Diploma Thesis

Significance of Cardiovascular Comorbidities in Coronavirus Disease 2019 (COVID-19)

submitted by

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Statement of Originality

I herewith declare that I have composed the present thesis myself and without use of any other than the cited sources and aids. Sentences or parts of sentences quoted literally are marked as such; other references with regard to the statement and scope are indicated by full details of the publications concerned.

Graz, 3rd December 2021 Valentin Zsilavecz m.p.

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List of abbreviations

95%-CI	95% confidence interval
ACE(2)	Angiotensin-converting enzyme (2)
ARDS	acute respiratory distress syndrome
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CK	creatine kinase
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
eGFR	estimated glomerular filtration rate
hsTnI	high sensitive troponin I
hsTnT	high sensitive troponin T
ICU	intensive care unit
IL-10	interleukin 10
IL-2R	interleukin 2 receptor
IL-6	interleukin 6
INR	international normalized ratio
LDH	lactatedehydrogenase
MERS-CoV	middle east respiratory syndrome coronavirus
MI	myocardial infarction
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OR	odds ratio
PAI-1	plasminogen activator inhibitor-1
pCO2	partial pressure of carbon dioxide
PCT	procalcitonin
RAAS-system	renin-angiotensin-aldosterone-system
ROC curve	receiver operating characteristic curve
RR	risk ratio
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-1/2	severe acute respiratory syndrome coronavirus type 1/2
SO2	oxygen saturation
SVT	supraventricular tachycardia
TIA	transient ischemic attack
TMPRSS2	transmembrane protease serine 2
TNF-α	tumor necrosis factor alpha
VT	ventricular tachycardia
WBC	white blood cell count

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Zusammenfassung

Hintergrund

PatientInnen, die aufgrund einer Infektion mit SARS-CoV-2 im Krankenhaus behandelt werden müssen, haben häufig kardiovaskuläre Risikofaktoren oder leiden an bereits vorbekannten kardiovaskulären Erkrankungen. Außerdem entwickeln sich bei einem beträchtlichen Anteil an COVID-19-PatientInnen Symptome, die über einen längeren Zeitraum bestehen und nicht einer anderen Ursache zugeordnet werden können ("Post-COVID-19-Syndrom"). In dieser Arbeit werden Daten von PatientInnen, die mit einer SARS-CoV-2-Infektion am Universitätsklinikum Graz behandelt wurden, zur Prävalenz von kardiovaskulären Vorerkrankungen und Risikofaktoren, zum Outcome im Krankenhaus und zum Outcome nach 6 Monaten präsentiert.

Methoden

96 PatientInnen, die im Zeitraum zwischen Februar und Anfang Mai 2020 mit einer mittels PCR-Test gesicherten SARS-CoV-2-Infektion am Universitätsklinikum Graz behandelt wurden, wurden in diese Studie eingeschlossen. Es wurden alle kardiovaskulären und nicht-kardiovaskulären Vorerkrankungen, kardiovaskuläre Risikofaktoren, die Laborparameter bei der Aufnahme ins Krankenhaus und das Outcome im Krankenhaus erhoben. Außerdem wurde das Outcome drei bzw. sechs Monate nach Entlassung aus dem Krankenhaus erhoben.

Resultate

Der Großteil der in dieser Studie eingeschlossenen PatientInnen litt an kardiovaskulären Risikofaktoren (69.8%) und/oder kardiovaskulären Vorerkrankungen (46.9%). 25 PatientInnen (26.0%) wurden im Laufe ihres Krankenhausaufenthalts auf einer Intensivstation behandelt und 26 PatientInnen (27.1%) verstarben im Krankenhaus. PatientInnen mit vorbekannter Herzinsuffizienz (OR: 13.1; 95%-KI: 2.5-67.2; p: 0.002), ischämischer Herzerkrankung (OR: 5.7; 95%-KI: 1.6-20.1; p: 0.006) und Diabetes (OR: 13.2; 95%-KI: 3.4-51.9; p: <0.001) hatten ein höheres Risiko, im Krankenhaus zu versterben.

Von den 70 PatientInnen, die nach dem initialen Krankenhausaufenthalt noch am Leben waren, wurden 18 (25.7%) während des Follow-Up-Zeitraumes zumindest einmal erneut im Krankenhaus behandelt und 7 (10.0%) verstarben. Alle verstorbenen PatientInnen hatten kardiovaskuläre Risikofaktoren (arterieller Hypertonus, Fettstoffwechselstörungen, Diabetes) oder litten an vorbekannten kardiovaskulären Erkrankungen.

Insgesamt verstarben 33 PatientInnen (34.4%) entweder während des ersten Krankenhausaufenthalts oder während des Follow-Ups. PatientInnen mit kardiovaskulären Vorerkrankungen hatten ein deutlich erhöhtes Mortalitätsrisiko.

Conclusio

Viele PatientInnen, die während der ersten Welle mit einer SARS-CoV-2-Infektion am Universitätsklinikum Graz behandelt werden mussten, wiesen kardiovaskuläre Vorerkrankungen und/oder Risikofaktoren auf. Vorbekannte Herzinsuffizienz, ischämische Herzerkrankung und Diabetes waren deutlich mit einem erhöhten Mortalitätsrisiko assoziiert. 10% aller PatientInnen, die nach ihrem initialen Krankenhausaufenthalt noch am Leben waren, verstarben im Laufe der darauffolgenden sechs Monate, wobei alle diese PatientInnen an kardiovaskulären Vorerkrankungen und/oder Risikofaktoren litten.

Abstract

Background

Pre-existing cardiovascular disease and risk factors are frequent in hospitalized SARS-CoV-2 infected patients and strongly affect outcomes. Furthermore, studies suggest that a considerable proportion of hospitalized patients with COVID-19 develops symptoms that persist for more than twelve weeks and cannot be explained by an alternative diagnosis ("Post-COVID-19 syndrome"). Here, we report data on the prevalence of cardiovascular disease, risk factors and hospital outcome as well as six months outcome of COVID-19 first-wave inpatients at the University Hospital of Graz, Austria.

Methods

A registry of 96 patients with PCR-confirmed SARS-CoV-2 infection that were treated at the University Hospital of Graz between February and the beginning of May was established and a prospective follow-up was conducted. Patients were characterized regarding pre-existing cardiovascular disease, risk factors, other chronic diseases, laboratory results and intra-hospital, 3- and 6-month outcomes were determined.

Results

The majority of hospitalized patients with SARS-CoV-2 infection (77.1%) had pre-existing cardiovascular diseases (46.9%) and/or cardiovascular risk factors (69.8%). 25 patients (26.0%) were admitted to the ICU and 26 patients (27.1%) died. The adjusted (sex, age, BMI) odds ratios for death were significantly higher in patients suffering from heart failure (OR: 13.1; 95%-CI: 2.5-67.2; p: 0.002), ischemic heart disease (OR: 5.7; 95%-CI: 1.6-20.1; p: 0.006) and diabetes (OR: 13.2; 95%-CI: 3.4-51.9; p: <0.001).

Of the 70 patients discharged from hospital, 18 patients (25.7%) were at least once re-hospitalized and 7 patients (10.0%) died during the follow-up period. All deaths occurred in the group of patients with pre-existing cardiovascular disease or at least one cardiovascular risk factor (arterial hypertension, diabetes, dyslipidaemia).

In total, 33 patients (34.4%) died either during hospitalization or the follow-up period. The presence of pre-existing cardiovascular disease was significantly associated with a higher mortality.

Conclusion

The prevalence of cardiovascular disease and/or risk factors is high in patients with PCR-confirmed SARS-CoV-2 infection requiring inpatient care. Heart failure, ischemic heart

disease, and diabetes were predictors of intra-hospital mortality and cardiovascular patients were at higher risk of being treated at the ICU and ventilated. 10% of all patients that were available for follow-up died within six months after discharge from hospital and all deaths occurred in patients with pre-existing cardiovascular disease and/or risk factors.

1. Introduction

SARS-CoV-2 is a novel coronavirus that was first detected in patients with pneumonia in Wuhan (China) in December 2019 (1). Initially, reported cases were limited to Asia. However, at the end of February 2020 the first infections were also reported in Austria (7). Due to previous research on two other human-pathogenic coronaviruses, namely SARS-CoV-1 and MERS-CoV, it is already known that the prevalence of cardiovascular and metabolic diseases (e.g. diabetes, hypertension, metabolic syndrome) is high in infected patients (2). That is why the suspicion arose that this connection could also exist with the novel coronavirus. In a study in which 385 patients who survived SARS and 135 patients who died from SARS were included diabetes and hyperglycemia were associated with a higher morbidity and mortality (3). Early studies on these assumptions have revealed a significantly higher prevalence of pre-existing cardiovascular disease, cerebrovascular disease, diabetes and hypertension in patients with COVID-19 that had to be treated in an intensive care unit (ICU) (4). In an analysis of 99 RT-PCR-confirmed cases of SARS-CoV-2 infection that were hospitalized in January 2020 40% had pre-existing cardio- or cerebrovascular diseases (5). A review that included six separate studies with a total of 1527 patients showed significantly higher proportions of patients with hypertension (RR: 2.0; 95%-CI: 1.5-2.7; $p<0.001$) and cardio-cerebrovascular disease (RR: 3.3; 95%-CI: 2.0-5.4; $p<0.001$) among severe cases requiring intensive care than with other severe cases that were not admitted to an intensive care unit (6). Additionally, the analysis of two studies on cardiac injuries with COVID-19 revealed that 8% of the included patients suffered cardiac injury with a significantly higher incidence in ICU patients (RR: 13.5; 95%-CI: 3.6-50.5; $p<0.001$) (6).

These findings suggest that pre-existing cardiovascular disease or cardiovascular risk factors increase the susceptibility to an infection with SARS-CoV-2 and the risk of a more severe course of the disease. Furthermore, COVID-19 seems to lead to cardiac injury via mechanisms that have not been fully understood yet.

The aim of this diploma thesis is to characterize all patients with PCR-confirmed SARS-CoV-2 infection that were treated at the University Hospital of Graz between February and the beginning of May 2020 in terms of pre-existing cardiovascular disease, cardiovascular risk factors, chronic diseases and outcome during hospitalization. In addition, we investigated whether any of these conditions can predict the intra-hospital outcome. All

patients – with the exception of those who died during the initial hospital stay – were contacted by phone approximately six months after discharge to track any abnormalities in their state of health (e.g. hospitalizations, persisting symptoms, newly diagnosed diseases) during the follow-up period.

2. Potential mechanisms of cardiovascular involvement in SARS-CoV-2 infection

2.1 Pathophysiology of infection

Like the previously discovered coronaviruses MERS-CoV and SARS-CoV-1, SARS-CoV-2 belongs to the group of betacoronaviruses. Uptake of all coronaviruses into host cells is mediated by spike proteins, which gives the family of coronaviruses its name due to the crown-like arrangement. As previously reported with SARS-CoV-1, the novel coronavirus shows affinity to membrane bound ACE2, which thus serves as a receptor for virus binding. In addition, these coronaviruses lead to downregulation of ACE2 in the lungs (8). ACE2 was detected in type I and II alveolar epithelial cells, in nasal and oral mucosa, in bronchial epithelial cells, in enterocytes and muscle cells in the small intestine, in the kidney, in endothelial cells and in the heart (13,61). This could partially explain the involvement of organ systems other than the respiratory tract, the occurrence of non-respiratory symptoms (e.g. diarrhea) and the possibility of virus detection in stool in some cases (14). However, to enable fusion of host cells and the virus a modification of the viral structure by the transmembrane protease serine 2 (TMPRSS2) is necessary (9).

2.2 Cardiovascular involvement in COVID-19

Renin-Angiotensin-Aldosterone-System

ACE2 plays a role in the RAAS-system and may partially mediate cardiovascular involvement in SARS-CoV-2 infection. Unlike ACE, which allows the conversion of Angiotensin-I to Angiotensin-II, ACE2 converts Angiotensin-II to Angiotensin-(1-7). Angiotensin-II leads to renal sodium and fluid retention, inflammation, vasoconstriction, oxidative stress, increased coagulation and fibrosis, which is why excessive RAAS-activation has negative effects on the cardiovascular system (10). In contrast, Angiotensin-(1-7) has vasodilating and anti-inflammatory effects (11). One hypothesis suggests that SARS-CoV-2 infection leads to an imbalance in the RAAS-system by suppressing the protective effects of ACE2 and promoting pro-inflammatory effects of Angiotensin-II (12). This effect could also exacerbate an imbalance in the RAAS-system that already existed prior to the infection. In a study that included over 10.000 patients higher plasma concentrations of ACE2, which could be a counter-regulatory reaction in response to an excessive RAAS-activation (16), were associated with a higher total and cardiovascular mortality rate and higher incidences of heart failure, myocardial infarction, stroke and

diabetes (15). This might indicate that cardiovascular diseases are associated with an imbalance in the RAAS-system and thus a limited ability to respond to further disturbances in the RAAS-system caused by an infection with SARS-CoV-2. This could make patients with pre-existing cardiovascular diseases or risk factors more susceptible to a SARS-CoV-2 infection and an adverse outcome due to the reduced ability to compensate the effects of SARS-CoV-2 on the RAAS-system.

Myocardial injury in COVID-19

Several studies have shown that in some cases myocardial injury occurs in COVID-19 patients leading to an adverse intra-hospital outcome. In a case series of 138 hospitalized patients the concentrations of high sensitive troponin I (hsTnI) were significantly higher in patients that required intensive care than in patients that did not need intensive care (11.0pg/ml vs. 5.1pg/ml; p: 0.004) (4). In another study that included 416 hospitalized patients 82 patients suffered cardiac injury, which was defined as blood levels of hs-TNI above the 99th-percentile reference limit. These patients were significantly older and had a higher prevalence of cardiovascular diseases and risk factors. In addition, the proportions of patients who required invasive or non-invasive ventilation, who suffered ARDS or acute kidney injury and who died were significantly higher in patients with cardiac injury (17). An American multi-center study detected elevated troponin-I levels in 985 of 2.736 hospitalized COVID-19 patients and a higher prevalence of cardiovascular diseases (e.g. atrial fibrillation, heart failure, coronary artery disease) in patients with troponin-I elevation. Higher troponin-I levels were also found to be associated with a higher risk of death (troponin I 0.03-0.09ng/ml: adjusted HR: 1.75, $p<0.001$; troponin I >0.09 ng/ml: adjusted HR: 3.03, $p<0.001$)(18). An Italian multicenter study that included 614 hospitalized COVID-19 patients found elevated levels of troponin (either troponin I or T) in 278 patients (45.3%). Furthermore, patients with elevated troponin levels were at higher risk of intra-hospital mortality (HR: 1.71; 95%-CI: 1.13-2.59; p: 0.01) and complications (e.g. acute heart failure, acute kidney injury, pulmonary embolism, multiorgan failure) (64).

Although the exact mechanisms leading to cardiac injury in the setting of COVID-19 have not yet been elucidated, there are some hypotheses that may be considered.

Myocarditis

One way how an infection with SARS-CoV-2 could potentially lead to cardiac injury is via inflammatory damage that could be either caused by direct viral infiltration into myocardial

tissue or by indirect immune-mediated inflammation. A research group which analyzed cardiac tissue samples of 21 deceased patients found increased interstitial infiltration by macrophages in 18 of these patients. Furthermore, lymphocytic and multifocal myocarditis with infiltration of $CD3^+$ T lymphocytes and $CD68^+$ macrophages were observed in 3 cases (62). In our own preliminary analysis of cardiac tissue samples from patients who died from SARS-CoV-2 infection we confirmed mildly increased leucocyte numbers.

In a German study including 39 deceased patients who tested positive for SARS-CoV-2 before death cardiac tissue samples were collected and analyzed. Direct detection of SARS-CoV-2 was possible in the cardiac tissue of 24 patients. However, a difference in leucocyte numbers or an infiltration of inflammatory cells into cardiac tissue was not found when comparing patients with and without detection of the virus (63). Mostly, SARS-CoV-2 was detected in non-cardiomyocyte cells.

Reduced cardiac reserve

In patients with pre-existing cardiovascular disease severe infections lead to an imbalance between an increased metabolic demand, which is four to eight times higher compared to the physiological cardiac workload (20) and a decreased cardiac reserve, which may result in instability of chronic cardiovascular disease (19). In addition, COVID-19 pneumonia and other severe lung diseases can result in decreased oxygen uptake into the blood, which could further limit impaired myocardial oxygen delivery in pre-existing cardiovascular disease and at worst lead to a type II myocardial infarction. One study that investigated the incidence of acute myocardial infarction within 7 days after testing positive for respiratory syncytial virus, influenza A/B virus or other viruses, showed increased incidence ratios for the occurrence of acute myocardial infarction. However, the incidence ratios did not increase significantly after day 7 (58). Similar results could be shown in a recent Swedish study including over 85.000 COVID-19 patients and nearly 350.000 matched control patients. The odds ratios for acute myocardial infarction (OR: 3.41; 95%-CI: 1.58-7.36) and ischemic stroke (OR: 3.63; 95%-CI: 1.69-7.80) were significantly elevated within the first two weeks following COVID-19 onset (59).

Immune dysregulation and hyperinflammation

Several studies suggest that serum levels of pro-inflammatory cytokines are associated with the severity of the disease course. In some cases, COVID-19 causes an aggressive inflammatory reaction that is called “cytokine storm” due to the massive release of

inflammatory cytokines (22). In an early Chinese study that included 29 patients with mild to critical infection increased levels of IL-2R und IL-6 were shown to be significantly associated with disease severity (21). Another study showed similar results with significantly increased IL-6 and d-dimer concentrations in patients with severe illness (23). In a retrospective study by Chen et al., severe cases of COVID-19 were associated with lymphopenia and significantly higher concentrations of IL-2R, IL-6, IL-10, TNF-α and d-dimer (24). These findings suggest that an excessive immune response is linked to an unfavorable prognosis and multi-organ damage. However, the exact mechanisms that may lead to immune-mediated cardiac injury remain to be clarified.

Adverse drug effects

Some drugs that were administered to many patients due to their SARS-CoV-2 infection may have an impact on the electrical conduction system in the heart and on the prevalence of arrhythmias. Chloroquine and hydroxychloroquine were frequently prescribed only at the beginning of the pandemic, because no definitely positive effects on the course of the disease could be demonstrated (25). However, approximately 10% of all patients that were treated with hydroxychloroquine developed QT-prolongation and in some cases high-dose hydroxychloroquine therapy seems to be associated with ventricular arrhythmia (26). Therapy with azithromycin, also commonly administered to treat COVID-19 patients, alone and in combination with hydroxychloroquine resulted in a high prevalence of severe QTc-prolongation >500ms (OR: 1.43, 95%-CI: 1.13-1.82), with a thereby increased risk of torsade de pointes tachycardias (27,28). These drug-induced effects on the cardiovascular system could contribute to cardiac involvement in COVID-19 patients with preexisting cardiovascular disease.

Thrombosis and plaque destabilization

Severe systemic inflammation could lead to plaque destabilization and rupture via release of cytokines resulting in acute coronary insufficiency and myocardial damage (29). This increased vulnerability may be triggered by immune cytokines and proteases that are released by cells of the immune system, which could lead to degradation and disturbed formation of fibrous components of the plaque's cap resulting in increased risk of rupture (30). In addition, thromboembolic events are potential complications in the setting of COVID-19 due to a shifted balance between fibrinolysis and thrombosis. A French study that included 26 patients with severe COVID-19 receiving heparin either therapeutically or prophylactically showed a high prevalence of venous thromboembolism in both groups (69%

of all patients; 6 patients with pulmonary embolism) (32). A series of autopsies in Germany identified deep venous thrombosis in 7 of 12 examined patients and pulmonary embolism as the direct cause of death in 4 patients suggesting that infection-triggered thrombosis plays an important role in fatalities (33). This effect is not unique to COVID-19 and has been demonstrated in other severe infections (31). However, the increased thrombotic risk in COVID-19 patients may be caused by the imbalance in the RAAS-system with higher angiotensin-II levels leading to impaired fibrinolysis via increased release of plasminogen activator inhibitor-1 (PAI-1) (31). The increased thrombotic potential in patients with COVID-19 may lead to a higher risk of coronary occlusion and myocardial damage due to thrombus formation in coronary vessels accompanied by endothelial dysfunction and angiotensin-II-related vasoconstriction (34). In addition, the occurrence of pulmonary embolisms can subsequently lead to cardiac injury due to increased pulmonal arterial pressure and resulting right heart strain.

3. Methods

First, we performed a retrospective data acquisition of all 96 patients who were hospitalized with PCR-confirmed SARS-CoV-2 infection at the University Hospital of Graz between 23th of January and 3rd of May 2020. For this purpose data such as symptoms and laboratory findings at admission, imaging findings, pre-existing and chronic diseases, cardiovascular risk factors, medication and outcome during hospitalization were collected. In addition, a follow up phone call was conducted approximately six months after discharge.

3.1 Study population

All included patients were treated at the University Hospital of Graz in the period from February to the beginning of May 2020 and tested positive for SARS-CoV-2 by PCR-testing. However, hospitalization did not occur in all patients due to COVID-19 and some of the included patients did not have any symptoms attributable to their SARS-CoV-2 infection. Patients who were younger than 18 at the time of data collection were excluded. The ethical committee of the Medical University of Graz approved the study (32-400 ex 19/20 and 32-585 ex 19/20) and patients provided informed consent for prospective follow-up.

3.2 Data collection

In addition to the collection of data concerning body weight, height, sex, age, ethnicity and length of hospital stay medical records were also screened for pre-existing cardiovascular disease (e.g. heart failure, valvular heart disease, ischemic heart disease), cardiovascular risk factors (e.g. hypertension, diabetes, dyslipidemia, smoking) and chronic diseases (e.g. chronic kidney disease, malign neoplasms, COPD, asthma). If available, symptoms, laboratory findings, imaging findings and vital signs on admission to hospital were obtained. Data concerning the patients' permanent medication and therapeutic measures implemented in hospital were also collected. Additionally, various parameters such as occurrence of respiratory failure, acute coronary syndrome, myocarditis or pneumonia, need for treatment in an intensive care unit, need for invasive or non-invasive ventilation and death were acquired to estimate intra-hospital outcome.

3.3 Comparison of outcome and risk evaluation

To assess the impact of pre-existing cardiovascular disease and risk factors on the outcome, two different patient groups were defined. If no risk factors or pre-existing cardiovascular disease could be identified, patients were assigned to the group of "non-cardiovascular patients". All others were defined as "cardiovascular patients" and subclassified based on

cardiovascular risk factors (arterial hypertension, diabetes, dyslipidemia) and pre-existing cardiovascular diseases (heart failure, ischemic heart disease, history of myocardial infarction, moderate/severe valvular heart disease, congenital heart disease, atrial fibrillation, other supraventricular or ventricular arrhythmias, elevated pulmonary pressure, cardiomyopathy, heart transplantation, ventricular assist device, pacemaker, implantable cardioverter defibrillator, peripheral artery disease, cardiac resynchronization therapy, stroke or transient ischemic attacks). Intra-hospital outcome (primarily intra-hospital death and need for intensive care) was compared between cardiovascular and non-cardiovascular patients (significance level: $p<0.05$). Additionally, the outcome of non-cardiovascular patients was compared to the outcome of several subgroups of cardiovascular patients (e.g. patients with diabetes/hypertension/heart failure).

Odds ratios for death or ICU admission were calculated in univariate regression analyses and later adjusted for some potential confounding factors (age, sex, body mass index). Subsequently, multivariate regression analyses were conducted including all variables that were significantly associated with increased risk of death or ICU admission in prior analyses.

To determine whether abnormalities in laboratory parameters on admission were associated with worse intra-hospital outcome, values for all obtained parameters were compared between patients with different outcomes. Furthermore, univariate regression analyses were performed and odds ratios for death or ICU admission were calculated. Laboratory parameters that were found to be significantly associated with death or ICU admission were considered in multivariate regression models (including age, sex, body mass index). In addition, a mortality risk score was created including demographic and laboratory variables that were associated with increased risk of death in uni- and multivariate regression models.

3.4 Follow-Up

First, the medical records of all 70 patients who were available for follow-up after hospitalization in the electronic health record database "Medocs" were reviewed to determine whether hospitalization or death had occurred during the follow-up period. All patients who were still alive after six months were contacted via phone and asked about persistent or new health problems, new-onset diseases, re-hospitalizations and changes in medication. If it was not possible to interview the respective persons for example because of dementia or because a patient could not be reached by phone, authorized contact persons or the responsible caregivers in the case of nursing home residents were asked about the

patient's health status. The follow-up of patients for whom no one could be reached by phone was exclusively performed by reviewing patient records. All respondents were first informed about the study and were asked to sign an informed consent form.

3.5 Statistical Analysis

Data analysis was performed with SPSS Vol. 26. Demographic data were compared between cardiovascular and non-cardiovascular patients by using the chi-square test or Fisher's exact test in categories with binary values (e.g. symptoms on admission) and a two-tailed t-test or the Mann-Whitney-U test in categories with continuous values such as age or length of hospital stay depending on whether the requirements for a parametric test were fulfilled (normality tests). To determine whether cardiovascular risk factors and pre-existing cardiovascular diseases had an influence on the intra-hospital outcome (e.g. intra-hospital death, need for intensive care), the outcome of non-cardiovascular patients and several subgroups of cardiovascular patients was compared by using the chi-square test or Fisher's exact test with a significance level of $p<0.05$. Additionally, binary logistic regression analyses were performed to determine the influence of various parameters such as cardiovascular disease, risk factors, chronic diseases, age, sex and body mass index on the outcome (significance level: $p<0.05$) and to calculate odds ratios adjusted for sex, age and body mass index. All factors that were identified as significant risk factors for death or ICU admission in univariate regression analyses were included in multivariate regression models. Laboratory findings of patients with different intra-hospital outcome were compared by using a t-test for independent samples or the Mann-Whitney-U test depending on whether the requirements for a parametric test were fulfilled (normality tests). Intra-hospital and overall survival analyses were performed by using the Kaplan-Meier method and differences in survival were checked for significance by using the log-rank test.

4. Results

A total of 96 patients diagnosed with SARS-CoV-2 infection who were treated at the University Hospital of Graz were analyzed. The median age was 76.0 years (minimum: 26 years, maximum: 100 years) and 53.1% were female. 64.6% were older than 70 years and 32.3% older than 80 years. In total, 25 patients (26.0%) had to be transferred to an intensive care unit, 26 patients (27.1%) required non-invasive ventilation, 14 patients (14.6%) required invasive ventilation (6 of these patients required non-invasive and invasive ventilation during their hospital stay), 34 patients (35.4%) suffered from respiratory failure and 26 patients (27.1%) died during initial hospitalization. The median length of hospital stay was 8.0 days and patients who required intensive care spent 16.5 days at an intensive care unit. The median age at death was 80.0 years and 50.0% of all deceased patients were older than 80 years.

The most common symptoms at hospital admission were fever (53.1% of all patients), dyspnea (47.9%), fatigue/tiredness (41.7%) and cough (29.2%). Other reported symptoms were orthopnea (7.3%), gastrointestinal symptoms (15.6%), chest pain (4.2%), sore throat (4.2%), myalgia (4.2%), runny nose (4.2%) and altered smell or taste (4.2%). Fever (p: 0.036) and gastrointestinal symptoms (p: <0.001) occurred significantly more often in non-cardiovascular patients than in cardiovascular patients. The prevalence of all other symptoms did not differ significantly between these two groups (**Table 1**).

74 patients had at least one pre-existing cardiovascular disease or risk factor (arterial hypertension, diabetes, dyslipidemia) and were therefore assigned to the group of cardiovascular patients. Some patients suffered from chronic, non-cardiovascular diseases like chronic obstructive pulmonary disease or asthma (16.7% of all patients), malignant neoplasms (22.9%) or chronic kidney disease (33.3%) (**Table 2**).

4.1 Cardiovascular patients

74 patients with a median age of 76.5 years (minimum: 26 years, maximum: 100 years) were assigned to the group of cardiovascular patients. Of these 74 patients, 56.8% were female and the median BMI was 26.5 kg/m² (**Table 1**). 45 patients (46.9% of all patients) suffered from at least one pre-existing cardiovascular disease and 67 patients (69.8%) had at least one cardiovascular risk factor (arterial hypertension, diabetes, dyslipidemia). The most common pre-existing cardiovascular diseases were atrial fibrillation (19 patients - 19.8%), ischemic heart disease (18 patients - 18.8%), peripheral artery disease (15 patients - 15.6%) and

history of stroke or transient ischemic attacks (14 patients - 14.6%). Frequently present cardiovascular risk factors were arterial hypertension (60 patients - 62.5%), diabetes type II (23 patients - 24.0%) and dyslipidemia (36 patients - 37.5%). 21.6% of all cardiovascular patients suffered from COPD or asthma, 24.3% had a diagnosed malignant neoplasm and 35.1% had chronic kidney disease (**Table 2**).

Of all cardiovascular patients, 20 patients (27.0%) had to be treated in an intensive care unit, 13 patients (17.6%) required invasive ventilation, 18 patients (24.3%) required non-invasive ventilation and 22 patients (29.7%) died. Cardiovascular patients spent an average of 8.0 days in hospital and 16.0 days in an ICU. The median age at death was 80.0 years and 37.0% of all deceased patients in the group of cardiovascular patients were older than 80 years (**Table 3**).

4.2 Non-cardiovascular patients

22 patients with a median age of 72.0 years (minimum: 36 years, maximum: 92 years) had no cardiovascular risk factors or pre-existing cardiovascular disease and were therefore assigned to the group of non-cardiovascular patients. 40.9% of all non-cardiovascular patients were female and the median BMI was 24.8 kg/m². Common chronic, non-cardiovascular diseases were malignant neoplasms (18.2% of all non-cardiovascular patients) and chronic kidney disease (18.2%).

In the group of non-cardiovascular patients 5 patients (22.7%) were treated in an intensive care unit, 1 patient (4.5%) required invasive ventilation, 8 patients (36.4%) needed non-invasive ventilation and 4 patients (18.2%) died. The median length of hospitalization was 10.0 days and non-cardiovascular patients were treated in an ICU for 17.0 days. Non-cardiovascular patients died at a median age of 87.5 years and 75.0% of the deceased patients in this group were older than 80 years (**Table 3**)

Table 1. Baseline characteristics of patients hospitalized with SARS-CoV-2 infection. Cardiovascular patients were defined as patients with at least one pre-existing cardiovascular disease and/ or risk factor (hypertension, diabetes, dyslipidemia). Comparisons in categories with binary variables were performed using the chi-square test or Fisher's exact test. In categories with continuous variables a two-tailed t-test or the Mann-Whitney-U test were used. Continuous variables are given as median plus interquartile range. BMI denotes body mass index, GI-symptoms gastrointestinal symptoms.

	Cardiovascular patients	**Non-cardiovascular patients**	**p-values**
Number	74 (77.1%)	22 (22.9%)	
Sex distribution			0.191
Male	32 (43.2%)	13 (59.1%)	
Female	42 (56.8%)	9 (40.9%)	
Age	76.5 years (IQR: 66.0-82.0)	72.0 years (IQR: 51.0-78.0)	0.088
Distribution [%]			
<50 yr	2 (2.7%)	5 (22.7%)	
50-60 yr	11 (14.9%)	3 (13.6%)	
60-70 yr	10 (13.5%)	3 (13.6%)	
70-80 yr	24 (32.4%)	7 (31.8%)	
>80 yr	27 (36.5%)	4 (18.2%)	
BMI [kg/m²]	26.5 (IQR: 23.6-31.3)	24.8 (IQR: 22.6-26.8)	**0.041**
Length of hospital stay	8.0 days (IQR: 4.0-20.0)	10.0 days (IQR: 6.0-18.0)	0.669
Symptoms at admission			
Dyspnea	36 (48.6%)	10 (45.5%)	0.792
Fever	35 (47.3%)	16 (72.7%)	**0.036**
Tiredness/fatigue	30 (40.5%)	10 (45.5%)	0.681
Cough	18 (24.3%)	10 (45.5%)	0.056
Orthopnea	7 (9.5%)	0 (0.0%)	0.346
GI-Symptoms	6 (8.1%)	9 (40.9%)	**0.001**
Chest pain	4 (5.4%)	0 (0.0%)	0.571
Sore throat	4 (5.4%)	0 (0.0%)	0.571
Runny nose	3 (4.1%)	1 (4.5%)	1.000
Myalgia	2 (2.7%)	2 (9.1%)	0.224
Altered smell or taste	2 (2.7%)	2 (9.1%)	0.224

4.3 Comparison of non-cardiovascular and cardiovascular patients

The two groups of patients described above were compared by using a two-tailed t-test or the Mann-Whitney-U test in categories with quantitative values (e.g. age, length of hospitalization, body mass index) and the chi-square test or Fisher's exact test in categories with binary values such as death or need for intensive care. The proportion of female patients was higher in the group of cardiovascular patients, but did not reach statistical significance (p: 0.191). In terms of age, cardiovascular patients tended to be older (p: 0.088) with an absolute difference in the median age of 4.5 years. The body mass index was significantly higher in cardiovascular patients (p: 0.041) (**Table 1**). The prevalence of death (p: 0.285), need for intensive care (p: 0.687) and need for invasive ventilation (p: 0.129) was higher in cardiovascular patients, but did not reach statistical significance. The same applies to the age at death (p: 0.316). The proportion of patients who required non-invasive ventilation was higher in the group of non-cardiovascular patients (p: 0.265) (**Table 3**). The length of hospital stay (p: 0.669) and the duration of stay on ICU (p: 0.972) did not differ significantly between cardiovascular and non-cardiovascular patients.

These data suggest that cardiovascular patients had a significantly higher BMI and tended to be older. In addition, the proportion of patients who died or needed invasive ventilation or intensive care tended to be higher in cardiovascular patients compared to non-cardiovascular patients. Cardiovascular patients also died at a younger age.

Table 2. Prevalence of pre-existing cardiovascular diseases, cardiovascular risk factors and chronic diseases in hospitalized patients with SARS-CoV-2 infection. MI denotes myocardial infarction, SVT supraventricular tachycardia, VT ventricular tachycardia, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease. Chronic kidney disease includes all patients with stadium III or higher (GFR <60ml/min).

	Total number (% of all patients)
Cardiovascular disease	45 (46.9%)
Heart failure	12 (12.5%)
HFpEF	3
HFmrEF	1
HFrEF	7
not specified	1
Ischemic heart disease	18 (18.8%)
History of MI	8 (8.3%)

Valvular heart disease	10 (10.4%)
Atrial fibrillation	19 (19.8%)
Other SVT or VT	4 (4.2%)
Pacemaker	3 (3.1%)
Peripheral artery disease	15 (15.6%)
Stroke or TIA	14 (14.6%)
Cardiovascular risk factors	
Arterial hypertension	60 (62.5%)
Dyslipidemia	36 (37.5%)
Diabetes mellitus type II	23 (24.0%)
Current smoker	8 (8.3%)
Former smoker	18 (18.8%)
Chronic disease	
COPD/Asthma	16 (16.7%)
Malignant neoplasm	22 (22.9%)
Chronic kidney disease	32 (33.3%)

Table 3. Intra-hospital outcome of patients hospitalized with SARS-CoV-2 infection. Comparisons in categories with binary values were performed using the chi-square test or Fisher's exact test. In categories with continuous variables, a two-tailed t-test or the Mann-Whitney-U test was used. Continuous variables are given as median plus interquartile range. ICU denotes intensive care unit.

	Cardiovascular patients (n=74)	**Non-cardiovascular patients (n=22)**	**p-values**
Length of hospital stay	8.0 days (IQR: 4.0-20.0)	10.0 days (IQR: 6.0-18.0)	0.669
Length of stay on ICU	16.0 days (IQR: 6.0-20.0)	17.0 days (IQR: 8.0-17.0)	0.972
Invasive ventilation	13 (17.6%)	1 (4.5%)	0.178
Non-invasive ventilation	18 (24.3%)	8 (36.4%)	0.265
ICU	20 (27.0%)	5 (22.7%)	0.687
Respiratory failure during hospitalisation	27 (36.5%)	7 (31.8%)	0.688
Death	22 (29.7%)	4 (18.2%)	0.285
Distribution [%]			
<50 yr	0 (0.0%)	0 (0.0%)	
50-60 yr	1 (4.5%)	0 (0.0%)	1.000
60-70 yr	1 (4.5%)	1 (25.0%)	0.289
70-80 yr	10 (45.5%)	0 (0.0%)	0.136
>80 yr	10 (45.5%)	3 (75%)	0.593
Age at death	80.0 years (IQR: 78.0-83.0)	87.5 years (IQR: 77.0-90.5)	0.316

4.4 Risk factors for death or ICU admission

The group of cardiovascular patients was further divided according to the exact pre-existing cardiovascular disease and/or risk factor. The outcome (e.g. ICU admission, death) of patients in the respective subgroups was subsequently compared to the outcome of non-cardiovascular patients by using the chi-square test or Fisher's exact test.

In general, the rate of deaths in patients with pre-existing cardiovascular disease (16 out of 45; 35.6%) was higher than in non-cardiovascular patients (4 out of 22; 18.2%). However, it did not reach the level of statistical significance (p: 0.144). The highest rates of fatalities were present in patients with heart failure (9 out of 12; 75.0%; p: 0.005) and ischemic heart disease (11 out of 18; 61.1%; p: 0.005). The rates of deceased patients in these two subgroups were significantly higher than in non-cardiovascular patients. In other subgroups (e.g. valvular heart disease, peripheral artery disease) no statistically significant differences could be observed compared to non-cardiovascular patients despite clearly higher mortality rates, which is at least partly due to the low number of included patients. In patients with cardiovascular risk factors or non-cardiovascular chronic diseases, only pre-existing diabetes (14 out of 23; 60.9%; p: 0.003) was associated with a significantly increased mortality rate. For other cardiovascular risk factors (e.g. arterial hypertension, dyslipidemia) no significant association with a higher mortality rate could be shown. The proportion of deaths was also higher in patients with COPD/asthma (43.8%; p: 0.086) and chronic kidney disease (40.6%; p: 0.081), although no statistically significant difference could be demonstrated (**Table 4; Figure 1**).

The proportion of patients that had to be treated in an intensive care unit was not significantly higher in patients with pre-existing cardiovascular disease in comparison to non-cardiovascular patients (26.7% vs. 22.7%; p: 0.728). Ischemic heart disease (50.0%; p: 0.072), valvular heart disease (50.0%; p: 0.123), heart failure (41.7%; p: 0.247), diabetes (39.1%; p: 0.235), dyslipidemia (36.1%; p: 0.285) and COPD/asthma (50.0%; p: 0.080) were associated with higher rates of patients who required intensive care without reaching statistical significance (**Table 5; Figure 1**).

In summary, it can be stated that the proportion of deceased patients and patients that were treated in an ICU tended to be higher in cardiovascular patients. Some pre-existing cardiovascular diseases (e.g. heart failure, ischemic heart disease) and risk factors (e.g. diabetes) were associated with a significantly worse outcome compared to non-cardiovascular patients.

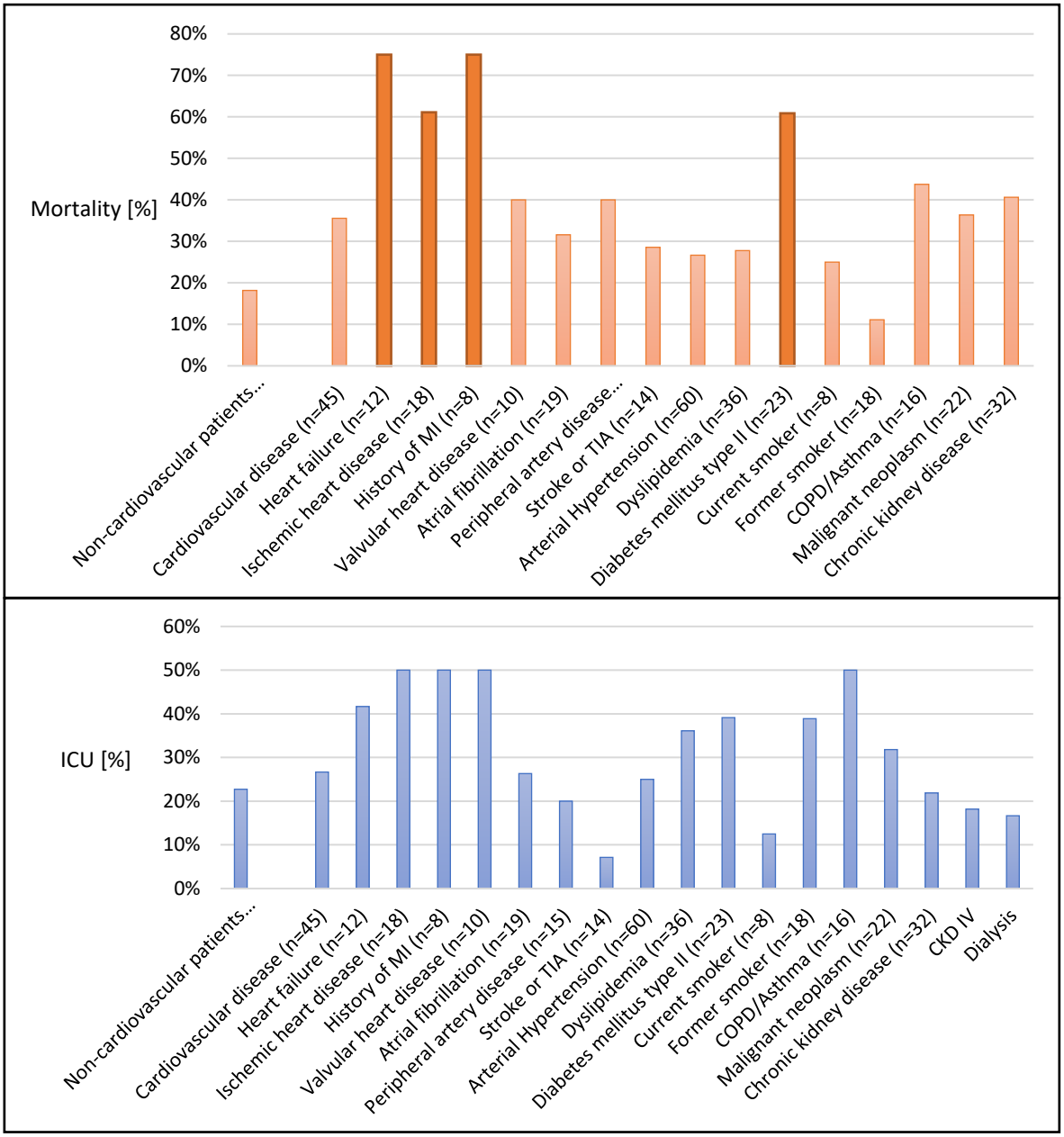

Figure 1. Proportion of deceased patients (upper graphic) and patients who required intensive care (lower graphic) in several subgroups in comparison to non-cardiovascular patients. Subgroups in which statistically significant differences in comparison to non-cardiovascular patients were present are represented by highlighted bars.

Logistic regression analyses

In order to investigate the influence of age, sex, body mass index, cardiovascular risk factors, pre-existing cardiovascular disease and chronic diseases on the patients' outcome binary logistic regression analyses were performed. This allows the identification of factors that after adjustment for age, sex and body mass index, still show a significant influence on the outcome of patients.

Subgroups in which significantly elevated adjusted odds ratios for death occurred were patients with heart failure (OR: 13.1; 95%-CI: 2.5-67.2; p: 0.002), ischemic heart disease (OR: 5.7; 95%-CI: 1.6-20.1; p: 0.006) and type II diabetes (OR: 13.2; 95%-CI: 3.4-52.0; p: <0.001). Some other diseases like valvular heart disease (OR: 2.3; 95%-CI: 0.479-10.877; p: 0.300) and peripheral artery disease (OR: 2.0; 95%-CI: 0.6-7.4; p: 0.287) were also associated with a higher risk of death without reaching statistical significance (**Table 4; Figure 2**). Significantly increased odds ratios for treatment in an intensive care unit were present in patients with ischemic heart disease (OR: 6.7; 95%-CI: 1.9-23.1; p: 0.003), valvular heart disease (OR: 7.2; 95%-CI: 1.5-33.9; p: 0.012), dyslipidemia (OR: 4.5; 95%-CI: 1.5-13.9; p: 0.009) and COPD/asthma (OR: 5.1; 95%-CI: 1.5-17.6; p: 0.010) (**Table 5; Figure 3**).

In addition, multivariate regression analyses including age, sex, body mass index and all factors that were associated with a significantly increased risk of death or need for intensive care in univariate regression models (p: <0.05; OR: >1) were carried out. It was shown that older age (OR: 1.1; 95%-CI: 1.0-1.2; p: 0.005) and pre-existing diabetes type II (OR: 11.1; 95%-CI. 2.5-49.4; p: 0.002) led to a significantly increased risk of death. In addition, female patients were at significantly lower risk of death (OR: 0.2; 95%-CI: 0.1-0.9; p: 0.033). Odds ratios for death in patients with ischemic heart disease (OR: 3.9; 95%-CI: 0.8-18.5; p: 0.082) and heart failure (OR: 2.8; 95%-CI: 0.4-19.4; p: 0.307), which were shown to be significantly elevated in previously applied models, did not reach the level of significance in this multivariate regression model. A significantly increased odds ratio for treatment in an intensive care unit was obtained in patients with COPD/asthma (OR: 4.4; 95%-CI: 1.1-17.9; p: 0.037). Ischemic heart disease (OR: 3.8; 95%-CI: 0.9-16.1; p: 0.075), valvular heart disease (OR: 2.6; 95%-CI: 0.4-17.8; p: 0.320) and dyslipidemia (OR: 2.8; 95%-CI: 0.8-9.8; p: 0.106) were also associated with a higher risk of requiring intensive care, but did not reach statistical significance.

From the aforementioned models, we concluded that older patients, male patients and patients with pre-existing diabetes type II have a significantly higher risk of intra-hospital death. Moreover, some types of pre-existing cardiovascular disease (e.g. heart failure and ischemic heart disease) led to an increased mortality risk. Pre-existing chronic pulmonary disease (COPD/asthma) was a predictor for ICU admission. Furthermore, the presence of some subtypes of cardiovascular disease (e.g. ischemic heart disease, valvular heart disease)

and cardiovascular risk factors resulted (e.g. dyslipidemia) in a higher risk of requiring intensive care.

Table 4. Odds ratios for death in patients with cardiovascular disease, risk factors or chronic disease. Total numbers of deaths were always compared to non-cardiovascular patients by using the chi-square test or Fisher's exact test. Binary logistic regression analyses were performed and odds ratios were adjusted for age, sex and BMI. MI denotes myocardial infarction, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease. Chronic kidney disease includes all patients with stadium III or higher (GFR <60ml/min).

	Total number of deaths (%; p-value)	**Unadjusted OR for death** (95% CI; p-value)	**Adjusted OR for death** (95% CI; p-value)
Age [years]	-	**1.06** (1.02-1.11; **0.004**)	-
Female sex	-	0.44 (0.18-1.11; 0.083)	-
BMI [kg/m²]	-	1.00 (0.92-1.09; 0.957)	-
Cardiovascular disease (n=45)	16 (35.6%; 0.144)	2.26 (0.90-5.69; 0.083)	1.88 (0.66-5.34; 0.236)
Heart failure (n=12)	8 (**75.0%**; **0.002**)	**11.82** (2.88-48.47; **0.001**)	**13.06** (2.54-67.21; **0.002**)
Ischemic heart disease (n=18)	11 (**61.1%**; **0.005**)	**6.60** (2.19-19.87; **0.001**)	**5.74** (1.64-20.07; **0.006**)
History of MI (n=8)	6 (**75.0%**; **0.007**)	**10.20** (1.91-54.52; **0.007**)	**9.82** (1.59-60.67; **0.014**)
Valvular heart disease (n=10)	4 (40.0%; 0.218)	1.94 (0.50-7.52; 0.338)	2.28 (0.48-10.88; 0.300)
Atrial fibrillation (n=19)	6 (31.6%; 0.469)	1.32 (0.44-3.93; 0.623)	0.90 (0.27-3.03; 0.863)
Peripheral artery disease (n=15)	6 (40.0%; 0.258)	2.03 (0.64-6.42; 0.226)	2.03 (0.55-7.42; 0.287)
Stroke or TIA (n=14)	4 (28.6%; 0.683)	1.09 (0.31-3.84; 0.892)	0.78 (0.20-3.09; 0.727)
Cardiovascular risk factors			
Arterial hypertension (n=60)	16 (26.7%; 0.428)	0.95 (0.37-2.39; 0.906)	0.65 (0.21-1.98; 0.444)

Dyslipidemia (n=36)	10 (27.8%; 0.407)	1.06 (0.42-2.67; 0.906)	0.93 (0.33-2.64; 0.893)
Diabetes mellitus type II (n=23)	14 (**60.9%**; **0.003**)	**7.91** (2.79-22.40; **<0.001**)	**13.20** (3.35-51.97; **<0.001**)
Current smoker (n=8)	2 (25.0%; 0.645)	0.89 (0.17-4.71; 0.890)	0.73 (0.12-4.29; 0.724)
Former smoker (n=18)	2 (11.1%; 0.673)	0.28 (0.06-1.32; 0.108)	0.27 (0.05-1.41; 0.121)
Chronic disease			
COPD/Asthma (n=16)	7 (43.8%; 0.147)	2.50 (0.82-7.61; 0.107)	1.69 (0.51-5.56; 0.389)
Malignant neoplasm (n=22)	8 (36.4%; 0.176)	1.78 (0.64-4.92; 0.268)	1.65 (0.51-5.37; 0.407)
Chronic kidney disease (n=32)	13 (40.6%; 0.081)	**2.68** (1.06-6.82; **0.038**)	1.48 (0.50-4.44; 0.480)

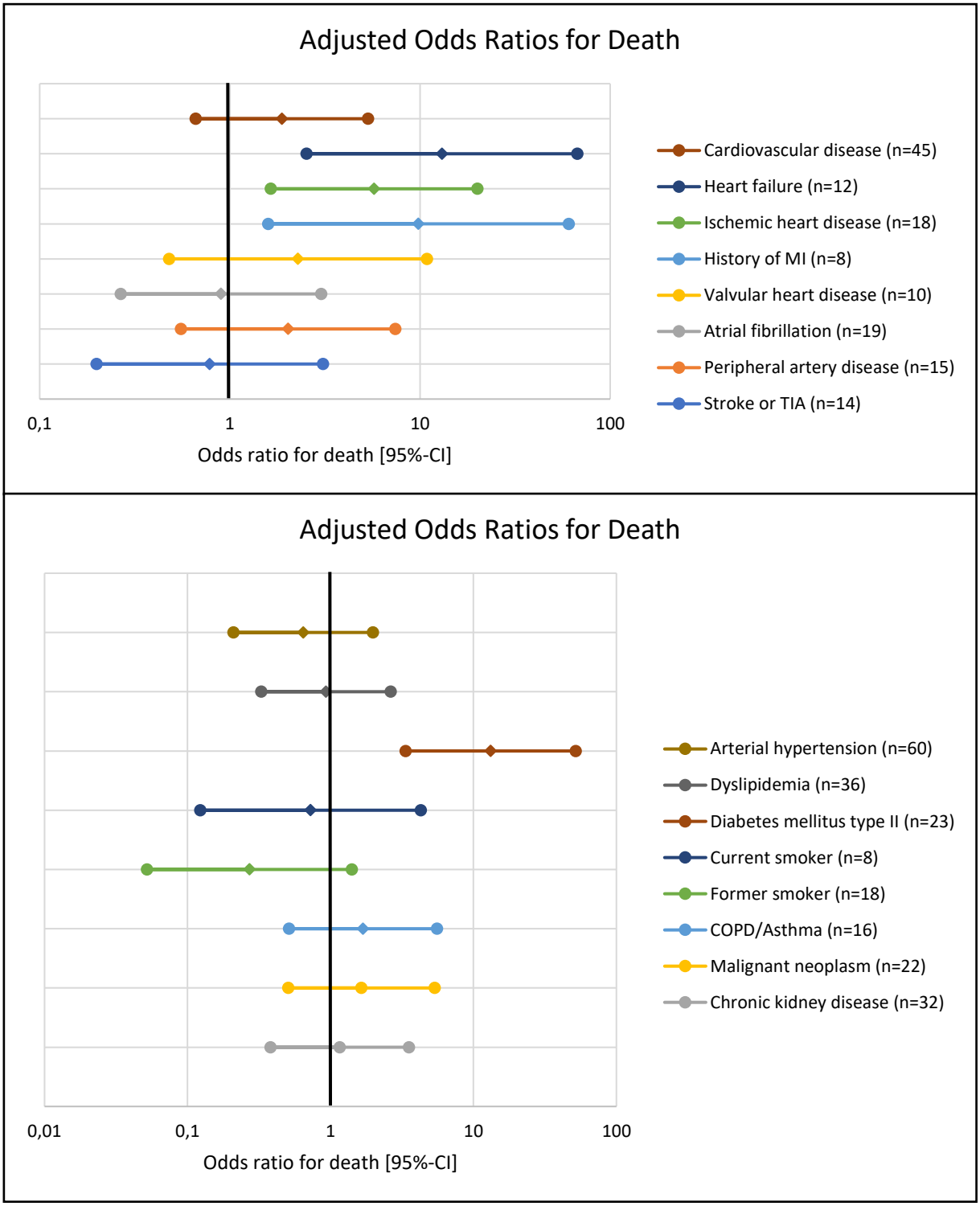

Figure 2. Odds ratios for death in several subgroups. Odds ratios were adjusted for sex, body mass index and age. 95%-CI denotes 95% confidence intervall.

Table 5. Odds ratios for ICU admission in patients with cardiovascular disease, risk factors or chronic disease. Total numbers of ICU admissions were always compared to non-cardiovascular patients by using the chi-square test or Fisher's exact test. Binary logistic regression analyses were performed and odds ratios were adjusted for age, sex and body mass index. MI denotes myocardial infarction, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease. Chronic kidney disease includes all patients with chronic kidney disease stage III or higher (GFR <60ml/min).

	Total number of ICU admissions (%; p-value)	**Unadjusted OR for ICU admission** (95% CI; p-value)	**Adjusted OR for ICU admission** (95% CI; p-value)
Age [years]	-	0.97 (0.94-1.00; 0.079)	-
Female sex	-	0.39 (0.15-1.00; 0.05)	-
BMI [kg/m²]	-	1.03 (0.95-1.12; 0.487)	-
Cardiovascular disease (n=45)	12 (26.7%; 0.728)	1.06 (0.43-2.65; 0.896)	1.50 (0.55-4.07; 0.429)
Heart failure (n=12)	5 (41.7%; 0.271)	2.29 (0.65-8.00; 0.196)	2.91 (0.75-11.27; 0.122)
Ischemic heart disease (n=18)	9 (50.0%; 0.072)	**3.88** (1.32-11.35; **0.014**)	**6.68** (1.93-23.06; **0.003**)
History of MI (n=8)	4 (50.0%; 0.195)	3.19 (0.73-13.88; 0.122)	**5.30** (1.06-26.46; **0.042**)
Valvular heart disease (n=10)	5 (50.0%; 0.217)	3.30 (0.87-12.56; 0.080)	**7.24** (1.55-33.88; **0.012**)
Atrial fibrillation (n=19)	5 (26.3%; 1.000)	1.02 (0.33-3.19; 0.976)	1.54 (0.45-5.29; 0.496)
Peripheral artery disease (n=15)	3 (20.0%; 1.000)	0.67 (0.17-2.60; 0.564)	0.64 (0.16-2.64; 0.541)
Stroke or TIA (n=14)	1 (7.1%; 0.370)	0.19 (0.02-1.50; 0.114)	0.23 (0.03-1.96; 0.180)
Cardiovascular risk factors			
Arterial Hypertension (n=60)	15 (25.0%; 0.832)	0.87 (0.34-2.21; 0.764)	0.97 (0.34-2.83; 0.960)
Dyslipidemia (n=36)	13 (36.1%; 0.285)	2.26 (0.89-5.72; 0.085)	**4.52** (1.47-13.88; **0.009**)
Diabetes mellitus type II (n=23)	9 (39.1%; 0.235)	2.29 (0.84-6.25; 0.106)	2.11 (0.72-6.17; 0.173)
Current smoker (n=8)	1 (12.5%; 1.000)	0.38 (0.05-3.26; 0.378)	0.37 (0.04-3.28; 0.375)

Former smoker (n=18)	7 (38.9%; 0.267)	2.12 (0.72-6.27; 0.174)	2.10 (0.68-6.45; 0.196)
Chronic disease			
COPD/Asthma (n=16)	8 (50.0%; 0.080)	**3.71** (1.21-11.32; **0.022**)	**5.08** (1.47-17.59; **0.010**)
Malignant Neoplasm (n=22)	7 (31.8%; 0.498)	1.45 (0.51-4.12; 0.483)	1.29 (0.44-3.83; 0.646)
Chronic kidney disease (n=32)	7 (21.9%; 1.000)	0.72 (0.26-1.94; 0.512)	0.78 (0.26-2.37; 0.666)

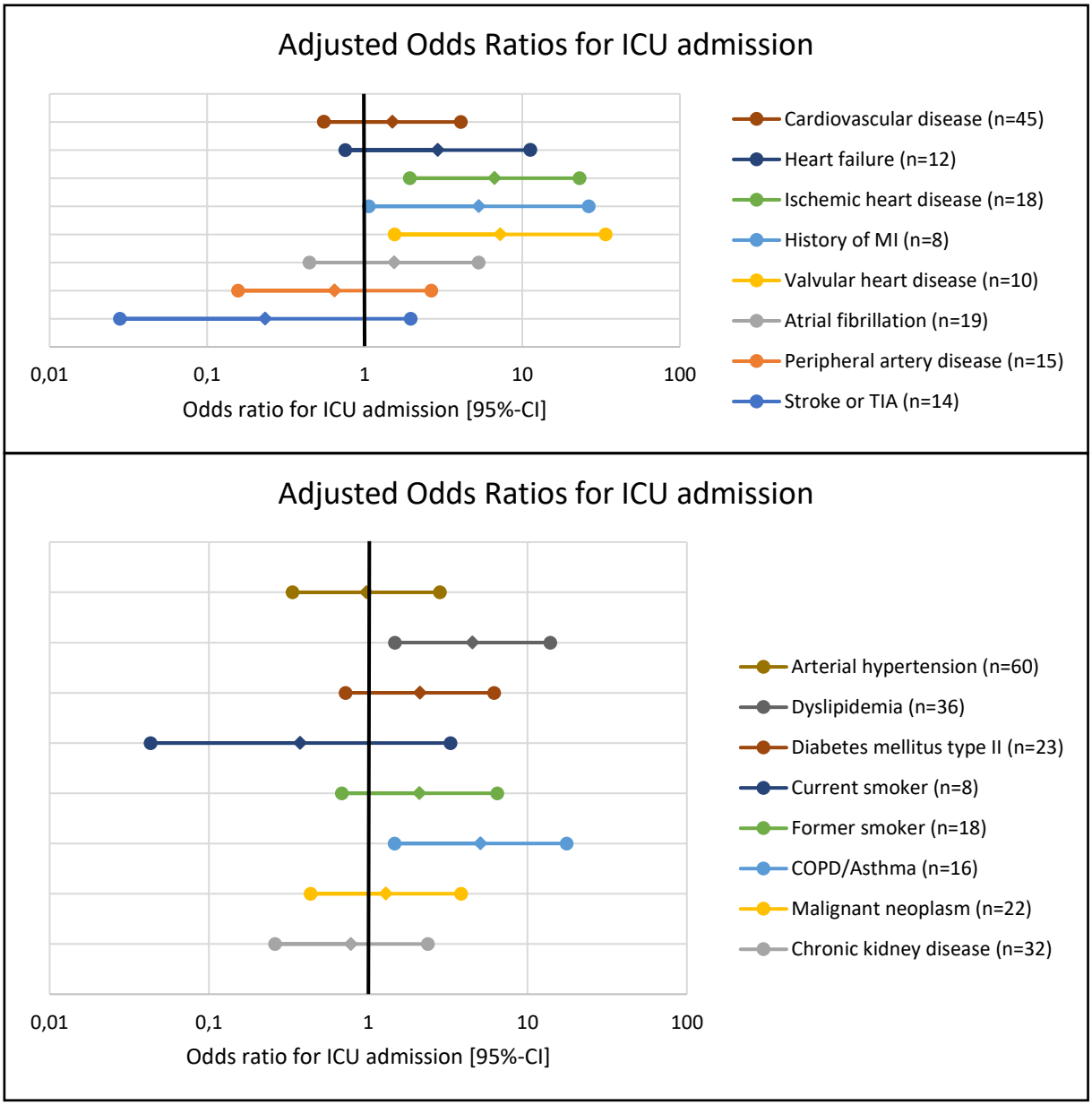

Figure 3. Odds ratios for ICU admission in several subgroups. Odds ratios were adjusted for sex, body mass index and age. 95%-CI denotes 95% confidence intervall, ICU intensive care unit.

4.5 Laboratory findings

When possible, all available laboratory parameters on admission were obtained for each patient. Subsequently, it was investigated whether elevations or depressions of laboratory parameters were associated with a worse intra-hospital outcome (e.g. death, need for intensive care).

Initially, laboratory parameters in cardiovascular and non-cardiovascular patients were compared. It was shown that blood urea nitrogen values were significantly higher in cardiovascular patients (25 mg/dL vs. 23 mg/dL; p: 0.043). All other recorded laboratory parameters including hsTnT and NT-proBNP did not differ significantly between these two groups.

Several laboratory parameters were significantly higher or lower in patients that died in comparison to patients that did not die. Parameters that were significantly higher in deceased patients are lactate (1.2 vs. 1.0 mmol/L; p: 0.044), procalcitonin (0.38 vs. 0.08 ng/mL; p: <0.001) and IL-6 (202.0 vs. 49.1 pg/mL; p: <0.001), hsTnT (80 vs. 19 pg/mL; p: 0.001), creatinine (1.3 vs. 0.9 mg/dL; p: <0.001), blood urea nitrogen (28 vs. 17 mg/dL; p: 0.001) and potassium (4.4 vs. 4.1 mmol/L; p: 0.017). Significantly lower levels were observed for arterial pH (7.43 vs. 7.46; p: 0.001), eGFR (43.0 vs. 70.5; p: 0.001) and albumin (3.6 vs. 3.9 mg/dL; p: 0.037) (**Table 6**).

A few laboratory parameters differed significantly between patients who required intensive care and patients that were not treated in an intensive care unit. Platelet count (200 vs. 235 $x10^9$/L; p: 0.024) and arterial oxygen saturation (91.3 vs. 94.5%; p: 0.003) were significantly lower and procalcitonin (0.21 vs. 0.11 ng/ml; p: 0.026) and IL-6 (115.0 vs. 50.8 pg/mL; p: 0.004) were significantly higher in patients that were treated in an intensive care unit (**Table 7**).

These findings suggest that higher concentrations of inflammatory parameters on admission (e.g. procalcitonin, IL-6) were present in patients who died or required intensive care during hospitalization with SARS-CoV-2 infection. In addition, signs of organ damage or dysfunction in laboratory tests (e.g. elevated creatinine, blood urea nitrogen, hsTnT) were more common in later deceased patients.

In order to determine whether abnormalities in certain laboratory parameters lead to a higher risk of death or need for intensive care, univariate regression analyses were performed and odds ratios for death and ICU admission were calculated. Higher levels of arterial pCO_2

(OR: 1.86; p: 0.047), lactate (OR: 2.18; p: 0.034), procalcitonin (OR: 8.21; p: 0.020), IL-6 (OR: 1.02; p: 0.003), hsTnT (OR: 1.03; p: 0.011), creatinine (OR: 1.51; p: 0.028), blood urea nitrogen (OR: 1.04; p: 0.006) and sodium (OR: 1.08; p: 0.046) were significantly associated with a higher risk of death. The same applies to lower blood levels of albumin (OR: 0.37; p: 0.043) and a lower eGFR that was estimated using the CKD-EPI equation (OR: 0.97; p: 0.003) **(Table 8)**. A significantly higher risk of needing treatment in an intensive care unit was observed in patients with decreased arterial oxygen saturation (OR: 0.89; p: 0.021) and low platelet counts (OR: 0.99; p: 0.037) (**Table 9**).

Subsequently, multivariate regression models were designed to identify laboratory parameters that may allow to estimate on admission whether poor intra-hospital outcome is likely to occur. Laboratory parameters measured in less than half of all patients (e.g. troponin) were excluded to obtain a large enough number of valid cases. In addition, to reduce the number of included variables, which was necessary due to the small study population, only one renal (eGFR) and one inflammatory parameter (procalcitonin) were considered in the following multivariate regression analysis. Consequently, the finally included parameters, besides age, sex and body mass index, were arterial pCO_2 (>6 kPa), lactate (>2.0 mmol/L), procalcitonin (>0.5 ng/mL), albumin (<3.4 mg/dL) and eGFR (<60 ml/min/1.73m²).

In this regression model higher age (p: 0.015) and procalcitonin levels over 0.5 ng/mL (p: 0.012) significantly correlated with increased mortality. Female sex was identified as a significantly protective factor (p: 0.014). These factors and serum albumin levels, although narrowly failing to reach statistical significance (p: 0.088), were used to create a score for mortality risk in hospitalized patients with a SARS-CoV-2 infection. This mortality risk score is composed as follows: one point for male sex, one point for age between 70 and 80 years, two points for age over 80 years and one point each for serum procalcitonin level over 0.5 ng/mL and serum albumin level under 3.4 mg/dL on admission (minimum value: 0; maximum value: 5). Of 61 patients, out of which 18 patients died during hospitalization, all

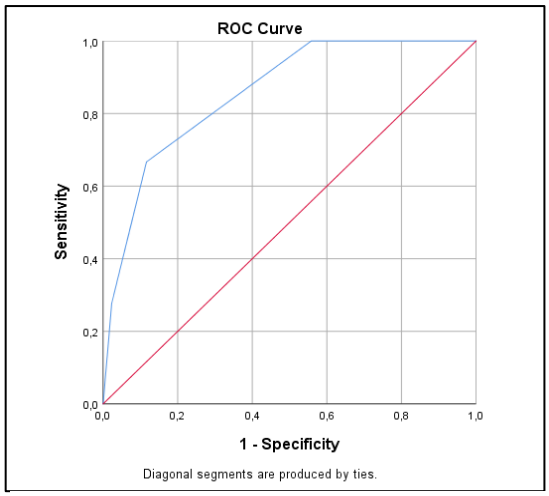

Figure 4. Receiver operating characteristic curve for a mortality risk score including age, sex, albumin and procalcitonin levels on admission. AUC (area under the curve): 0.857 (95%-CI: 0.761-0.954; p: <0.001).

necessary parameters for calculation of a risk score value were collected. In this cohort, patients with a score of 0 and 1 had an intra-hospital mortality rate of 0.0% while patients with a score of 4 had a mortality rate of 83.3%. No patient achieved a score of 5 points. Patients with a risk score value under 3 had an intra-hospital mortality rate of 13.6%, whereas patients with a score ≥3 had a mortality rate of 70.6%. The area under ROC curve for this score and intra-hospital mortality was 0.857 (95%-CI: 0.761-0.954; p: <0.001) (**Figure 4**). The strong increase of the mortality rate between a risk score value of 2 and of 3 points might be due to the great influence of advanced age and male sex on the risk of death. Only 3 out of 26 patients that died during the hospital stay were under the age of 70 and all these patients were male. This means that every deceased patient had a risk score value of at least 1 when just taking age and sex into account. However, by adding the two above mentioned laboratory parameters to the risk score the area under the curve (AUC: 0.857 vs. 0.716) and the overall quality of the risk score model (overall quality: 0.76 vs. 0.58) could be improved.

Table 6. Laboratory findings on admission. Comparisons were performed between deceased patients and patients that have not died yet using a two-tailed t-test or the Mann-Whitney-U test.

	Deaths [Median + IQR]	**Non-Deaths** [Median + IQR]	**p-values**
Arterial pH	**7.43** [7.40-7.44]	**7.46** [7.44-7.49]	**0.001**
Arterial pCO_2 [kPa]	4.63 [4.33-5.45]	4.39 [4.07-4.77]	0.104
SO_2 [%]	91.7 [89.1-95.3]	94.3 [91.7-95.7]	0.292
Lactate [mmol/L]	**1.2** [0.8-1.9]	**1.0** [0.7-1.2]	**0.044**
Inflammation			
hsCRP [mg/L]	67.6 [48.0-144.3]	46.7 [12.2-103.5]	0.099
Procalcitonin [ng/mL]	**0.38** [0.17-0.66]	**0.08** [0.03-0.15]	**<0.001**
IL-6 [pg/mL]	**202.0** [68.7-549.0]	**49.1** [26.3-91.1]	**<0.001**
Hemoglobin [g/L]	13.1 [11.1-14.8]	13.2 [11.7-14.4]	0.952
White blood cell count [$x10^9$/L]	8.0 [5.4-11.7]	7.1 [5.3-10.4]	0.289
Platelet count [$x10^9$/L]	211 [171-274]	228 [162-282]	0.878
hs-Troponin-T [pg/mL]	**80** [29-93]	**19** [8-26]	**0.001**
NT-proBNP [pg/mL]	2005 [365-3145]	689 [256-3228]	0.726
Creatine kinase [U/L]	152 [62-291]	85 [53-133]	0.144
Lactatedehydrogenase [U/L]	305 [231-406]	341 [243-481]	0.578
Creatinine [mg/dL]	**1.3** [1.0-2.5]	**0.9** [0.8-1.2]	**<0.001**
eGFR [ml/min/1.73m²]	**43.0** [24.0-60.0]	**70.5** [50.0-88.5]	**0.001**

Blood urea nitrogen [mg/dL]	**28** [20-38]	**17** [11-24]	**0.001**
Albumin [mg/dL]	**3.6** [3.1-4.0]	**3.9** [3.6-4.2]	**0.037**
D-Dimer [mg/mL]	1.57 [1.23-2.24]	1.25 [0.65-2.66]	0.407
INR	1.1 [1.0-1.1]	1.0 [0.9-1.1]	**0.037**
Prothrombin time [s]	32 [28-36]	29 [27-32]	**0.006**
Ferritin [g/L]	533 [345-1496]	413 [115-796]	0.463
Sodium [mmol/L]	139 [136-142]	139[135-141]	0.233
Potassium [mmol/L]	**4.4** [4.1-4.7]	**4.1** [3.7-4.5]	**0.017**

Table 7. Laboratory findings on admission. Comparisons were performed between patients who required intensive care and all other patients using a two-tailed t-test or the Mann-Whitney-U test.

	ICU [Median + IQR]	**Non-ICU** [Median + IQR]	**p-values**
Arterial pH	7.47 [7.40-7.49]	7.45 [7.43-7.48]	0.972
Arterial pCO_2 [kPa]	4.39 [4.04-5.52]	4.43 [4.07-4.92]	0.983
SO_2 [%]	**91.3** [84.6-93.6]	**94.5** [92.0-96.2]	**0.003**
Lactate [mmol/L]	1.1 [0.9-1.7]	1.0 [0.7-1.2]	0.094
Inflammation			
hsCRP [mg/L]	103.2 [37.5-144.3]	51.6 [12.2-92.9]	0.074
Procalcitonin [ng/mL]	**0.21** [0.10-0.73]	**0.11** [0.03-0.20]	**0.026**
IL-6 [pg/mL]	**115.0** [66.2-262.0]	**50.8** [26.3-93.2]	**0.004**
Hemoglobin [g/L]	13.9 [12.2-14.9]	13.0 [11.7-14.4]	0.283
White blood cell count [x10^9/L]	7.5 [5.2-10.7]	7.4 [5.4-10.4]	0.901
Platelet count [x10^9/L]	**200** [141-234]	**235** [176-305]	**0.024**
hs-Troponin-T [pg/mL]	23 [13-59]	23 [13-37]	0.867
NT-proBNP [pg/mL]	3116 [1683-3145]	511 [152-3228]	0.165
Creatine kinase [U/L]	115 [64-192]	84 [47-153]	0.122
Lactatedehydrogenase [U/L]	361 [269-538]	306 [231-440]	0.132
Creatinine [mg/dL]	1.0 [0.9-1.2]	1.0 [0.8-1.4]	0.758
eGFR [ml/min/1.73m²]	61.0 [43.0-81.0]	62.5 [39.0-82.0]	0.591
Blood urea nitrogen [mg/dL]	17 [13-26]	19 [14-30]	0.535
Albumin [mg/dL]	3.7 [3.3-4.2]	3.8 [3.3-4.1]	0.736
D-Dimer [mg/mL]	1.70 [1.37-2.98]	1.10 [0.58-2.24]	0.100
INR	1.0 [1.0-1.1]	1.0 [0.9-1.1]	0.878
Prothrombin time [s]	31 [28-33]	29 [27-32]	0.218
Ferritin [g/L]	345 [210-601]	559 [113-872]	0.881

Sodium [mmol/L]	136 [133-140]	139 [136-141]	0.073
Potassium [mmol/L]	4.1 [3.8-4.5]	4.2 [3.7-4.6]	0.864

Table 8. Univariate and multivariate regression analyses for laboratory findings on admission. 95%-CI denotes 95% confidence interval. Odds ratios were adjusted for sex, age and body mass index. Univariate regression analyses for sex, age and body mass index can be found in Table 4.

	Odds ratio for death [95%-CI; p-value]	**Adjusted odds ratio for death** [95%-CI; p-value]
Arterial pCO_2 [kPa]	**1.86** (1.01-3.44; **0.047**)	**2.73** (1.18-6.34; **0.019**)
SO_2 [%]	0.98 (0.90-1.07; 0.649)	0.93 (0.82-1.05; 0.220)
Lactate [mmol/L]	**2.18** (1.06-4.46; **0.034**)	**3.23** (1.19-8.76; **0.022**)
Inflammation		
hsCRP [mg/L]	1.00 (1.00-1.01; 0.119)	1.01 (1.00-1.01; 0.104)
Procalcitonin [ng/mL]	**8.21** (1.40-48.17; **0.020**)	**43.89** (3.57-540.11; **0.003**)
IL-6 [ng/pL]	**1.02** (1.01-1.03; **0.003**)	**1.02** (1.01-1.04; **0.009**)
Hemoglobin [g/L]	1.00 (0.81-1.22; 0.966)	0.96 (0.76-1.19; 0.685)
White blood cell count [x10^9/L]	1.09 (0.98-1.21; 0.110)	1.09 (0.97-1.22; 0.140)
Platelet count [x10^9/L]	1.00 (0.99-1.00; 0.607)	1.00 (0.98-1.00; 0.441)
hs-Troponin-T [pg/mL]	**1.03** (1.01-1.06; **0.011**)	**1.03** (1.00-1.06; **0.030**)
NT-proBNP [pg/mL]	1.00 (1.00-1.00; 0.854)	1.00 (1.00-1.00; 0.688)
Creatine kinase [U/L]	1.00 (1.00-1.00; 0.225)	1.00 (1.00-1.00; 0.070)
Lactatedehydrogenase [U/L]	1.00 (1.00-1.00; 0.305)	1.00 (1.00-1.00; 0.455)
Creatinine [mg/dL]	**1.51** (1.05-2.19; **0.028**)	**1.53** (1.03-2.28; **0.034**)
eGFR [ml/min/1.73m²]	**0.97** (0.96-0.99; **0.003**)	0.98 (0.96-1.00; 0.066)
Blood urea nitrogen [mg/dL]	**1.04** (1.01-1.07; **0.006**)	**1.03** (1.00-1.06; **0.049**)
Albumin [mg/dL]	**0.37**	**0.32**

	(0.14-0.97; **0.043**)	(0.10-0.99; **0.048**)
D-Dimer [mg/mL]	0.90 (0.61-1.33; 0.594)	0.94 (0.63-1.39; 0.740)
INR	0.99 (0.48-2.04; 0.971)	0.97 (0.44-2.12; 0.939)
Prothrombin time [s]	1.03 (0.97-1.08; 0.326)	1.02 (0.97-1.08; 0.491)
Ferritin [g/L]	1.00 (1.00-1.00; 0.781)	1.00 (1.00-1.00; 0.351)
Sodium [mmol/L]	**1.08** (1.00-1.17; **0.046**)	1.05 (0.97-1.14; 0.255)
Potassium [mmol/L]	2.14 (0.99-4.62; 0.053)	2.22 (0.91-5.41; 0.078)

Table 9. Univariate and multivariate regression analyses for laboratory findings on admission. 95%-CI denotes 95% confidence interval. Odds ratios were adjusted for sex, age and body mass index. Univariate regression analyses for sex, age and body mass index can be found in Table 5.

	Odds ratio for ICU admission [95%-CI; p-value]	**Adjusted odds ratio for ICU admission** [95%-CI; p-value]
Arterial pCO_2 [kPa]	1.24 (0.74-2.06; 0.416)	1.32 (0.77-2.26; 0.319)
SO_2 [%]	**0.89** (0.81-0.98; **0.021**)	**0.87** (0.77-0.98; **0.018**)
Lactate [mmol/L]	1.65 (0.86-3.17; 0.132)	1.66 (0.86-3.22; 0.130)
Inflammation		
hsCRP [mg/L]	1.00 (1.00-1.01; 0.122)	1.00 (1.00-1.01; 0.166)
Procalcitonin [ng/mL]	1.05 (0.60-1.86; 0.857)	1.25 (0.66-2.37; 0.503)
IL-6 [ng/pL]	1.00 (1.00-1.00; 0.308)	1.00 (1.00-1.00; 0.179)
Hemoglobin [g/L]	1.05 (0.85-1.30; 0.638)	1.02 (0.82-1.25; 0.888)
White blood cell count [$x10^9$/L]	1.01 (0.91-1.13; 0.809)	1.03 (0.92-1.14; 0.633)
Platelet count [$x10^9$/L]	**0.99** (0.99-1.00; **0.037**)	1.00 (0.99-1.00; 0.119)
hs-Troponin-T [pg/mL]	1.00 (0.99-1.02; 0.689)	1.01 (0.99-1.03; 0.294)

NT-proBNP [pg/mL]	1.00 (1.00-1.00; 0.746)	1.00 (1.00-1.00; 0.648)
Creatine kinase [U/L]	1.00 (1.00-1.00; 0.255)	1.00 (1.00-1.00; 0.427)
Lactatedehydrogenase [U/L]	1.00 (1.00-1.00; 0.460)	1.00 (1.00-1.00; 0.460)
Creatinine [mg/dL]	0.89 (0.59-1.34; 0.573)	0.88 (0.57-1.35; 0.554)
eGFR [ml/min/1.73m²]	1.00 (0.99-1.02; 0.587)	1.00 (0.98-1.02; 0.997)
Blood urea nitrogen [mg/dL]	0.99 (0.96-1.02; 0.484)	0.99 (0.96-1.03; 0.720)
Albumin [mg/dL]	0.89 (0.342-2.296; 0.804)	0.72 (0.233-2.219; 0.567)
D-Dimer [mg/mL]	0.99 (0.80-1.23; 0.912)	1.02 (0.82-1.29; 0.817)
INR	0.51 (0.09-2.91; 0.451)	0.63 (0.18-2.29; 0.486)
Prothrombin time [s]	1.00 (0.95-1.06; 0.941)	0.99 (0.93-1.05; 0.991)
Ferritin [g/L]	1.00 (1.00-1.00; 0.459)	1.00 (1.00-1.00; 0.559)
Sodium [mmol/L]	0.92 (0.84-1.01; 0.075)	0.92 (0.84-1.02; 0.106)
Potassium [mmol/L]	0.83 (0.38-1.81; 0.636)	1.04 (0.46-2.37; 0.922)

4.6 Follow-up

About six months after hospitalization with a SARS-CoV-2 infection a follow up of all available patients was performed by reviewing patient charts and contacting patients or authorized contact persons by phone. 70 patients with an average age of 70.1 years were still alive after the initial hospitalization and were thus available for the follow-up. The majority of available patients was female (58.6%) and the average BMI was 27.4 kg/m². 18 patients (25.7%) were non-cardiovascular patients and 52 patients (74.3%) had at least one pre-existing cardiovascular disease or risk factor. 18 patients (25.7%) were at least once re-hospitalized during the follow-up period for any reason and two of these patients were treated due to an urgent cardiovascular cause. Seven patients (10.0%) died during the follow-up, the mean age at death being 78.6 years (**Table 10**).

Persisting symptoms

56 of the 63 patients who were still alive at the time of the phone interview could be included in the follow-up by interviewing either the patients themselves or authorized contact persons. The most common symptoms that persisted longer than three months after discharge from hospital were dyspnoea (11 patients – 19.6%), weakness (7 patients – 12.5%), decreased physical ability (7 patients – 12.5%), loss of memory (5 patients – 8.9%) and vertigo (5 patients – 8.9%). In the first three months, 16 patients (28.6%) reported suffering from persisting dyspnea. Dyspnea that persisted longer than three months occurred significantly more often in cardiovascular patients than in non-cardiovascular patients (28.2% vs 0.0%; p: 0.015) (**Table 11**).

Table 10. Characteristics of patients available for follow-up. Comparisons were made between cardiovascular and non-cardiovascular patients by using the chi-square test or Fisher's exact test in categories with binary variables and by using a two-tailed t-test or the Mann-Whitney-U test in categories with continuous variables. Continuous variables are given as median plus interquartile range.

	Cardiovascular patients	Non-cardiovascular patients	p-values
Number	52 (74.3%)	18 (25.7%)	
Sex distribution			**0.04**
Male	18 (34.6%)	11 (61.1%)	
Female	34 (65.4%)	7 (38.9%)	
Age	74.0 years (IQR: 60.5-81.0)	64.0 years (IQR: 49.0-78.0)	**0.039**
BMI [kg/m²]	26.6 (IQR: 23.8-31.3)	24.6 (IQR: 22.0-27.0)	**0.033**
Hospitalization			
at least once during Follow-Up	16 (30.8%)	2 (11.1%)	0.126
at least one urgent cardiovascular hospitalization	2 (3.8%)	0 (0.0%)	1.000
Death during Follow-Up	7 (13.5%)	0 (0.0%)	0.178
Age at death	73.0 years (IQR: 68.0-72.0)	-	

Table 11. Persisting symptoms during follow-up period. Comparisons were made between cardiovascular and non-cardiovascular patients by using the Fisher's exact test.

	Total (n=56)	Cardiovascular patients (n=39)	Non-cardiovascular patients (n=17)	p-value
Dyspnea (0-3 months)	16 (28.6%)	14 (35.9%)	2 (11.8%)	0.107
Dyspnea (3-6 months)	11 (19.6%)	11 (28.2%)	0	**0.024**
Weakness	7 (12.5%)	6 (15.4%)	1 (5.9%)	0.421
Decreased physical ability	7 (12.5%)	4 (10.3%)	3 (17.6%)	0.662
Loss of memory	5 (8.9%)	4 (10.3%)	1 (5.9%)	1.000
Vertigo	5 (8.9%)	3 (7.7%)	2 (11.8%)	0.634

Comparison of non-cardiovascular and cardiovascular patients

In the group of cardiovascular patients, 65.4% were female, whereas most non-cardiovascular patients (61.1%) were male. The median age of cardiovascular patients was 74.0 years, which is 10.0 years higher than in non-cardiovascular patients (p: 0.039). In addition, the body mass index was significantly higher in cardiovascular patients than in non-cardiovascular patients (26.6 kg/m² vs. 24.6 kg/m²; p: 0.033). The rate of patients that were at least once re-hospitalized during the follow-up period was nearly three times higher in cardiovascular patients (30.8%). However, this difference did not reach statistical significance (p: 0.126). All seven deaths during the follow-up occurred in the group of cardiovascular patients thus leading to a mortality rate of 13.5% for these patients (p: 0.178). The median age at death was 73.0 years (**Table 10**).

In order to identify predictors of re-hospitalization or death during the follow-up period regression analyses for a composite endpoint were performed. Cardiovascular patients (OR: 6.3; 95%-CI: 1.3-30.5; p: 0.021) and patients with atrial fibrillation (OR: 3.8; 95%-CI: 1.1-13.2; p: 0.038) or hypertension (OR: 3.5; 95%-CI: 1.1-11.0; p: 0.031) were identified to be at significantly increased risk of re-hospitalization or death (**Table 12**).

Table 12. Odds ratios for re-hospitalization and death during follow-up period in patients with cardiovascular disease, risk factors or chronic disease. Binary logistic regression analyses were performed and odds ratios for death during follow-up, re-hospitalization and for a combined endpoint (death and/or re-hospitalization) were calculated. In categories with empty fields no reasonable values for odds ratios and confidence intervals could be determined. Cardiovascular patients were defined as patients with at least one pre-existing cardiovascular disease and/or risk factor.

	Odds Ratios for re-hospitalization [95%-CI; p-value]	**Odds Ratios for death during follow-Up** [95%-CI; p-value]	**Odds Ratios for death and/or re-hospitalization** [95%-CI; p-value]
Cardiovascular patients (n=52)	3.56 (0.73-17.32; 0.116)		**6.35** (1.32-30.45; **0.021**)
Cardiovascular disease (n=29)	2.17 (0.73-6.44; 0.162)	2.03 (0.42-9.84; 0.381)	2.55 (0.93-6.95; 0.068)
Ischemic heart disease (n=7)	1.18 (0.21-6.66; 0.855)	1.58 (0.16-15.45; 0.693)	1.40 (0.29-6.81; 0.679)
Valvular heart disease (n=6)	1.50 (0.25-8.98; 0.657)	5.90 (0.86-40.54; 0.071)	4.10 (0.69-24.18; 0.120)
Atrial fibrillation (n=13)	**3.21** (0.91-11.36; **0.070**)	1.89 (0.32-11.04; 0.479)	**3.77** (1.08-13.18; **0.038**)
Peripheral artery disease (n=9)	0.80 (0.15-4.28; 0.798)	1.15 (0.12-10.80; 0.905)	0.89 (0.20-3.90; 0.873)
Stroke or TIA (n=10)	1.29 (0.30-5.61; 0.738)	2.75 (0.46-16.63; 0.271)	2.00 (0.52-7.72; 0.315)
Cardiovascular risk factors			
Arterial hypertension (n=44)	2.57 (0.74-8.87; 0.136)	3.95 (0.45-34.79; 0.216)	**3.50** (1.12-10.96; **0.031**)
Dyslipidemia (n=26)	1.11 (0.37-3.33; 0.86)	1.30 (0.27-6.35; 0.742)	1.21 (0.44-3.31; 0.712)
Diabetes mellitus type II (n=9)	0.80 (0.15-4.28; 0.798)	3.20 (0.52-19.72; 0.210)	1.52 (0.37-6.29; 0.560)
Current smoker (n=6)	0.55 (0.06-5.08; 0.600)		0.33 (0.04-3.03; 0.329)
Former smoker (n=16)	0.95 (0.26-3.44; 0.941)	1.40 (0.25-8.01; 0.705)	1.11 (0.35-3.51; 0.865)
Chronic disease			
COPD/Asthma (n=9)	0.80 (0.15-4.28; 0.798)	3.20 (0.52-19.72; 0.210)	1.52 (0.37-6.29; 0.560)
Malignant neoplasm (n=14)	1.20 (0.32-4.44; 0.785)	1.70 (0.29-9.84; 0.554)	1.46 (0.44-4.82; 0.534)
Chronic kidney disease/Dialysis (n=19)	1.04 (0.32-3.47; 0.944)	1.08 (0.19-6.12; 0.929)	1.07 (0.36-3.20; 0.904)

4.7 Survival analysis

As previously reported, 26 patients died during the initial hospitalization with SARS-CoV-2 infection and seven additional patients died during the follow-up period. Of these 33 patients 29 patients (87.9%) had at least one pre-existing cardiovascular disease or risk factor and only four deceased patients (12.1%) belonged to the group of non-cardiovascular patients. To determine whether this difference in survival was significant, a survival time analysis using the Kaplan-Meier method and log-rank test were performed. For this purpose, the period between the patients' hospital admission and end of the follow-up was considered. Although the proportion of patients who survived was lower in the cardiovascular group at all time points, this difference was not statistically significant (p: 0.097) (**Figure 5**).

In addition, survival was compared between patients with and without manifest pre-existing cardiovascular disease. The cumulative survival in patients with pre-existing cardiovascular disease was lower at each timepoint showing a statistically significant difference (p: 0.032). Taken together, over 44% of all patients with manifest cardiovascular disease (20 out of 45 patients) died either during initial hospitalization or during the follow-up period. In contrast, this rate was only about 25% in patients without pre-existing cardiovascular disease (13 out of 51 patients) (**Figure 6**).

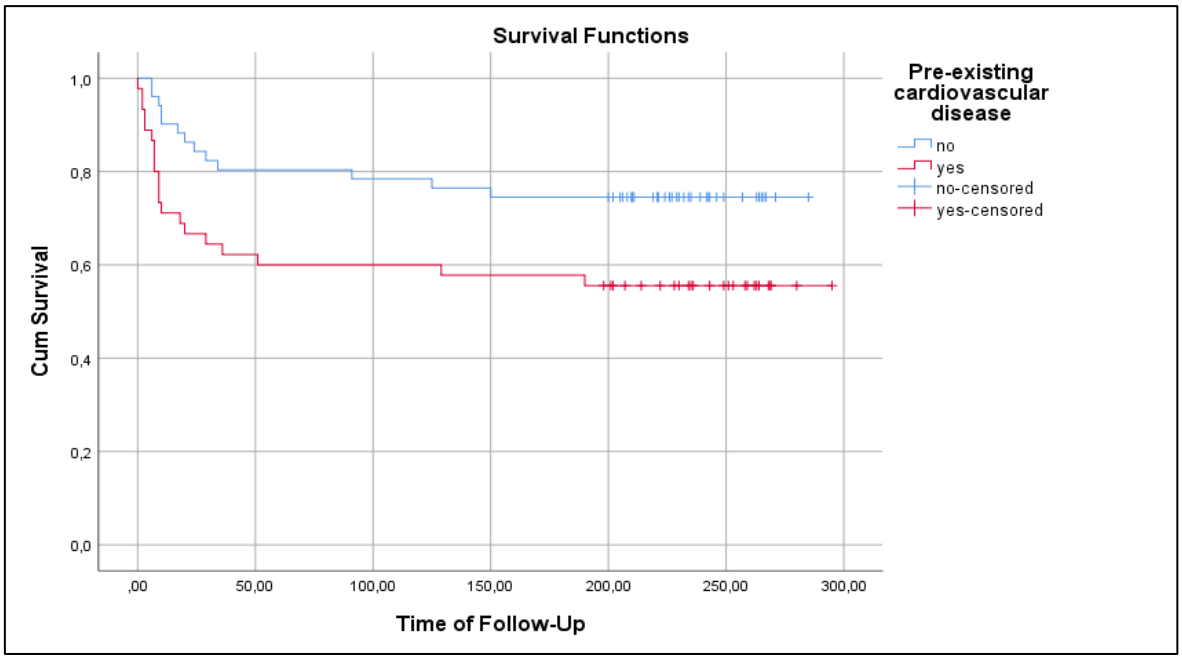

Figure 5. Survival analysis of hospitalization and follow-up period with Kaplan-Meier method in patients with and without pre-existing cardiovascular disease. Log-rank test showed a statistically significant difference between patients with and without pre-existing cardiovascular disease (p: 0.032).

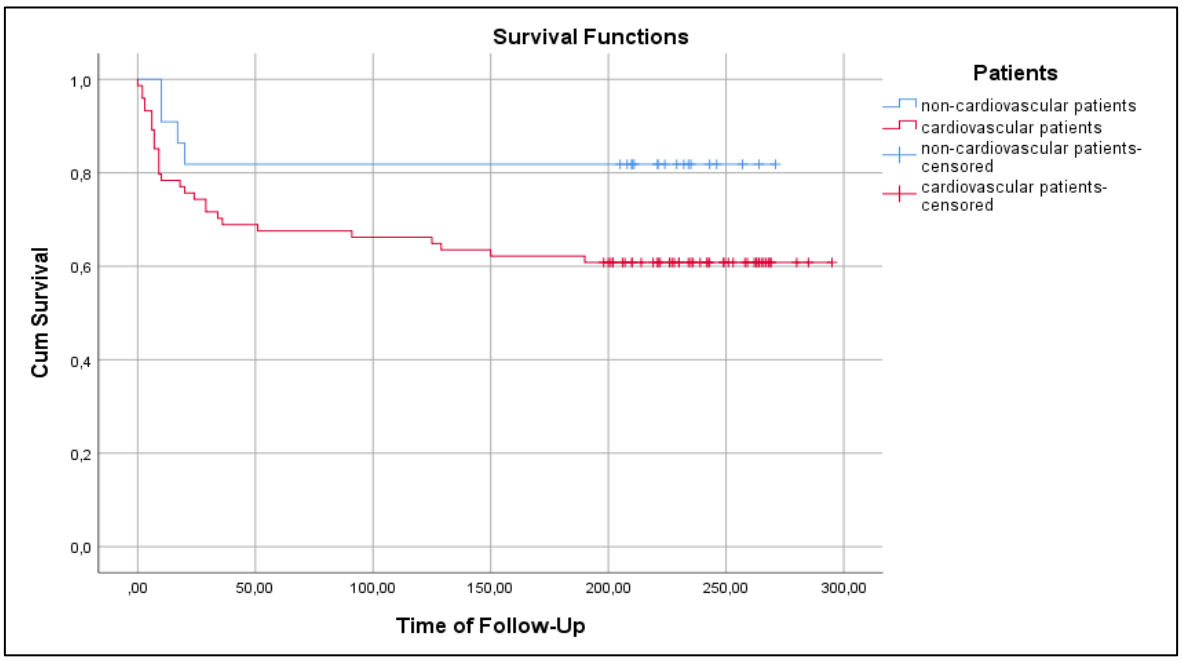

Figure 6. Survival analysis of hospitalization and follow-up period with Kaplan-Meier method in cardiovascular patients compared to patients who had neither cardiovascular risk factors nor pre-existing cardiovascular diseases. Log-rank test showed no significant difference between cardiovascular and non-cardiovascular patients (p: 0.078).

5. Discussion

Prevalence of cardiovascular diseases and risk factors

This retrospective analysis showed that the prevalence of pre-existing cardiovascular disease and risk factors was high among hospitalized patients with SARS-CoV-2 infection. Over three quarters of all included patients had at least one pre-existing cardiovascular disease (47% of all patients) and/or risk factor (70% of all patients). The most prevalent diseases and risk factors were arterial hypertension, diabetes, dyslipidemia, atrial fibrillation, ischemic heart disease, peripheral artery disease and heart failure. These observations are consistent with the results of other studies, some of which were performed with substantially larger study populations. In an American study that included over 900.000 hospitalized COVID-19 patients similar prevalence of diabetes (34.7%), hypertension (62.0%) and heart failure (12.8%) was observed (35). Another study in which 5.279 COVID-19 patients in New York City were included also showed high prevalence of hypertension (62.0%), diabetes (34.7%), hyperlipidemia (42.4%), heart failure (12.8%) and coronary artery disease (22.0%). 70.6% of all included patients had some kind of pre-existing cardiovascular condition and 52.1% suffered from at least one pre-existing cardiovascular disease (36). In a German study including 2.343 COVID-19 inpatients the most frequently observed pre-existing cardiovascular conditions were hypertension (57.0%), diabetes (24.0%) and heart failure (19%). Other chronic diseases that were observed in this study were chronic kidney disease (19%), chronic obstructive pulmonary disease (12%) and asthma (12%) (37).

Factors associated with intra-hospital mortality and need for intensive care

There is evidence that the presence of manifest cardiovascular disease and cardiovascular risk factors is associated with the disease severity and intra-hospital outcome in first-wave inpatients with SARS-CoV-2 infection who were treated at the University Hospital of Graz. After adjusting for age, sex and body mass index several cardiovascular diseases and risk factors were identified as predictors of intra-hospital death and need for intensive care. Especially the presence of ischemic heart disease, heart failure and diabetes led to a significantly increased risk of death. Chronic obstructive pulmonary disease or asthma, dyslipidemia, ischemic heart disease and valvular heart disease had a significant influence on the risk of being treated in an intensive care unit. Due to the rather small study population of 96 hospitalized patients multivariable regression analyses could be reasonably performed with a maximum of six to seven variables. Therefore, in addition to age, sex and body mass

index only those factors were included that were associated with a significantly increased risk of death or need for intensive care in univariate analyses.

Several studies suggest that diabetes is associated with poor outcome and higher risk of death in patients with COVID-19. A meta-analysis including a total of 6.452 COVID-19 patients showed a significant association between the presence of diabetes and mortality (RR: 2.12; 95%-CI: 1.44-3.11; p: <0.001), severe disease course (RR: 2.45; 95%-CI: 1.79,-3.35; p: <0.001) and disease progression (RR: 3.31; 95%-CI: 1.08-10.14; p: 0.04) (38). However, diabetes was not significantly associated with increased need for intensive care (RR: 1.47; 95%-CI: 0.38-5.67; p: 0.57) (38). In another systematic review of 33 studies with a total of 16.003 patients with COVID-19 diabetes was also significantly associated with increased mortality (OR: 1.90; 95%-CI: 1.37-2.64; p: <0.01) and severity (OR: 2.16; 95%-CI: 1.74-2.68; p: <0.01) (39). Other risk factors mentioned above are also frequently referred to as predictors of death and disease severity. Hypertension (OR: 2.5; 95%-CI: 2.1-3.1; p: <0.001), diabetes (OR: 2.0; 95%-CI: 1.7-2.3; p: <0.001) and coronary heart disease (OR: 3.8; 95%-CI: 2.1-6.9; p: <0.001) were shown to be associated with an increased risk of death in a systematic review of 4.659 patients with COVID-19 (40). In an American study including 2.741 hospitalized COVID-19 patients the presence of heart failure was associated with a higher risk of critical illness (OR: 1.93; 95%-CI: 1.4-2.6; p: <0.001) and death (HR: 1.54; 95%-CI: 1.2-1.9; p: <0.001). For other cardiovascular diseases and risk factors like diabetes, hypertension and chronic artery disease a statistically significant influence on mortality and severity could not be shown (36). A study of 3.080 Spanish patients including 152 patients with pre-existing congestive heart failure revealed that the proportion of deceased patients was significantly higher in patients with pre-existing chronic heart failure (48.7% vs. 19.0%; p: <0.001). However, the proportion of patients who required mechanical ventilation (1.4% vs. 6.1%; p: 0.017) or intensive care (1.4% vs. 6.4%; p: 0.013) was significantly lower in patients with chronic heart failure (41). In a meta-analysis including nearly 50.000 COVID-19 patients, hypertension (OR: 2.5; 95%-CI: 2.1-2.9), diabetes (OR: 2.3; 95%-CI: 1.9-2.7) and pre-existing cardiovascular disease (OR: 3.1; 95%-CI: 2.6-3.8) were also found to be associated with a significantly increased risk of severe illness or death (42). An Italian cohort study including 3.988 critically ill patients showed significantly higher mortality in patients with a history of chronic pulmonary obstructive disease, type 2 diabetes and hypercholesterolemia. In contrast to several other studies and systematic reviews, the presence of hypertension was not identified as an independent risk factor for

death in these Italian patients (43). Analyses of the data of the multicenter and multinational PCHF-COVICAV registry, which also includes the data of our patients from Graz, showed that hospitalized COVID-19 patients with a history of heart failure were at significantly increased risk of in-hospital death (OR: 1.93; 95%-CI: 1.44-2.59; p: <0.001). Interestingly, a considerable proportion of patients in this registry suffered an acute heart failure event during their hospital stay (186 out of 1.282 patients; 15%), which was also shown to be associated with increased in-hospital mortality (OR: 3.10; 95%-CI: 2.24-4.29; p: <0.001) (60). An umbrella review including a total of 84 systematic reviews and meta-analyses (total number of patients not given) found that diabetes (OR: 2.09; 95%-CI: 1.80-2.42), renal disease (OR: 3.07; 95%-CI: 2.43-3.88), hypertension (OR: 2.50; 95%-CI: 2.02-3.11), liver disease (OR: 2.81; 95%-CI: 1.31-6.01), obesity (OR: 2.18; 95%-CI: 1.10-4.34), cardiovascular disease (OR: 2.65; 95%-CI: 1.86-3.78) and cerebrovascular disease (RR: 2.75; 95%-CI: 1.54-4.89) are associated with higher mortality in hospitalized COVID-19 patients (65).

The identified risk factors for intra-hospital death in SARS-CoV-2 positive patients that were treated at the University Hospital of Graz are largely consistent with findings of large-scale comparative studies. Diabetes and pre-existing heart failure were commonly found to be risk factors for death and severe illness. Compared with other studies, the presence of cardiovascular disease could not be shown to be significantly associated with an increased mortality rate, although the risk of death also tended to be higher in patients with pre-existing cardiovascular disease from Graz. This could probably be explained by the relatively small number of patients that were included into the study. However, a significant effect could be demonstrated for several subgroups of cardiovascular disease like heart failure and ischemic heart disease, which were also identified as risk factors for death in several other studies.

For some diseases and risk factors that might reasonably be expected to be associated with increased mortality and risk for treatment in ICU either no significant association or no association at all could be demonstrated in this study. For example chronic kidney disease, history of stroke or transient ischemic attack, peripheral artery disease and current smoking tended to be unexpectedly associated with decreased risk of needing intensive care, which might be due to the low numbers of patients in several subgroups of cardiovascular disease, risk factors or chronic disease. Hypertension, which was the most observed cardiovascular risk factor, was not identified as a significant predictor of death in this study. Comparative studies also have not reached consensus on whether hypertension significantly increases the

risk of death in COVID-19 patients. While some studies and systematic reviews have shown a significant association between the presence of hypertension and the risk of death (40,42), other studies suggest that hypertension does not affect mortality (36,43). These inconsistent results could be caused by differences in the geographical and ethnical composition of patients in different studies. Studies in which no statistically significant association between hypertension and mortality could be shown mainly included patients from Europe and Northern America (36,43). In contrast, in systematic reviews and meta-analyses in which hypertension was identified as an independent risk factor for death the majority of included studies was conducted in China (40,42).

Patients from Graz with chronic obstructive pulmonary disease or asthma, dyslipidemia, ischemic heart disease or valvular heart disease were at greater risk of being admitted to an intensive care unit. Other studies also suggest that the presence of chronic obstructive pulmonary disease is associated with a higher risk of need for intensive care. In a meta-analysis including seven Chinese studies with a total of 1.813 patients chronic obstructive pulmonary disease (OR: 17.8; 95%-CI: 6.6-48.2), hypertension (OR: 4.4; 95%-CI: 2.6-7.5) and cardiovascular disease (OR: 3.7; 95%-CI: 2.2-6.0) were significantly associated with ICU admission. Diabetes (OR: 2.7; 95%-CI: 0.7-10.6) was not found to be a significant risk factor for admission to an intensive care unit (44). Another systematic review that included 61 trials with a total of more than 10.000 COVID-19 patients identified chronic obstructive pulmonary disease as the strongest risk factor for ICU admission (RR: 5.6, 95%-CI: 2.7-11.8; p: <0.001) and need for invasive ventilation (RR: 6.53, 95% CI: 2.70-15.84, p: <0.001) (45). In a Swedish case control study including 1.981 COVID-19 patients and 7.924 healthy controls, hypertension (OR: 1.3; 95%-CI: 1.2-1.5; p: <0.001), type II diabetes (OR: 2.4; 95%-CI: 2.1-2.8; p: <0.001), asthma (OR: 3.6; 95%-CI: 2.8-4.7; p: <0.001), obesity (OR: 2.3; 95%-CI: 1.8-3.1; p: <0.001) and chronic renal failure (OR: 2.3; 95%-CI: 1.6-3.2; p: <0.001) were found to be independent risk factors for admission to an intensive care unit. In contrast to several other studies, chronic obstructive pulmonary disease was not associated with an significantly increased risk of ICU admission (OR: 1.3; 95%-CI: 1.0-1.8; p: 0.09) (46).

In contrast to risk factors for mortality, for which the results of most studies are largely concordant, consensus has not yet been reached on independent risk factors for admission to an intensive care unit. For patients from Graz as well as for patients in several other studies chronic respiratory diseases like asthma and chronic obstructive pulmonary disease, turned

out to be independent risk factors for ICU admission. Moreover, a significant association for cardiovascular risk factors (e.g. hypertension, diabetes) and cardiovascular disease could be found in some studies. In the 96 patients included in this study hypertension, diabetes and cardiovascular disease were not significantly associated with a higher risk for ICU admission. This could be due to the rather small number of patients included and the resulting small subgroup sizes. Indeed, the risk of being treated in an intensive care unit tended to be higher in patients with diabetes or cardiovascular disease. This difference might have reached statistical significance in a larger study population. Some specific cardiovascular diseases such as ischemic heart disease and valvular heart disease could be identified as significant risk factors for ICU admission. Due to the fact that in most studies patients with cardiovascular disease were not further subdivided it is difficult to compare these results with other studies.

Dyslipidemia, which was significantly associated with ICU admission in this study, has hardly been identified as a risk factor in comparable studies. In a meta-analysis including seven studies with a total of 6.922 patients dyslipidemia was shown to be significantly associated with severe COVID-19 infections (RR: 1.39; 95%-CI: 1.0-1.9). However, no other potential influencing factors or confounders such as age and nutritional status were considered in this study (47). In an American study including 689 COVID-19 patients alongside diabetes (OR: 3.31, 95% CI: 1.84-5.96), asthma (OR: 4.33, 95%-CI: 2.18-8.58), chronic obstructive pulmonary disease (OR: 4.26, 95%-CI: 1.87-9.77) and cardiovascular disease (OR: 5.59, 95%-CI: 2.57-12.14) pure hypercholesterolemia (OR: 3.77, 95%-CI: 1.25-11.36) was found to be associated with a higher risk for admission to an intensive care unit. However, this study is currently only available as a pre-print and has not been peer-reviewed yet (48).

Laboratory parameters

In addition to the influence of risk factors and pre-existing diseases it was also investigated whether abnormalities in laboratory parameters were associated with an increased risk of death or ICU admission. In univariate analyses it could be shown that mean values for arterial pH, lactate, procalcitonin, interleukin-6, hsTnT, creatinine, blood urea nitrogen, albumin and potassium differed significantly between deceased patients and survivors on admission. Patients that were treated in an intensive care unit had significantly higher levels of inflammatory parameters (IL-6, procalcitonin) and lower oxygen saturations and platelet counts. Some of these findings are consistent with the results of other studies with larger

numbers of included patients. A previously mentioned New York cohort study including 5.279 patients showed that hypoxia (for oxygen saturation <88%: HR: 2.0; 95%-CI: 1.6-2.5) and elevated levels of C-reactive protein (HR: for all abnormal levels >3.5), d-dimer (>2500 ng/ml: HR: 2.2; 95%-CI: 1.6-3.0) and troponin (>1 ng/ml: HR: 2.1; 95%-CI: 1.4-3.2) at presentation were risk factors for death in COVID-19 patients. The same abnormalities in laboratory parameters were also found to be associated with an increased risk of critical illness (36). Another American cohort study including a total of 446 patients, that mainly focused on five laboratory parameters in COVID-19 patients, found that elevations in these parameters (troponin I ≥0.34 ng/mL; BNP ≥300 pg/mL; CRP ≥84 mg/dL; d-dimer ≥6106 ng/mL, ferritin ≥2000 ng/mL) correlated with significantly higher proportions of deceased patients (except for CRP) and patients that were admitted to an ICU. In a multivariable regression model only elevated troponin (OR: 4.4; 95%-CI: 2.3-8.3; p: <0.001), age (>75 y: OR: 15.6; 95%-CI: 6.2-39.2; p: <0.001) and hypoxia on presentation (OR: 3.2; 95%-CI: 1.5-7.0; p: 0.003) were identified as independent predictors of 30-day mortality. Therefore, these factors were used to develop a 30-day mortality risk score (49). However, these findings are not directly comparable to the study results from Graz, because the laboratory findings were obtained at different times. In fact, in this American study the highest measured values for each parameter and not the values at presentation were analyzed. In a retrospective multi-center study including 364 COVID-19 patients, laboratory values on admission were compared between deceased patients and survivors. Significant differences could be shown for white blood cell count (p: <0.001), urea (p: <0.001), creatinine (p: 0.030), bicarbonate (p: 0.001), C-reactive protein (p: <0.001), lactate dehydrogenase (p: 0.013) and d-dimer (p: <0.001). However, some parameters like procalcitonin and IL-6 were not considered in this study. For some parameters (e.g. troponin I) that were found to be risk factors for poor outcome in other studies no significant association with severity or death could be shown (50). A meta-analysis including 52 mainly Chinese studies with a total of 6.320 COVID-19 patients also showed that abnormalities in several laboratory parameters were associated with ICU admission and mortality. Increased odds for ICU admission were found in patients with elevated levels of white blood cell count (OR: 5.2, 95%-CI: 3.0-9.1; p: <0.001), neutrophils (OR: 6.3, 95%-CI: 2.1-19.0; p: 0.001), d-dimer (OR: 4.2, 95%-CI: 1.9-9.4; p: <0.001) and prolonged prothrombin time (OR: 2.2, 95%-CI: 1.2-4.0; p: 0.012). Furthermore, odds for elevation of white blood cell count (OR: 5.2, 95%-CI: 3.0-9.1; p: <0.001), neutrophils (OR: 6.3, 95%-CI: 2.1-19.0; p: 0.001), ferritin (OR: 5.5, 95%-CI: 1.6-18.8; p: 0.006), d-dimer (OR: 6.4, 95%-CI: 4.7-8.6; p: <0.001), ESR (OR: 1.8, 95%-CI: 1.2-2.9; p:

0.008), procalcitonin (OR: 5.7, 95%-CI: 2.2-14.9; p: <0.001), C-reactive protein (OR: 7.1, 95%-CI: 3.2-15.5; p: <0.001), IL-6 (OR: 13.9, 95%-CI: 7.6-25.4, p: <0.001) and prolongation of prothrombin time (OR: 3.2, 95%-CI: 1.6-6.5; p: 0.001) were significantly higher in deceased patients. In this systematic review, however, no clear details were given at which point of time the laboratory testing was performed (51). An American cohort study that included 2736 patients in which troponin-I was measured within 24 hours after admission showed that after adjusting for disease severity and relevant clinical factors even slightly elevated levels of troponin-I (0.03-0.09 ng/mL) were associated with significantly elevated mortality (HR: 1.8, 95%-CI: 1.4-2.2; p: <0.001). In addition, higher troponin-I concentrations were found to be significantly associated with a higher risk of death (OR: 3.0, 95%-CI: 2.4-3.8; p: <0.001) (52).

As suggested by the above-mentioned studies, it has not yet been conclusively clarified which laboratory parameters are associated with ICU admission or death and could thus be predictors of intra-hospital outcome. Elevated inflammatory parameters (e.g. C-reactive protein, procalcitonin, IL-6) and elevated troponin levels were found to be risk factors for death in several studies including this one. Elevated concentrations of d-Dimer and ferritin, which were associated with worse outcome and mortality in some studies, were not elevated in deceased patients and patients that were admitted to ICU in Graz. In fact, d-Dimer and ferritin concentrations tended to be unexpectedly low in these patients, which may be due to the rather small number of patients with whom d-dimer (27 patients – 28.1%) or ferritin (23 patients – 24.0%) levels were measured on admission. In addition, some of the studies cited above used the maximally measured laboratory values during hospitalization rather than the values on admission to hospital, which could also partly explain deviating results.

Although some of the results of this study are consistent with several other studies in terms of laboratory parameters, they are of limited value mainly because of the rather small study population, which also limited the number of variables included in multivariate regression analyses. In addition, a few laboratory parameters such as hsTnT, d-dimer, ferritin and NT-proBNP were only measured in less than one third of all patients. Inflammatory parameters on admission (C-reactive protein, IL-6 and procalcitonin), on the other hand, were measured in the majority of the included patients and were elevated in deceased patients and patients that were admitted to ICU suggesting worse outcome in patients with severe inflammation.

Follow-up and persisting symptoms

Subsequently, a follow-up by phone was performed approximately six months after discharge from hospital. The most commonly reported persisting symptoms during the follow-up period were dyspnea, weakness, decreased physical ability, vertigo and memory disorders. In comparison, in some other studies and systematic reviews the proportion of COVID-19 patients with persisting symptoms was clearly higher. In a Chinese cohort study 1.733 COVID-19 patients were interviewed and examined approximately 180 days after discharge from hospital. The most frequently persisting symptoms were fatigue or muscle weakness (63% of all patients), sleep difficulties (26%) and anxiety or depression (23%) (53). In another cohort study that included 180 mainly not hospitalized COVID-19 patients the follow-up was performed approximately 125 days after symptom onset. Over half of all patients reported at least one persistent symptom and the most prevalent symptoms were loss of smell and taste, fatigue and headache (54). A meta-analysis including 15 studies with a total of 47.190 patients showed that the most frequently reported symptoms (follow-up time: 14-110 days) were fatigue (58%; 95%-CI: 42-73), headache (44%; 95%-CI: 13-78), attention disorder (27%; 95%-CI: 19-36), hair loss (25%; 95%-CI: 17-34) and dyspnea (24%; 95%-CI:14-36) (55). The clearly lower proportions of patients who reported persistent symptoms in our study could be partly explained by the rather long follow-up period and the follow-up design. The fact that patients themselves described their symptoms and symptoms were not collected on the basis of a predefined questionnaire may have resulted in patients reporting fewer symptoms. In addition, due to the modality of the follow-up it was difficult to assess the exact course and severity of symptoms. In some patients, the follow-up was performed with contact persons who do not live with the patients or with nursing staff, which may have led to fewer persisting symptoms being reported, especially in patients living in nursing homes.

This study also showed that nearly 30% (18 patients) of all non-deceased patients were at least once re-hospitalized for various reasons and 10% (7 patients) died during the follow-up period. Only 3.8% (2 patients) were hospitalized due to an urgent cardiovascular cause. 3 of 7 deaths were caused by respiratory complications and all fatalities occurred in patients with pre-existing cardiovascular disease and/or risk factors. Cardiovascular patients (OR: 6.3; 95%-CI: 1.3-30.5; p: 0.021) and especially patients with hypertension (OR: 3.8; 95%-CI: 1.1-13.2; p: 0.038) were at higher risk for rehospitalization or death during the follow-up period. In a retrospective cohort study including 47.780 English COVID-19 patients, that is currently available as a preprint, 29.4% of all patients were readmitted to hospital and

12.3% died after a mean follow-up period of 140 days (standard deviation: 50 days) after discharge. Compared to matched controls rates for death and re-hospitalization during follow-up were 7.7 (95%-CI: 7.2-8.3) and 3.5 (95%-CI: 3.4-3.6) times higher in hospitalized COVID-19 patients (56). In an American smaller-scale retrospective study including 2.179 hospitalized COVID-19 patients 19.9% were re-hospitalized and 9.1% died within 60 days after discharge from hospital. The most frequently recorded diagnoses at re-admission, besides COVID-19, were sepsis (8.5%), pneumonia (3.1%) and heart failure (3.1%) (57). Findings for re-hospitalization/re-admission and death during follow-up in patients from Graz are consistent with the findings of larger-scale follow-up studies. However, the rate of hospitalizations due to non-acute conditions, which caused the majority of re-hospitalizations in patients from Graz, was not explicitly mentioned in the above-cited studies.

6. Limitations

This retrospective study including 96 patients that were treated at the University Hospital of Graz has several limitations that must be considered in the interpretation of the findings. First of all, the study population was rather small, which may have led to unexpected results for mortality risk and risk for ICU admission in some subgroups (e.g. lower risk for ICU admission in patients with chronic kidney disease or history of stroke/transient ischemic attack). The small size of the study population also severely limited the number of variables that could be implemented in regression analyses, which led to the fact that some potential confounders and influencing factors were not considered. In addition, some trends that might have reached statistical significance in larger study populations could not be statistically validated. Another limitation is that a few included patients were not primarily hospitalized due to infection with SARS-CoV-2, but for various other reasons.

In terms of laboratory findings, results for some parameters such as d-dimer and troponin should be interpreted with caution, as they have only been measured in less than one third of all patients. For this reason, troponin levels on admission were not integrated into the mortality risk score, although in univariate regression analyses troponin was significantly associated with increased risk of death.

Furthermore, the modalities of follow-up, which was carried out exclusively by phone, could affect the informative value of findings. The prevalence of reported persisting symptoms was rather low in comparison to other studies, which could partly be due to the fact that

some follow-up interviews were not conducted with the patients themselves, but with contact persons or nursing staff. In addition, the facts that patients had to report symptoms themselves and no predefined questionnaire was used might also have limited the number of reported symptoms.

Lastly, COVID-19 variants and changes in treatment as well as the availability of vaccination developed in the recent year. Our cohort represents first-wave hospitalized patients with SARS-CoV-2 infection referred to the University Hospital of Graz. Generalizing findings to other and more recent cohorts must be performed cautiously.

7. Conclusions

The prevalence of cardiovascular disease and risk factors was high in first-wave patients with a SARS-CoV-2 infection that were treated at the University Hospital of Graz between February and beginning of May 2020. Diabetes, manifest ischemic heart disease and heart failure were significant predictors of intra-hospital mortality and patients with any cardiovascular disease tended to be at higher risk of death. Furthermore, the presence of dyslipidemia, chronic obstructive pulmonary disease, ischemic heart disease or valvular heart disease was associated with an increased risk of admission to an intensive care unit. Abnormalities in several laboratory parameters on admission to hospital were shown to be associated with increased mortality (e.g. arterial pH, inflammatory parameters, hsTnT, creatinine, blood urea nitrogen) or risk for admission to an ICU (e.g. arterial oxygen saturation, procalcitonin, IL-6, platelet count).

A follow-up which was conducted approximately six months after discharge from hospital revealed that a considerable proportion of patients reported persisting symptoms. Most commonly mentioned disorders were dyspnea, weakness and decreased physical ability, vertigo and memory disorder. In addition, nearly one third of all patients were re-hospitalized for any reason and 10% died during the follow-up period.

Summing up, approximately 40% of all patients with at least one pre-existing cardiovascular disease or risk factor and over 44% of all included patients with pre-existing cardiovascular disease died either in hospital during initial admission or during the follow-up period. Therefore, it can be stated that the presence of pre-existing cardiovascular disease and/or risk factors is associated with worse outcome in hospitalized patients with SARS-CoV-2 infection.

8. References

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[1] For this paper only the abstract was available in English. The main part of the paper was written in Chinese.

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