% within column	12.35%	8.86%	10.67%	
Loop recorder	Count	21	17	38	-19.05%
	% within row	55.26%	44.74%	100%	
	% within column	12.35%	10.76%	11.59%	
Total	Count	170	158	328	-7.06%
	% within row	51.83%	48.17%	100%	
	% within column	100%	100%	100%	

Data are presented in numbers if not otherwise indicated

*Implantable cardioverter defibrillator

†Cardiac resynchronization therapy

Before Covid-19 (group A) there was a male predominance (N=97, 57.06%) and fewer female patients (N=73, 42.94%). Similar male predominance was seen during COVID-19 (N=90, 56.96%) compared to N=68, 43.04% female patients. No statistical difference could be detected using the chi-squared test ($P=0.986$) between the two groups.

The normality of age distribution of both patient groups can be seen in Figure 2 and was tested using the Shapiro-Wilk test. A deviation of normality was detected: $P=0.005$ and $P=0.001$ for group A and B respectively.

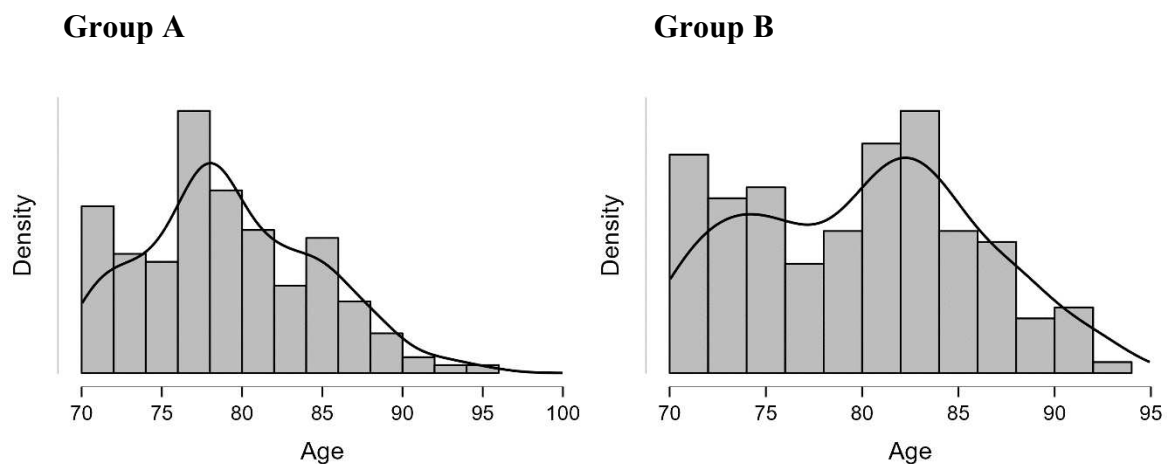


Figure 3. Age distribution

A comparison of age, duration of hospital stays and BMI is presented in Table 2. The median age in group A was 79 years (IQR=76, 83) while group B during the pandemic had a median age of 81 years (IQR=75, 84). No statistical difference could be deduced using the Mann-Whitney U test ($P=0.208$).

There has been a prolonged duration of hospital stays in patients during the COVID-19 pandemic. The Median was 9 days (IQR=6, 13) compared to the median of 8 days (IQR=5, 13) in group A. However, the P -value of 0.845 in the Mann-Whitney U test, indicates no significant difference.

To check whether there was a significant difference in obesity between the two groups, the BMI was compared using the Mann-Whitney U test. With a *P*-value of 0.956 the difference is not significant. The median of group A was 28.05 (IQR=25.18, 32.5) and in group B 28.30 (IQR=25.16, 31.2).

Table 3. Comparison of groups

	Age (years)		Duration of stay (days)		BMI * (kg/m ²)	
	A	B	A	B	A	B
Valid patients	170	158	170	158	80	75
Median	79.00	81.00	8.00	9.00	28.05	28.30
IQR †	7.00	9.00	8.00	7.00	7.33	6.05
25 th percentile	76.00	75.00	5.00	6.00	25.18	25.15
75 th percentile	83.00	84.00	13.00	13.00	32.50	31.20
Shapiro-Wilk	0.976	0.968	0.901	0.781	0.954	0.928
<i>P</i> ‡	0.005	0.001	<0.001	<0.001	<0.001	<0.001
Mann-Whitney U	12349.500		13262.000		3016.000	
<i>P</i> §	0.208		0.845		0.956	

Data are presented as numbers if not otherwise indicated

*Body-Mass-Index

†Interquartile range

‡Shapiro-Wilk test

§Mann-Whitney U test

Table 3 presents a comparison of the laboratory parameters Troponin T, NT-proBNP and CRP between the groups A and B at hospital admission. To compare Troponin T between the groups, we had to exclude 19 patients in group A and 11 patients in group B because of missing data. The median for group A was 0.03 (IQR=0.02, 0.04) and for group B comparable with 0.03 (IQR=0.02, 0.05). The Mann-Whitney U test detected no significant difference ($P=0.401$).

Data from the hormone NT-proBNP was missing in 74 patients of group A and in 72 patients of group B. The median was with 1481 (IQR=577.5, 3669.5) higher in the pre COVID-19 group A than in group B during the pandemic (Median=1428.5, IQR=525.4, 4921.75). However, the Mann-Whitney test could not detect any statistically significant difference ($P=0.633$).

Comparing the acute-phase protein CRP, one patient in group B had to be excluded for missing data. The Medians were 3.00 (IQR=1.40, 10.43) for group A and 2.80 (IQR=1.10, 7.90) for group B. Again, no significant difference could be found ($P=0.611$) using the Mann-Whitney U test.

Table 4. Comparison of laboratory parameters at admission

	Troponin T (ng/ml)		NT-proBNP* (ng/l)		CRP† (mg/l)	
	A	B	A	B	A	B
Valid patients	151	147	96	86	170	157
Median	0.03	0.03	1481.00	1425.50	3.00	2.80
IQR‡	0.03	0.03	3092.00	4396.00	9.03	6.80
25 th percentile	0.02	0.02	577.50	525.40	1.40	1.10
75 th percentile	0.04	0.05	3669.50	4921.75	10.43	7.90
Shapiro-Wilk	0.112	0.069	0.539	0.625	0.493	0.462
<i>P</i> §	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mann-Whitney U	10474.000		3958.000		13780.000	
<i>P</i>	0.401		0.633		0.611	

Data are presented as numbers if not otherwise indicated

* N-terminal pro-B-type natriuretic peptide

† C-reactive Protein

‡ Interquartile range

§ Shapiro-Wilk test

|| Mann-Whitney U test

5. DISCUSSION

As mentioned in the Introduction section, there has been an observed decline in hospital admission and visits due to cardiac arrhythmias or acute coronary syndrome during the COVID-19 outbreak (32, 33). Therefore, we hypothesized that there would be also a decline in CIED implantations, which was also indicated by data published so far. In the retrospective analysis of Bollmann *et al.* a 15-27% reduction of interventional treatments has been observed (32). However, there was no comparison in the age group above seventy years. In Coburg, even though there were in total 293 Cardiac device implantations in the pre COVID-19 year and only 237 in the first pandemic year, which makes a decrease of 19.1%, the difference between those two years was not as drastic in the elderly population with a decrease of only 7.1%. Our study showed that in Coburg during the first pandemic year, the pacing health care in the elderly population could be sustained, regarding total numbers.

However, a decline of 33.3% (from 21 to 14) in CRT and 23.1% in ICD implantations during the pandemic could be the result of fear of patients to go to the hospital and contract the corona virus. Additionally, patient misinterpretation of thoracic discomfort as noncardiac could explain lower implantation numbers. Furthermore, there could have been a more cautious approach to implantations in COVID-19 times. Left ventricular lead implantations (in CRT devices) are more time consuming, more complex, have higher perioperative complications and make it difficult if the Intensive Care Unit (ICU) is already full with Covid patients (45). Other than ICD devices, which have a preventive purpose, pacemakers are implanted in symptomatic patients where fear of a corona infection is subordinated.

Furthermore, we could not find significantly higher laboratory parameters (Troponin T, NT-proBNP, CRP) at admission during the pandemic compared to before the COVID-19 outbreak. Various data have shown worse cardiac biomarkers in Covid patients but not how the restrictions, the staff and material shortage, the prioritising in hospitals and the attitude of patients during the pandemic has affected all other patients' health condition previous to a CIED implantation (46, 47). What we can assume from these results is that the health condition of patients older than 70 years was not different between the groups and therefore treatment with a CIED was not hindered or delayed by the COVID-19 restrictions.

Previous research has shown an increase in body weight during the COVID-19 pandemic, but our results could not reflect that (48). The BMI was trended higher with 28.3 kg/m² in Group B during the first Covid year compared to 28.1 kg/m² in group A. What we can see from our data however is that the experimental group B had not significant higher BMI

values, but both groups are classified as overweight, a risk factor for heart failure and coronary heart disease (49, 50) .

The hypothesis that CIED patients will be older during the first pandemic year cannot be confirmed. The median age was 81 years compared to 79 years in the year before the outbreak. However, this difference is not statistically significant. One has to bear in mind that these medians are of the age group older than 70 and not of all CIED patients. Possible explanation for the age difference could be the prioritisation of more vulnerable groups during the ongoing pandemic.

In a multicentre, pan-European observational study, the mean hospital stay at the cardiology department was significantly shorter during the pandemic in 2020 in comparison to 2019 (4.9 ± 5.0 versus 5.9 ± 7.2 , $P < 0.0001$) (51). In contrast, the results of length of hospital stays in our study did not reach statistical significance; in the experimental group B during the pandemic, the hospital stays were 9 days, compared to a median of 8 days in the control group A. This difference can have various reasons, such as possible SARS-CoV-2 infection or merely isolation as contact person, perioperative complications, supply difficulties for the operation, personnel shortage, etc. Yet interestingly, it can be deduced that there was no obvious aim to minimize hospitalization time, as was suggested by Sokolski *et al.*

The mayor limitation in this study was its sample size. Dissimilarities between the groups in the types and the number of cardiac devices did not reach significance due to the small sample size. Moreover, there are limitations to the conclusion about the Body-Mass-Index, as we only compared the BMI at admission and didn't have previous data. Additionally, the comparison was not between the same patients, rather between two patient groups receiving the same treatment at different times.

6. CONCLUSIONS

1. A significant reduction of total CIED implantations in der elderly could not be detected during the COVID-19 pandemic. The absolute reduction amounts to 7.1%.
2. Elderly CIED patients had a slightly longer stay of one day in the hospital during the COVID-19 pandemic. However, the difference did not achieve statistical significance.
3. The compared laboratory parameters Troponin T, NT-proBNP and CRP had no significant trend to higher values in the experimental group during the pandemic, reflecting comparable health conditions at admission.
4. The median age and Body-Mass-Index were higher in patients during the pandemic but did not reach significance.
5. There was no significant impact of COVID-19 on the cardiac device therapy in Coburg.

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8. SUMMARY

Objectives: The aim of this study was to determine the impact of the COVID-19 pandemic on the implantation rates and types of Cardiac Implantable Electronic Devices (CIEDs) in the elderly population in Coburg. Compared was the year before the SARS-CoV-2 outbreak with the first COVID-19 pandemic year. Moreover, we will compare various variables of CIED patients before and during the COVID-19 pandemic to deduce further consequences of the ongoing pandemic.

Materials and methods: A retrospective observational study was conducted at the department of cardiology of the hospital Coburg, Germany. Included were patients being 70 years of age or older with de novo implantation of a CIED and divided into 2 groups according to two time spans. A total of 328 patients were included. The control group A contains collected data from 170 patients of the pre COVID-19 year March 1st 2019 – February 28th 2020 whereas the experimental group B includes 158 implantations during the first corona pandemic year from March 1st 2020 until February 28th 2021. Following variables were included and compared between the groups: age, gender, type of CIED, Body-Mass-Index (BMI), length of hospital stay and laboratory parameters Troponin T, n-terminal prohormone of brain natriuretic peptide (NT-proBNP) and C- reactive protein (CRP).

Results: A reduction of 7.1% in total CIED implantations could be observed between the year before the SARS-CoV-2 outbreak and the first pandemic year. Reduced Cardiac Resynchronization Therapy (CRT) (-33.33%), Implantable Cardioverter-Defibrillator (ICD) (-23.08%) and Loop recorder (-19.05%) implantations were performed whereas more pacemaker implantations (+1.74%) were performed during the first pandemic year. However, no statistically significant difference between the cardiac device implantations could be detected ($P=0.616$). The median age in group A was 79 years (IQR=76, 83) and 81 years (IQR=75, 84) in group B. No statistical difference could be deducted using the Mann-Whitney U test ($P=0.208$). There was no significant difference in recording parameters Troponin T, NT-proBNP and CRP ($P=0.401$, $P=0.633$, $P=0.611$ respectively) between the two groups at hospital admission. The median hospital stays were 8 (IQR=5, 13) and 9 (IQR=6, 13) days for group A and B respectively and did not reach statistical significance ($P=0.845$). No significant change in BMI ($P=0.956$) could be detected between the groups (A:28.1 kg/m² vs. B:28.3 kg/m²).

Conclusion: The ongoing COVID-19 pandemic had no statistically significant effect on CIED implantations in the elderly population in Coburg during the first year.

9. CROATIAN SUMMARY

Naslov: Evaluacija implantacije srčanog elektroničkog uređaja u starijih osoba: utjecaj COVID-19

Ciljevi: Cilj ove studije bio je utvrditi utjecaj pandemije COVID-19 na stope implantacije i vrste cardiac implantable electronic devices (CIEDs) u Coburgu. U usporedbi s godinom prije izbijanja SARS-CoV-2 s prvom godinom pandemije COVID-19. Štoviše, usporedit ćemo različite varijable pacijenata s CIED-om prije i tijekom pandemije COVID-19 kako bismo zaključili daljnje posljedice pandemije koja je u tijeku.

Materijali i metode: Retrospektivna opservacijska studija provedena je na kardiološkom odjelu bolnice u Coburgu u Njemačkoj. Uključeni su pacijenti u dobi od 70 godina ili stariji s de novo implantacijom CIED-a i podijeljeni u 2 skupine prema dva vremenska raspona. Uključeno je ukupno 328 bolesnika. Kontrolna skupina A sadrži prikupljene podatke od 170 pacijenata iz godine prije COVID-19 1. ožujka 2019 – 28. veljače 2020, dok eksperimentalna skupina B uključuje 158 implantacija tijekom prve godine pandemije korone od 1. ožujka 2020 do 28. veljače 2021. Sljedeće varijable bile su uključeni i uspoređeni između skupina: dob, spol, tip CIED-a, Body-Mass-Index (BMI), duljina boravka u bolnici i laboratorijski parametri Troponin T, n-terminal prohormone of brain natriuretic peptide (NT-proBNP) i C-reactive protein (CRP).

Rezultati: Smanjenje od 7,1% ukupnih implantacija CIED-a moglo se primijetiti između godine prije izbijanja SARS-CoV-2 i prve godine pandemije. Smanjena Cardiac Resynchronization Therapy (CRT) (-33,33%), Implantable Cardioverter-Defibrillator (ICD) (-23,08%) and Loop recorder (-19,05%) ugradnje su učinjene dok je u prvoj godini pandemije učinjeno više ugradnji pacemakera (+1,74%). Međutim, nije se mogla otkriti nikakva statistički značajna razlika između implantata srčanog uređaja ($P=0,616$). Medijan dobi u skupini A bio je 79 godina (IQR=76, 83) i 81 godina (IQR=75, 84) u skupini B. Pomoću Mann-Whitneyevog U testa ($P=0,208$) nije se mogla odbiti statistička razlika. Nije bilo značajne razlike u bilježenju parametara Troponin T, NT-proBNP i CRP ($P=0,401$, $P=0,633$, $P=0,611$ respektivno) između dvije skupine pri prijemu u bolnicu. Medijan boravka u bolnici iznosio je 8 (IQR=5, 13) odnosno 9 (IQR=6, 13) dana za skupinu A i B i nije postigao statističku značajnost ($P=0,845$). Nije bilo značajne promjene u BMI ($P=0,956$) između skupina (A:28,1 kg/m² u odnosu na B:28,3 kg/m²).

Zaključci: Pandemija COVID-19 koja je u tijeku nije imala statistički značajan učinak na implantacije CIED-a kod starije populacije u Coburgu tijekom prve godine.

10. CURRICULUM VITAE