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Predictors of worse outcome after postponing non-emergency cardiac interventions during the COVID-19 pandemic

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2023-002293).

To cite: Andreß S, Felbel D, Mack A, *et al*. Predictors of worse outcome after postponing non-emergency cardiac interventions during the COVID-19 pandemic. *Open Heart* 2023;**10**:e002293. doi:10.1136/openhrt-2023-002293

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Received 1 March 2023
Accepted 16 June 2023

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ABSTRACT

Objective Deferral of non-emergency cardiac procedures is associated with increased early emergency cardiovascular hospitalisation. This study aimed to identify predictors of worse clinical outcome after deferral of non-emergency cardiovascular interventions.

Methods This observational case-control study included consecutive patients whose non-emergency cardiac intervention has been postponed during COVID-19-related lockdown between 19 March and 30 April 2020 (n=193). Cox regression was performed to identify predictors of the combined 1-year end point emergency cardiovascular hospitalisation and death. All patients undergoing non-emergency interventions in the corresponding time period 2019 served as control group (n=216).

Results The combined end point of death and emergency cardiovascular hospitalisation occurred in 70 (36.3%) of 193 patients with a postponed cardiovascular intervention. The planned intervention was deferred by a median of 23 (19–36) days. Arterial hypertension (HR 2.27; 95% CI 1.00 to 5.12; p=0.049), chronic kidney disease (HR 1.89; 95% CI 1.03 to 3.49; p=0.041) as well as severe valvular heart disease (HR 3.08; 95% CI 1.68 to 5.64; p<0.001) were independent predictors of death or emergency hospitalisation. Kaplan-Maier estimators of the combined end point were 31% in patients with arterial hypertension, 56% in patients with severe valvular heart disease and 77% with both risk factors (HR 12.4, 95% CI 3.8 to 40.7; p<0.001) and only 9% in patients without these risk factors (log rank p<0.001). N-terminal pro-B-type natriuretic peptide (NT-proBNP) cut-point of ≥1109 pg/mL best predicts the occurrence of primary end point event in deferred patients (area under the curve 0.71; p<0.001; sensitivity 63.8%, specificity 69.4%).

Conclusion Our results suggest that patients with either arterial hypertension, chronic kidney or severe valvular heart disease are at very high risk for emergency hospitalisation and increased mortality in case of postponed cardiac interventions even in supposed stable clinical status. Risk seems to be even higher in patients suffering from a combination of these conditions. If the ongoing or future pandemics force hospitals again to postpone cardiac interventions, the biomarker NT-proBNP is an applicable parameter for outpatient monitoring to identify those at risk for adverse cardiovascular events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiac patients whose non-emergency cardiovascular intervention has been postponed during the COVID-19 pandemic were associated with worse clinical outcome.

WHAT THIS STUDY ADDS

⇒ Our study adds planned heart valve intervention, arterial hypertension and chronic kidney disease as relevant criteria to identify patients at higher risk for a poor outcome when being deferred.

⇒ Patients suffering from a combination of these risk factors are at even higher risk.

⇒ Measuring N-terminal pro-B-type natriuretic peptide levels might help to identify those at high or very risk for a poor outcome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the ongoing or future pandemics force hospitals again to postpone cardiac interventions, our study results help to identify and monitor those patients at higher risk for poor outcome, even in supposed stable clinical status.

INTRODUCTION

During the COVID-19 pandemic, hospitals were forced to reduce non-emergency hospital admissions and postpone medical interventions of lower priority to increase capacity for SARS-CoV2-infected patients in order to meet unprecedented demands of the healthcare system.[1] Most medical specialties were affected by these preventive measures.[2] Patients scheduled for interventional cardiology procedures representing a vulnerable population since often timely medical care is of the essence to avoid detrimental outcomes.[3] In this context, cardiologic societies developed strategies to distinguish between urgent and postponable cardiac procedures aiming to safely defer non-emergency appointments. Patients were deemed suitable for deferral,

in absence of severe symptoms, critical major disease-related findings or recent emergency cardiovascular hospitalisation.[4–8] However, current studies demonstrate that clinical outcomes of deferred patients classified as non-emergency were poorer when compared with patients, who received their planned cardiac interventions as scheduled. Affected patients were associated with increased emergency hospitalisations, death rates and signs of disease progression.[9 10] Given the poor outcomes of deferred cardiac patients during the current and ongoing COVID-19 pandemic, criteria to better assess the urgency of the individual treatment of each patient are desperately needed.

The present study aimed to identify predictors associated with poor clinical outcome in cardiac patients whose non-emergency cardiovascular intervention has been postponed during the COVID-19 pandemic.

METHODS

This observational case-control study included all consecutive patients, whose non-emergency appointments had been deferred at the Department of Medicine II at Ulm University Heart Center, Germany during the first COVID-19-related lockdown between 19 March and 30 April 2020 (study group). Patients scheduled for cardiac intervention due to (1) severe valve stenosis or regurgitation, (2) suspected or known significant coronary artery disease, (3) atrial or ventricular arrhythmia or (4) implantable cardioverter defibrillator and permanent pacemaker were eligible for this study. According to the current European Society of Cardiology (ESC) recommendations at that time, all patients were classified as 'lower priority' or 'non-emergency' and thus considered as deferrable. Non-emergency patients admitted in the corresponding period of the previous year 2019 (19 March and 30 April 2019) served as the seasonal control group.

Demographic, clinical and laboratory data at baseline, on the date of the actual performed intervention and at follow-up, as well as outcome data were extracted from our patient management system. Missing outcome data were supplemented by telephone interviews. Patients were routinely scheduled for outpatient clinical visits, including clinical assessment and focused cardiovascular examinations at 1, 3 and 6 months postprocedure and every 6 months thereafter. Symptoms were classified according to the New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) scales. Instrumental investigations included 12-lead ECG and evaluation of the left ventricular systolic function (LVSF) either by echocardiography (EOPIQ 7, Koninklijke Philips N.V. Eindhoven, The Netherlands) or ventriculography during cardiac catheterisation. LVSF was categorised by ejection fraction (LVEF) as normal (1), mildly impaired (2), moderately impaired (3) or severely impaired (4) based on guideline-specific recommendations.[11] In addition, blood samples were taken to measure highly sensitive cardiac troponin T, NT-proBNP and creatinine levels (ElectroChemo-Luminescence ImmunoAssay 'Eclia'-Roche, Cobas 8000, Module e801 and e601).

The primary end point was a composite of emergency cardiovascular hospitalisation or death.

Emergency cardiovascular hospitalisation was defined as every unplanned admission due to an acute cardiac event. The most common causes for emergency hospitalisation were, among others, acute coronary syndrome or other chest pain syndromes, heart failure, cardiac arrhythmia, progressive heart valve disease, hypertensive crisis and syncope. External emergency treatments were also taken into account and reassessed by our study team.

Patients' clinical outcomes were assessed for the subsequent 12 months following the original date of the scheduled non-emergency cardiac intervention (median follow-up 365 days (102–365)). The follow-up rate was 81.3% in study cohort 2020 and 83.8% in the reference cohort 2019. In the 2020 cohort, 365 days follow-up of patients without major adverse cardiovascular events (MACE) was 70.7% with a median of 365 days (329–365 days). Follow-up ended in patients with the occurrence of MACE with a median of 24 days (18–46 days). Moreover, the clinical outcome was analysed separately depending on the individual predictors of primary end point event to better assess their impact.

Statistical analysis

Continuous variables were presented as mean and SD or median and IQR, as appropriate. Normal distribution was tested using the Kolmogorov-Smirnow test. If a metric variable was not normally distributed at baseline, at the actual (deferred) date of intervention or at follow-up, all values were presented as median together with the IQR for better comparability. For some variables (NYHA class, CCS class, LVEF), the mean value with SD was shown for reasons of clarity and comprehensibility. Categorical variables were presented as number and percentage. Student's t-test, Mann-Whitney U test or χ^2 test were used to compare variables between the study and control group, where appropriate.

Variables potentially influencing MACE ($p<0.2$) were further analysed using univariate Cox regression as well as Pearson's and Spearman's rho correlation function. Variables with relevant correlation ($r>0.4$) were not further analysed (planned cardiac catheterisation and electrophysiological procedure). Multiple Cox regression included all significant and independent variables of univariate regression analysis. The raw incidence rates per variable and the incidence of an event of the primary end point were given as HR with 95% CIs. A receiver operating characteristic (ROC) curve analysis estimating sensitivity, specificity and area under the curve (AUC) was performed to assess the performance of the model, respectively. Youden Index was used to identify the optimal cut-off value for predicting attainment of the primary end point.

Time-to-event analyses were performed using Kaplan-Meier (KM) estimates and were compared with the

log-rank test. KM curves were generated for time to event. The differences in event rates are described by HR with the 95% CI.

A p value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS Statistics V.27 software (2020 version, IBM, Armonk, New York, USA).

RESULTS

Study population

Non-emergency cardiac intervention of 193 patients (study group) were deferred at our tertiary care centre between 19 March and 30 April 2020. 78 patients (40.4%) had been scheduled for cardiac catheterisation, 50 patients (25.9%) for transcatheter heart valve intervention, 56 patients (29.0%) for electrophysiological intervention and 9 patients (4.7%) for device implantation. The planned intervention was deferred by a median of 23 days (19–36 days). During the reference period between 19 March and 30 April 2019, 216 patients (control group) underwent cardiac intervention as scheduled. Of them, 94 patients (43.5%) received cardiac catheterisation, 48 patients (22.2%) transcatheter heart valve intervention, 57 patients (26.4%) electrophysiological intervention and 17 patients (7.9%) device implantation. Distribution of procedure type did not differ between 2019 and 2020 (p=0.397).

Baseline data of both groups are displayed in table 1. Median age was similar in both groups (75 (63–81) years vs 73 (64–79) years; p=0.363) and most patients were male (59.1% vs 66.2%; p=0.136). In both groups, more than three out of four patients suffered from arterial hypertension (77.5% vs 79.6%; p=0.599). In the control group of 2019, significantly more patients had dyslipidaemia (71.8% vs 61.8%; p=0.042) and a positive family history for cardiovascular disease (26.4% vs 14.6%; p=0.006) compared with those in the deferred cohort. In the study group, troponin level was slightly higher than in the control group (20 (10–35) ng vs 16 (9–28) ng; p=0.049). All other baseline characteristics were similarly distributed in both populations.

Predictors of poor clinical outcome in deferred cardiac patients

A primary end point event consisting of death or emergency hospitalisation occurred in 70 patients (36.3%) in the study group versus 38 in the control group (17.6%) (p<0.001). Of these, two patients (2.9%) died and 68 (97.1%) were admitted as an emergency. Based on the occurrence of the primary end point within 1-year follow-up, patients were divided into two groups (table 2). When compared with patients without primary end point event, patients with such a clinical incident suffered significantly more often from arterial hypertension (88.6% vs 71.1%; p=0.005) and chronic kidney disease (28.3% vs 13.3%; p=0.022). Furthermore, patients with primary end point event had higher NYHA class (2.3±1.2 vs 1.4±1.2; p<0.001), CCS class (0.9±1.3 vs 0.6±1.2; p<0.001) as well as higher levels of troponin (27 ng/L (14–44 ng/L) vs 14 ng/L (9–29 ng/L), p<0.001) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (1858 pg/mL (537–4501 pg/mL) vs 601 pg/mL (174–1632 pg/mL); p<0.001) at admission. Concerning the planned cardiac intervention, patients with primary end point event were significantly more often scheduled for transcatheter heart valve intervention (50% vs 12.2%, p<0.001), whereas patients without were more frequently planned for cardiac catheterisation (48.8% vs 25.7%, p=0.002).

Cox regression analysis identified arterial hypertension (HR 2.27; p=0.049), chronic kidney disease (HR 1.89; p=0.041) and severe valvular heart disease (HR 3.08; p<0.001) to be independently associated with increased risk of death or emergency hospitalisation within 365 days after the postponed cardiac intervention (table 3). Univariate Cox regression and Pearson's correlation matrix are presented in online supplemental tables 1 and 2. In the control group of 2019, these variables did not have a significant influence on the occurrence of the primary end point in the Cox regression analysis (online supplemental table 3).

In deferred patients with arterial hypertension or severe valvular heart disease, KM event estimators were 30.5% and 55.6%, while patients without these identified risk factors 1-year KM event rate was only 9.4%. In patients combining both risk factors, KM event rate was even 76.5% (HR 12.39, 95% CI 3.78 to 40.70; p<0.001). Time-to-event curves, obtained by KM analysis for 1-year event-free probability are displayed in figure 1.

Subgroup analysis

A total of 320 patients suffered from arterial hypertension (study group: 148 patients (77.5%); control group: 172 patients (79.6%); p=0.599). A primary end point event occurred in 62 patients in the study group and in 34 patients in the control group (KM estimates 43.0% and 20.8%; log-rank p<0.001; figure 2C). Additionally, the hospital stay before and after the cardiac procedure lasted significantly longer in deferred patients compared with those who underwent cardiac intervention as scheduled (4.5±4.7 days vs 2.8±2.6 days; p<0.001). Furthermore, even after the performed cardiac intervention, deferred patients had a significantly longer total hospital stay during the observation period, when admitted as an emergency (2.1±6.0 vs 0.3±3.7 nights; p=0.002). Data about the index and emergency hospital stays are displayed in the online supplemental table 4.

A total of 99 patients had severe heart valve stenosis or insufficiency (study group: 50 patients; control group 48 patients) and were scheduled for transcatheter heart valve replacement or repair. A primary end point event occurred in 35 patients in the study group and in 6 patients in the control group (KM estimates 73.0% and 12.5%; log-rank p<0.01; figure 2D).

The index hospital stay of both groups was of similar length (7.6±2.7 days vs 7.2±2.4 days; p=0.415), however,

Table 1 Baseline characteristics of deferred patients in 2020 and the control cohort 2019

	Study cohort 2020 N=193	Control cohort 2019 N=216	P value
Male (%)	114 (59.1%)	143 (66.2%)	0.136
Age, years	75 (63–81)	73 (64.25–79)	0.363
Arterial hypertension (%)	148 (77.5%)	172 (79.6%)	0.599
Dyslipidaemia (%)	97 (61.8%)	155 (71.8%)	**0.042**
Diabetes mellitus (%)	47 (29.9%)	50 (23.1%)	0.14
Family history of cardiovascular disease (%)	23 (14.6%)	57 (26.4%)	**0.006**
Smoker (%)	54 (34.3%)	80 (37.0%)	0.6
Obesity (%)	34 (21.7%)	55 (25.5%)	0.394
History of stroke/TIA (%)	19 (12.1%)	17 (7.9%)	0.172
Chronic pulmonary disease (%)	13 (8.3%)	13 (6.0%)	0.397
Chronic kidney disease (%)	29 (18.4%)	37 (17.1%)	0.759
Coronary artery disease (%)	118 (74.7%)	142 (65.7%)	0.063
NYHA class			
At baseline	1.9±0.8	1.9±0.8	0.33
At admission	1.9±2.2	1.7±1.2	0.719
CCS class			
At baseline	0.7±1.1	0.8±1.2	0.132
At admission	0.7±1.2	0.8±1.3	0.071
LVEF			
At baseline	2.4±1.2	2.2±1.2	0.088
At admission	1.9±1.1	2.0±1.3	0.754
Creatinine (µmol/L)			
At baseline	94 (80–110)	94 (74–116)	0.732
At admission	90 (71–116)	93 (73–115)	0.224
Troponin T (ng/L)			
At baseline	20 (10–35)	16 (9–28)	**0.049**
At admission	19 (10–63)	13 (8–42)	0.054
NT-proBNP (pg/mL)			
At baseline	832 (227–1943)	559 (164–1584)	0.273
At admission	786 (199–5524)	488 (135–1535)	0.195
Planned intervention			
Cardiac catheterisation	78 (40.4%)	94 (43.5%)	0.397
Electrophysiogical procedure	56 (29.0%)	57 (26.4%)	0.526
Device implantation	9 (4.7%)	17 (7.9%)	0.902
Heart valve intervention	50 (25.9%)	48 (22.2%)	0.184
Aortic valve stenosis	29	33	0.383
Mitral valve stenosis	2	0	
Mitral valve regurgitation	8	13	
Tricuspid valve regurgitation	11	1	
Aortic valve regurgitation	0	1	

Data are presented as counts with percentages, mean with SD or median with IQR as appropriate.
LVEF: (1=normal, 2=mildly impaired, 3=moderately impaired, 4=severely impaired).
Significant p values are presented in bold.
CCS, Canadian Cardiovascular Society; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Table 2 Baseline characteristics of patients stratified by the occurrence of MACE starting from their deferred appointment in the study cohort 2020

	MACE N=70	No MACE N=123	P value
Male (%)	35 (50%)	79 (64.2%)	0.053
Arterial hypertension (%)	62 (88.6%)	86 (71.1%)	**0.005**
Dyslipidaemia (%)	33 (63.5%)	64 (61.0%)	0.761
Diabetes mellitus (%)	20 (38.5%)	27 (25.7%)	0.101
Family history of cardiovascular disease (%)	6 (11.5%)	17 (16.2%)	0.438
Smoker (%)	16 (30.8%)	38 (36.2%)	0.501
Obesity (%)	13 (25.0%)	21 (20.0%)	0.474
History of stroke/TIA (%)	9 (17.3%)	10 (9.5%)	0.159
Chronic obstructive pulmonary disease (%)	6 (11.5%)	7 (6.7%)	0.297
Chronic kidney disease (%)	15 (28.3%)	14 (13.3%)	**0.022**
Coronary artery disease (%)	43 (81.1%)	75 (71.4%)	0.185
NYHA class			
At baseline	2.0±0.8	1.8±0.8	0.203
At admission	2.3±1.2	1.4±1.2	**<0.001**
CCS class			
At baseline	0.8±1.1	0.6±1.1	0.523
At admission	0.9±1.3	0.6±1.2	**0.045**
LVEF			
At baseline	2.6±1.1	2.2±1.1	0.495
At admission	2.0±1.2	1.8±0.9	0.3
Creatinine (µmol/L)			
At baseline	97 (73–136)	92 (81–106)	0.288
At admission	96 (78–138)	87 (65–109)	**0.004**
Troponin T (ng/L)			
Baseline	27 (15–39)	19 (10–32)	0.168
At admission	27 (14–44)	14 (9–29)	**<0.001**
NT-proBNP (pg/mL)			
Baseline	1034 (334–2544)	771 (164–1668)	0.171
At admission	1858 (537–4501)	601 (174–1632)	**<0.001**
NT-proBNP at admission ≥1109 pg/mL	44 (63.8%)	33 (30.6%)	**<0.001**
Intervention type			
Cardiac catheterisation	18 (25.7%)	60 (48.8%)	**0.002**
Electrophysiogical procedure	15 (21.4%)	41 (33.3%)	0.08
Device implantation	2 (2.9%)	7 (5.7%)	0.369
Heart valve intervention	35 (50%)	15 (12.2%)	**<0.001**
Aortic valve stenosis	19 (27.1%)	10 (8.1%)	
Mitral valve stenosis	2 (2.9%)	0	
Mitral valve regurgitation	7 (10.0%)	1 (0.8%)	
Tricuspid valve regurgitation	7 (10.0%)	4 (3.3%)	
Death	2 (2.9%)	0	0.06
Emergency admission	68 (35.2%)	0	**<0.001**

Data are presented as counts with percentages, mean with SD or median with IQR as appropriate.
Significant p values are presented in bold.
CCS, Canadian Cardiovascular Society; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction (1=normal, 2=mildly impaired, 3=moderately impaired, 4= severely impaired); MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Table 3 Multiple Cox regression for MACE in the 2020 cohort

	HR	95% CI	P value
Arterial hypertension	2.27	1.00 to 5.12	**0.049**
Heart valve intervention planned	3.08	1.68 to 5.64	**<0.001**
Chronic kidney disease	1.89	1.03 to 3.49	**0.041**
Male	1.21	0.68 to 2.16	0.522

Significant p values are presented in bold.

total hospital stay during the observation period was significantly longer in deferred patients when admitted as an emergency, even after the performed cardiac procedure (2.7±7.1 days vs 0 days; p=0.009) (online supplemental table 5).

A total of 66 patients presented with chronic kidney disease (study group: 29; control group 37 patients). The primary end point occurred in 15 patients in the study cohort and in 8 of the control cohort (KM estimates 53.6% vs 21.9%; log-rank p=0.006; figure 2B).

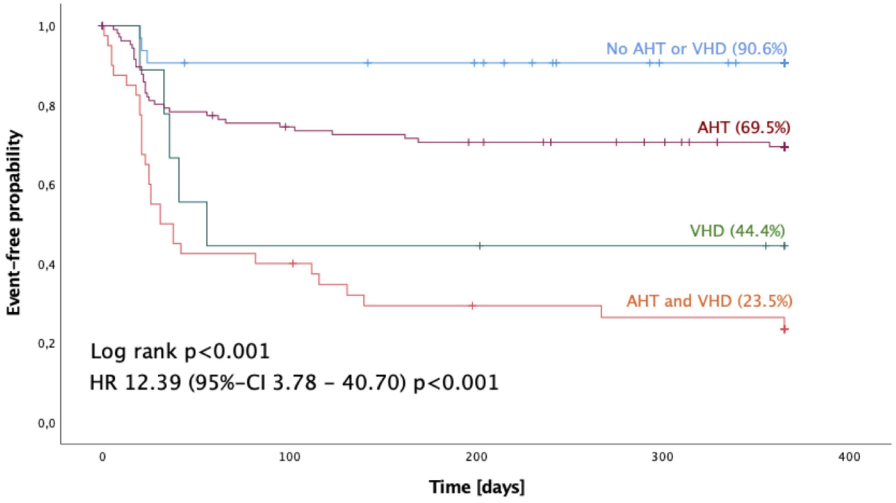
The hospital stay of the planned intervention was significantly longer in the study cohort (5.5±6.1 vs 3.4±3.6 days; p=0.021). Rates of emergency hospitalisations postintervention were comparable (p=0.143), whereas the emergency hospital stay was significantly longer postintervention (7.7±12.4 vs 1.7±7.9 days; p=0.002) (online supplemental table 6).

In patients combining arterial hypertension, chronic kidney and valvular heart disease, 1-year KM event rates were even 71.4% in the study group and 11.9% in the control group (log-rank p<0.009; figure 2E). Patients at risk from figure 2 are displayed in online supplemental table 7.

Cut-point of NT-proBNP for worse clinical outcome in deferred patients

Median NT-proBNP level at admission was 1858 pg/mL (537–4501 pg/mL) among deferred patients with primary end point event and 601 pg/mL (174–1632 pg/mL) without such a clinical incident (p<0.001). In contrast, NT-proBNP at the time of the actually planned cardiac intervention did not differ significantly between both study groups (1034 pg/mL (334–2544 pg/mL) vs 771 (164–1668 pg/mL); p=0.171).

An ROC analysis was performed to identify the optimal cut-off value of continuous and significantly tested variables in table 2. NT-proBNP at admission was able to predict 1-year mortality and emergency hospitalisation. ROC analysis demonstrated NT-proBNP to be highly sensitive and specific for the prediction of primary end point, as indicated by an area under the ROC curve (AUC) of 0.71 (0.63–0.79; p<0.001). The optimal NT-proBNP cut-point was 1109 pg/mL, which had 63.8% sensitivity and



Patients at risk in the 2020 cohort starting at the initially planned treatment date						
Months	0	1	3	6	9	12
No arterial hypertension or planned heart valve intervention	34	29	28	28	21	17
Arterial hypertension	108	85	79	73	69	61
Planned heart valve intervention	9	8	4	4	3	2
Arterial hypertension and planned heart valve intervention	40	22	16	11	9	9

Figure 1 Kaplan-Meier analysis of major adverse cardiovascular events starting from the initially planned date. HR was calculated for patients with both AHT and planned intervention of VHD. AHT, arterial hypertension; VHD, valvular heart disease and planned heart value intervention.

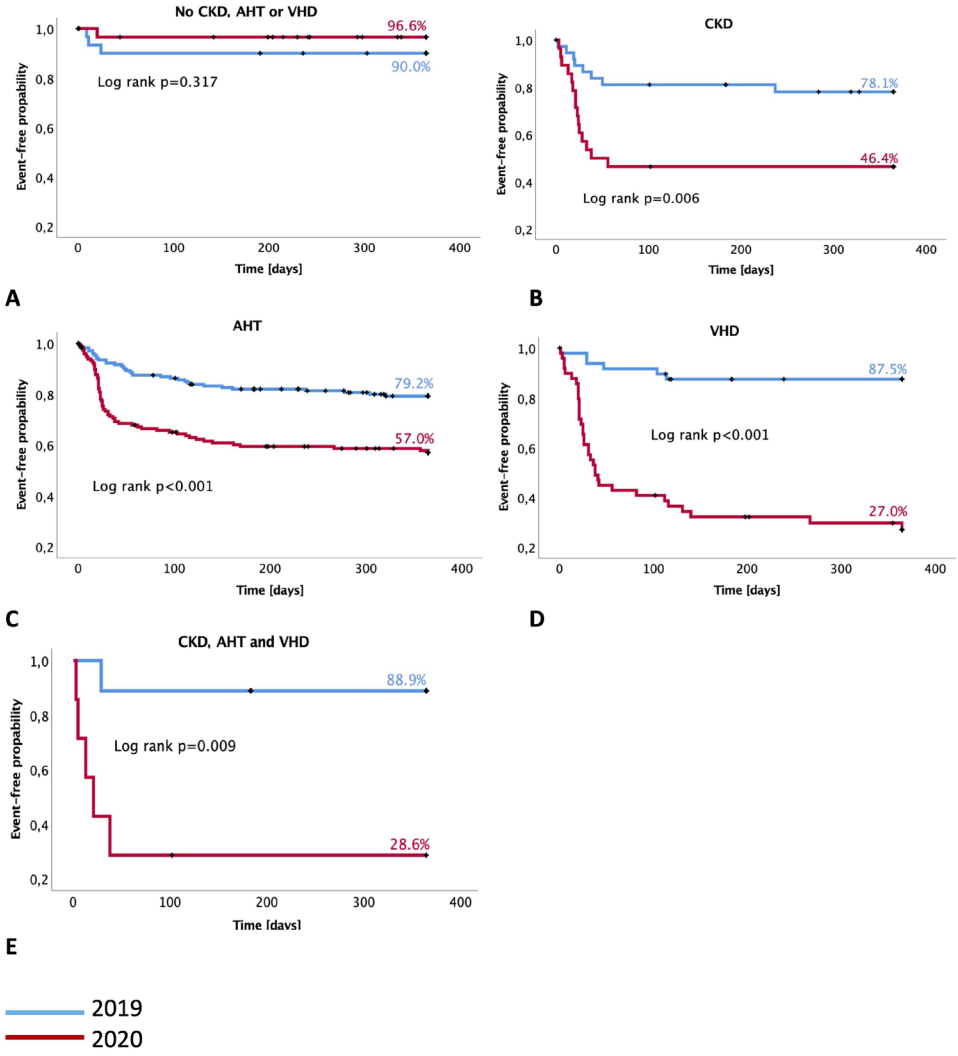


Figure 2 Major adverse cardiovascular events in 2019 and 2020 after the initially planned intervention date stratified by CKD, AHT and VHD. Patients at risk are displayed in online supplemental table 7. AHT, arterial hypertension; CKD, chronic kidney disease; VHD, valvular heart disease and planned heart value intervention.

69.4% specificity (figure 3). In patients with NT-proBNP ≥1109 pg/mL, primary end point rate was 63.8% (n=44) compared with 30.6% (n=33) in patients with NTproBNP <1109 pg/mL (p<0.001).

DISCUSSION

In the present study, we analysed criteria to identify high-risk patients for postponing non-emergency cardiovascular interventions. The main findings can be summarised as follows: arterial hypertension, chronic kidney and severe valvular heart disease were independent predictors for increased risk of death or emergency hospitalisation in deferred patients. When more than one of these risk factors were combined, risk was even higher. Compared with patients of the seasonal control group suffering from the same risk factors, risk of death or emergency hospitalisation was significantly higher in deferred patients. A NT-proBNP cut-point of ≥1109 pg/mL best predicts the occurrence of death and emergency hospitalisation in deferred patients.

During the 'first wave' of the COVID-19 pandemic, reports from all over the world have shown substantial reduction of around two-thirds in cardiac surgery and interventions when compared with the corresponding period in 2019.[12 13] Consequently, several cardiological societies developed strategies and recommendations to triage medical interventions and to identify patients who are in a condition allowing to safely defer non-emergency procedures.[4–8] Risk of delaying the procedure, risk of COVID-19 exposure outside patient's home environment and use of limited hospital resources were considered in the decision-making process regarding the optimal timing of cardiac interventions during the pandemic.[4] However, a recent study demonstrated that deferral of scheduled non-emergency cardiac interventions, despite being classified as postponable under current recommendations, was associated with significant increased emergency hospitalisations and death within 365 days, suggesting progression of disease.[9]

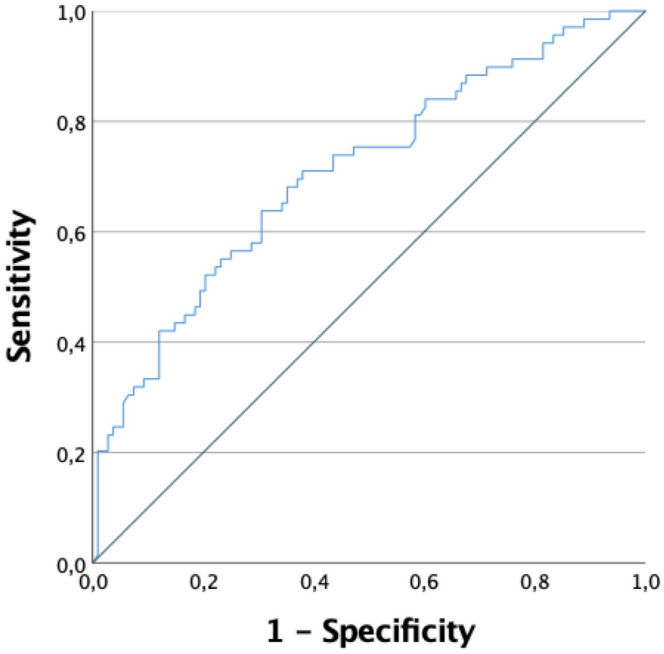


Figure 3 Receiver operating characteristic curve to identify the optimal N-terminal pro-B-type natriuretic peptide (NT-proBNP) cut-off for major adverse cardiovascular events in the 2020 cohort. Area under the curve: 0.71 (0.63–0.79), p<0.001; optimal NT-proBNP cut-off was calculated by Youden Index (1109 pg/mL, sensitivity 63.8%, specificity 69.4%).

The poor clinical outcomes of deferred cardiac patients underline the urgency of revised strategies for delivering appropriate healthcare during the current and future pandemics to patients with cardiac conditions representing a particularly vulnerable and challenging patient population. The present study adds new criteria to identify particularly precarious patients, whose planned intervention is better not to be postponed.

We demonstrated that the presence of chronic kidney disease almost and arterial hypertension was associated with a doubled risk, whereas severe valvular heart disease even with a tripled risk of emergency hospitalisations or death within 12-month follow-up. Patients with both arterial hypertension and severe valvular heart disease experienced emergency hospitalisation or death even at a 12 times higher risk.

In contrast, these predictors for an increased risk for death or emergency cardiovascular hospitalisation could not be determined in the control group of 2019. The results underscore the importance of interventional cardiology and the implementation of an appropriate cardiac intervention in time, since the mentioned predictors per se accumulate an increased risk for poorer clinical outcome. While chronic kidney disease and arterial hypertension are well-established cardiovascular risk factors and marker of poorer prognosis,[14 15] recent reports indicated that a longer waiting time in patients with severe valvular heart disease leads to higher morbidity and mortality as well. About 12% of transcatheter aortic valve implantation (TAVI)-eligible patients experienced heart failure hospitalisation after a wait time of almost 3 months[3] and even about 50% of patients pending on percutaneous mitral valve repair were hospitalised for heart failure after 180 days.[16] Furthermore, mortality rates were 2%–4.9% in TAVI-eligible patients after waiting times of 30–80 days and 8% after 1.5 months in patients scheduled for mitral valve repair.[3 16–18]

Our study results suggest that patients with arterial hypertension, chronic kidney or severe heart valve disease are at very high risk for unfavourable outcome and thus not seem to represent appropriate candidates for postponing their planned cardiac intervention even in supposed stable clinical status, especially if they suffer from both conditions.

However, how should these patients best be monitored if during a pandemic hospitals are again forced to postpone interventions even of these high-risk patients to prevent adverse cardiac events? Previous studies have shown the usefulness of regular measurements of the biomarkers BNP and NT-proBNP in the management of patients with chronic heart failure.[19 20] Short-term changes in natriuretic peptide levels predicted hospital stay and were associated with worse clinical outcome.[21–24] Furthermore, significant elevated levels of NT-proBNP were shown for deferred patients with severe valvular heart disease during wait time to correlate with an increase in emergency hospitals and death within 1 year after the postponed intervention.[9] BNP is a cardiac hormone produced from ventricular muscle cells in response to ventricular dilatation and pressure overload and correlates with NYHA class, left ventricular filling pressure, LVEF and other indices of heart failure.[21 25–30] In the present study, a NT-proBNP level >1109 pg/mL was associated with a significant increase of emergency hospital admissions and death in patients whose non-emergency interventions were postponed. A previous analysis evaluating NT-proBNP cut-points to identify acute heart failure yielded a cut-off value of 900 pg/mL for patients between 50 and 75 years and 1800 pg/mL for those aged >75 years, which strengthens our findings considering a median age of 75 years in our study, but further investigations are necessary.[31] Our study results suggest that a NT-proBNP-guided monitoring might be useful to identify those at high risk of clinical events and if postponing cardiac interventions is needed to identify for their just-in-time performance.

Limitations

The results of our study have to be interpreted with several confinements. Our analysis is a single-centre retrospective observational study carrying all the inherent limitations ascribed to such type of design, such as selection and misclassification bias. However, consecutive patients in the defined time period were included without patient exclusion or preselection aiming to reduce selection bias as much as possible. Additionally, due to the explorative character of this study, our results have to be interpreted

as hypothesis generating. Dyslipidaemia and family history of cardiovascular disease were higher in the reference cohort and troponin T levels 4 ng/L higher in the deferred cohort. However, the observed effect of deferral on MACE cannot be fully explained by these differences, but an impact cannot be completely excluded and should be considered when interpreting the observed results. Our approach to identify patients with deferrable cardiac interventions might be a matter of debate since recommendations varied by the publishing cardiac societies. However, in line with the current recommendations of the ESC only patients classified as 'lower priority' or 'non-emergency' were included in the present study. Moreover, we include a heterogenous group of patients with different types of heart disease as well as all postponed cardiac interventions aiming at an unbiased insight on the effects of deferring cardiac patients during the COVID-19 crisis. It is not known if patients of the study group were infected with SARS-CoV-2 during the observation time, which might have influenced our study results. Finally, although a large number of the most important baseline characteristics have been collected, it is possible that some parameters that may have influenced the clinical outcome were not recorded or available for analysis as they are not routinely collected in clinical practice. Furthermore, LVEF was only recorded categorically and not continuously as percentage.

CONCLUSION

Our study results suggest that patients with either arterial hypertension, chronic kidney or severe valvular heart disease are at very high risk for emergency hospitalisation and increased mortality in case of postponed cardiac interventions, even in supposed stable clinical status. Risk is even higher in patients suffering from a combination of these conditions. If the ongoing or future pandemics force hospitals again to postpone cardiac interventions, measuring NT-proBNP levels might help to identify those at high or very high risk.

Contributors Conceptualisation: TS and AI; methodology: DF, SA, MR and AM; software: AM, SA and DF; validation: TS, AI and DB; formal analysis: DF and SA; investigation: SA, DF and AM; data curation: SA and DF; writing—original draft preparation: DF, SA, TS and Sd'A; writing—review and editing: TS, WR, DB and AI; visualisation: DF and AM; supervision: TS, AI and WR; Guarantor: TS.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee (no. 250/20) of Ulm University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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