Cardiovascular outcome 6 months after severe coronavirus disease 2019 infection

Original Article

INFOGRAPHIC

Cardiovascular outcome 6 months after severe coronavirus disease 2019 infection

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Objectives: In coronavirus disease 2019 (COVID-19), cardiovascular risk factors and myocardial injury relate to increased mortality. We evaluated the extent of cardiac sequelae 6 months after hospital discharge in patients surviving ICU hospitalization for COVID-19.

Methods: All survivors of Maastricht-ICU were invited for comprehensive cardiovascular evaluation 6 months after discharge from ICU. Cardiac screening included an electrocardiogram, cardiac biomarkers, echocardiography, cardiac magnetic resonance (CMR) and, wherever indicated, cardiac computed tomography or coronary angiogram.

Results: Out of 52 survivors, 81% ($n = 42$) participated to the cardiovascular follow-up [median follow-up of 6 months, interquartile range (IQR) 6.1–6.7]. Eight patients (19%) had newly diagnosed coronary artery disease (CAD), of which two required a percutaneous intervention. Echocardiographic global longitudinal strain (GLS) was abnormal in 24% and CMR-derived GLS was abnormal in 12%, despite normal left ventricular ejection fraction in all. None of the patients showed elevated T_1 relaxation times and five patients (14%) had an elevated T_2 relaxation time. Late gadolinium enhancement (LGE) reflecting regional myocardial fibrosis was increased in eight patients (21%), of which three had myocarditis and three had pericarditis.

Conclusion: Cardiovascular follow-up at 6 months after ICU-admission for severe COVID-19 revealed that one out of five invasively mechanically ventilated survivors had CAD, a quarter had subclinical left ventricular dysfunction defined as reduced echocardiographic GLS, and 42% of the patients had CMR abnormalities (reduced LVEF, reduced GLS, LGE presence, and elevated T_2). On the basis of these findings, long-term cardiovascular follow-up is strongly recommended in all post-IC COVID-19 patients.

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Keywords: cardiac injury, cardiac MRI, coronavirus disease 2019, echocardiography, electrocardiography

Abbreviations: CAD, coronary artery disease; CMR, cardiac magnetic resonance; COVID-19, coronavirus disease 2019; GLS, global longitudinal strain; LGE, late gadolinium enhancement

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 [SARS-CoV-2, coronavirus disease (COVID-19)] resulted in an unprecedented challenge to the healthcare community with considerable morbidity and mortality worldwide [1,2]. On the one hand, patients with preexisting cardiovascular disease (CVD) tend to have a more severe disease course, and on the other hand, COVID-19 may worsen underlying CVD or even precipitate de novo cardiac complications [3–6]. Several studies reported that, during hospitalization, higher concentrations of cardiac biomarkers (i.e. troponin), indicating myocardial injury, were associated with higher mortality [2,7,8]. A surprisingly high number (78%) of mostly home recovered ambulatory patients with COVID-19 disease had abnormal findings on cardiac MRI (CMR) 3 months after COVID-19 infection [9]. These abnormalities included signs of myocardial fibrosis, inflammation, lower left ventricular ejection fraction (LVEF) (although still within normal ranges) compared with a matched control group. Whether COVID-19 has long-term cardiac implications, including significant coronary artery disease, myocarditis, or cardiac dysfunction, is currently unknown, as data on cardiovascular follow-up beyond 3 months are currently lacking. Therefore, we invited all COVID-19 patients, previously admitted to the ICU, for a comprehensive cardiovascular follow-up program, 6 months after discharge, including ECG, biomarker

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assessment, CMR, echocardiography, and coronary computed tomography (CT), if indicated.

METHODS

A detailed description of the methods is provided in the Supplemental Material, http://links.lww.com/HJH/B900 [10–21].

Study design and population

This study is a follow-up study on the prospective, longitudinal Maastricht Intensive Care COVID (MaastriCCht) cohort. All patients with COVID-19 treated in our ICU between March and May 2020 were prospectively included in the MaastriCCht cohort [Trial Register number (NL8613)]. Patients who survived invasive mechanical ventilation during ICU admission with proven COVID-19 infection based on at least one positive PCR for SARS-CoV-2 and/or a chest CT scan strongly suggestive for SARS-CoV-2 infection (CORADS scores 4–5) were included [22,23]. All ICU survivors ($n = 52$) who participated in the ICU follow-up at 3 months ($n = 48$) were invited for comprehensive cardiac work-up at 6 months, including medical history taking, querying cardiovascular risk factors (such as hypertension, hypercholesterolemia, diabetes mellitus), laboratory measurements, ECG, echocardiography, and CMR (Fig. 1). Data registry adhered to the FAIR data principle and the study adhered to the regulations of Helsinki [22]. The institutional review board of Maastricht University Medical Center+ (Maastricht UMC+) approved the study protocol (METC2020-2287/300769).

Biomarkers

Venous blood was sampled on the same day as echocardiography was performed. Our centers' reference values of parameters that are used in this study are: hs-TnT less than 14 ng/l, creatin kinase less than 225 U/l, NTproBNP less than 35 pmol/l, CRP less than 10 mg/l.

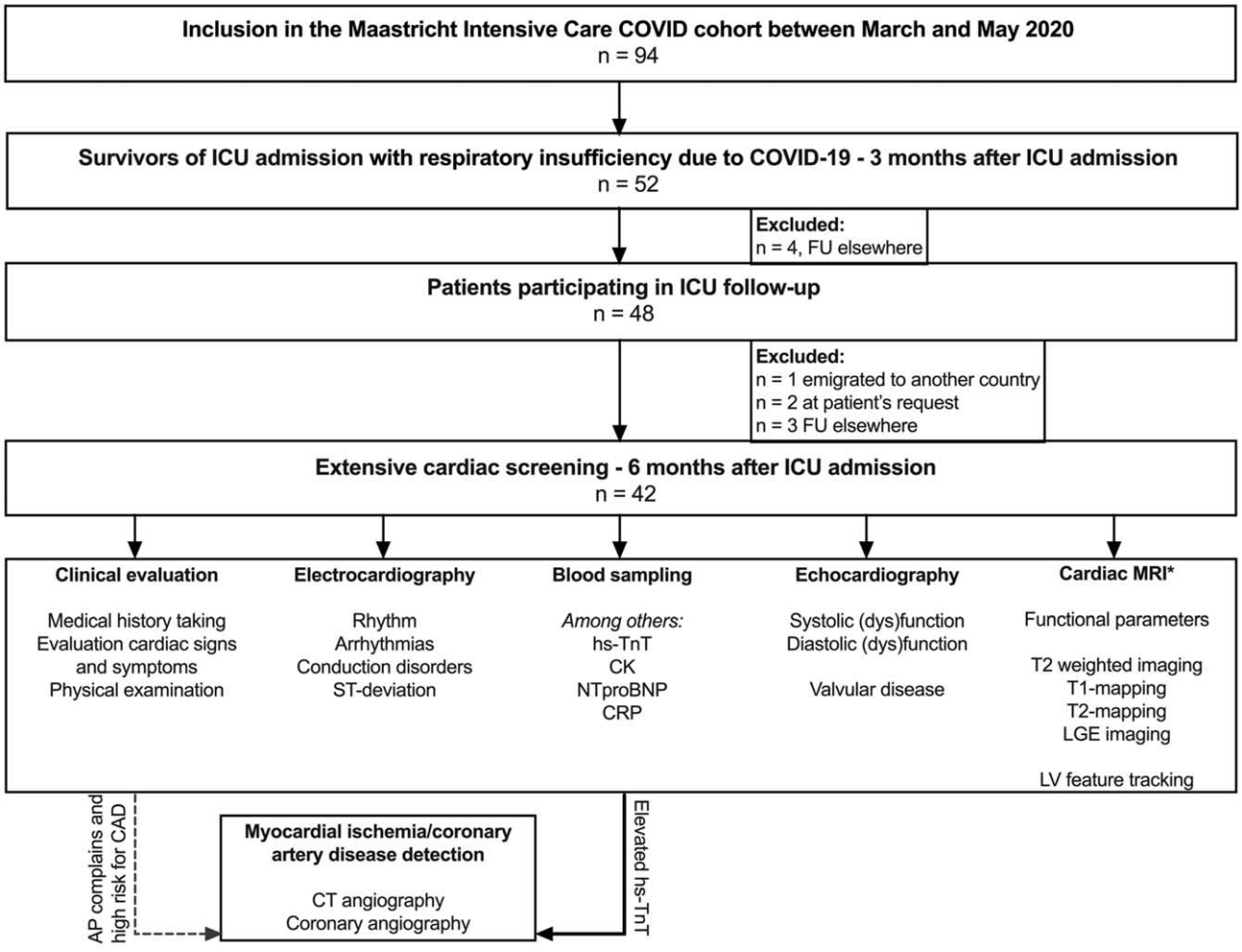

FIGURE 1 Flowchart of diagnostic work-up of all post-IC coronavirus disease survivors. During the first European pandemic wave between March and May 2020, the MaastriCCht cohort included 94 patients. Fifty-two patients were alive after 3 months of whom 48 participated in follow-up at 3 months (4 patients had follow-up elsewhere at 3 months). At 6 months after hospital discharge, 42 patients participated in the cardiac follow-up. One patient emigrated to another country, 2 patients did not undergo cardiac follow-up at their request, and 3 patients attended follow-up elsewhere. In total, 42 post-COVID-19 ICU survivors underwent cardiac screening. ∗Four patients had a contraindication for CMR [claustrophobia $n = 3$ and cardiac resynchronization therapy (CRTP), $n = 1$), resulting in 38 patients with CMR findings. AP, angina pectoris; CAD, coronary artery disease; CK, creatin kinase; CRP, C-reactive protein; CT, computed tomography; FU, follow-up; hs-TnT, high-sense troponin T; LGE, late gadolinium enhancement; LV, left ventricular; NTproBNP, natriuretic peptide.

Electrocardiography

All patients underwent a 12-lead ECG. An appropriate scoring system was predesigned (Appendix, http://links.lww.com/HJH/B900) by a team of four physicians, including a cardiologist specialized in clinical electrophysiology (K.V.), a cardiologist-intensivist (R.D.), a cardiologist in training (C.G.) and a clinical researcher (M.G.) in the field of COVID-19. ECG characteristics were systematically scored based on rhythm, conduction times, ST-deviation and T-wave abnormalities, and left ventricular (LV) hypertrophy.

Echocardiographic measurements

Echocardiographic measurements were performed on a phased-array echocardiographic Doppler system (iE33 system with S5-1 or X5-1 transducers, Philips Medical Systems, Best, the Netherlands), following the latest guidelines for cardiac chamber quantification [13]. Presence of diastolic dysfunction was defined as significant cardiac structural [increased left atrial volume index (LAVI) >34 ml/m^2 or left ventricle mass index (LVMI) ≥115 g/m^2 for men or ≥95 g/m^2 for women] or functional abnormalities [mean *E/é* ≥13and/or mean *é* septal and lateral wall <9 cm/s). Two-dimensional speckle tracking echocardiography (STE) was performed in the apical two-chamber, three-chamber, and four-chamber views [17]. The measurements were performed offline using dedicated software (TomTec Arena v2.0, TomTec imaging Systems, Unterschleissheim, Germany) by one trained investigator (A.R.).

Cardiac MRI

CMR was performed on a 1.5 Tesla system (Ingenia; Philips Medical Systems) equipped with a 32-channel torso coil. The acquisition protocol included cine imaging, late gadolinium enhancement (LGE) imaging to detect focal fibrosis, T_2 weighted imaging, native [5(3)3] and postcontrast [4(1)3(1)2] modified look-locker inversion (MOLLI) T_1 mapping, and gradient spin echo (GraSE) T_2 mapping. T_1 maps were acquired during a breath-hold. T_2 maps were acquired during a breath-hold or, alternatively, with a navigator when the breath-hold could not be completed. The postcontrast T_1 map was acquired approximately 10 min after an intravenous bolus of 0.2 mmol/kg body weight gadobutrol (Gadovist; Bayer Healthcare, Berlin, Germany) contrast injection. Immediately afterwards, LGE CMR was performed 10–15 min after an intravenous bolus of 0.2 mmol/kg body weight gadobutrol (Gadovist; Bayer Healthcare). LGE was considered present if observed in multiple views andextending beyond right ventricular (RV) insertion areas. T_1 and T_2 relaxation times were derived using dedicated software (Intellispace 11.2.40; Philips Medical Systems). A region of interest was drawn in the mid-septal area. The underlying images from which T_1 maps were reconstructed were subjected to automated translational motion correction to ensure that the different images are co-registered to each other. Three patients exhibited signs of late gadolinium enhancement in the septum. Therefore, these areas were excluded from the region of interest. We determined the highest segmental T_2 relaxation time as the changes in T_2 relaxation time may not be diffuse. For this purpose, the entire myocardium was delineated on the mid-ventricular short-axis slice and divided into six segments according to the American Heart Association (AHA) model. Values for T_1 and T_2 relaxation times were considered to be abnormal if they were larger than the mean + 2SDs compared with reference values from previous reports [abnormal T_1 and T_2:T_1 > 1077 ms for women, T_1 > 1047 ms for men [24]; T_2 > 67.6 ms for women, T_2 > 64.5 ms for men [19]. Myocardial strain measurements were performed offline using dedicated software (CAAS MR Solutions 5.2.1; Pie Medical Imaging, The Netherlands) by one trained independent investigator (Y.B.). Reference values for abnormal strain parameters for peak GLS and GCS were obtained from previous reports [20].

Pericarditis was defined as pericardial enhancement involving both pericardial layers. Active myocarditis was defined as the presence of nonischemic LGE in combination with associated signal intensity increase of T_2-weighted edema images. Healed (previous) myocarditis was defined as the presence of nonischemic pattern of LGE possibly matching with myocarditis, without increased signal intensity of T_2-weighted edema images [21].

Detection of coronary artery disease

All patients with typical angina pectoris complaints or elevated high-sensitivity troponin (hs-TnT) at 6 months follow-up underwent a computed tomography angiogram (CTA) and/or a coronary angiogram to detect coronary artery disease (CAD) (Fig. 1). As decided by our heart team, a percutaneous coronary intervention (PCI) was performed in case of significant CAD.

Statistical analysis

Variables are displayed as numbers (percentage), mean ± standard deviation, or median (IQR) as appropriate. Comparisons between groups were performed using χ^2 tests (or Fisher exact) for categorical data and independent *t*-test or Mann–Whitney *U*-test for continuous data, as appropriate. We considered a two-sided *P* value less than 0.05 to be statistically significant. All computations were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, New York, USA).

RESULTS

Patients' characteristics

During the first European pandemic wave between March and May 2020, the MaastriCCht cohort included 94 patients. Fifty-two patients were alive at 3 months follow-up, four attended follow-up elsewhere, and 48 attended the 3 months ICU follow-up in our hospital, of whom 42 patients participated in the cardiac follow-up at 6 months and were included in the current analysis (Fig. 1). Four patients had a contraindication for CMR [claustrophobia $n = 3$ and cardiac resynchronization therapy (CRTP), $n = 1$], resulting in 38 patients with CMR. Follow-up occurred at a median 6.4 (IQR 6.1–6.7) months after hospital discharge.

The mean age in our cohort was 64 ± 13 years, and male sex predominated (69%, Table 1). Medical history of cardiac disease (atrial fibrillation, coronary artery disease, cardiomyopathy or valvular disease) was reported in five patients (11%). At least one preexistent cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes mellitus,

TABLE 1. Clinical characteristics of the study population at 6 months follow-up

	All ($n = 42$)	Normal hs-TnT ($n = 30$)	Elevated hs-TnT ($n = 12$)	*P* value
Age, mean ± SD (years)	**64 ± 13**	62 ± 15	67 ± 7	0.27
Male sex, No. (%)	**29 (69)**	19 (63)	10 (83)	0.28
BMI, mean ± SD, (kg/m^2)	**28 ± 5**	28 ± 5	28 ± 4	0.98
ICU hospitalisation				
Origin of admission [No. (%)]				
Emergency department [No. (%)]	**10 (24)**	5 (17)	5 (38)	0.17
Hospital ward [No. (%)]	**22 (54)**	16 (53)	6 (50)	
Transfer from another ICU [No. (%)]	**10 (24)**	9 (30)	1 (8)	
APACHE II score on admission, median (IQR)	**16 (13–18)**	16 (13–17)	15 (11–19)	0.92
Invasive mechanical ventilation [No. (%)]	**42 (100)**	30 (100)	12 (100)	1.00
hs-TnT, median (IQR) (ng/l)	**35 (23–74)**	27 (19–52)	61 (39–101)	0.03
Minimum–maximum (ng/l)	**10–1125**	10-1125	16–234	
Length of ICU stay, median (IQR) (days)	**21 (11–33)**	19 (10–24)	34 (14–41)	0.02
Duration from intubation to follow-up (months) median (IQR)	**7.3 (6.8–7.7)**	7.2 (6.8–7.6)	7.6 (6.6–8.0)	0.27
Duration from discharge to follow-up (months), median (IQR)	**6.4 (6.1–6.7)**	6.4 (6.2–6.7)	6.4 (6.1–6.8)	0.67
Cardiovascular medical history				
Atrial fibrillation [No. (%)]	**2 (5)**	1 (3)	1 (8)	0.50
Coronary artery disease [No. (%)]	**1 (2)**	0	2 (17)	0.08
Cardiomyopathy [No. (%)]	**2 (5)**	2 (7)	0	1.00
Valvular disease [No. (%)]	**0**	0	0	
Cardiovascular risk factors				
Hypertension [No. (%)]	**12 (29)**	7 (23)	5 (3)	0.27
Hypercholesterolemia [No. (%)]	**6 (14)**	5 (17)	1 (8)	0.66
Diabetes mellitus type II [No. (%)]	**4 (10)**	3 (10)	1 (8)	1.00
Obesity [No. (%)]	**13 (31)**	9 (30)	4 (33)	1.00
COPD [No. (%)]	**0**			
Clinical presentation at 6 months follow-up				
NYHA class III or IV [No. (%)]	**11 (26)**	8 (27)	3 (25)	1.00
Chest pain [No. (%)]	**9 (21)**	6 (20)	3 (25)	0.70
Palpitations [No. (%)]	**6 (14)**	5 (17)	1 (8)	0.66
SBP, mean ± SD (mmHg)	**142 ± 42**	141 ± 49	145 ± 15	0.76
DBP, mean ±SD (mmHg)	**77 ± 30**	77 ± 35	77 ± 11	0.95
Heart rate, mean ± SD, BPM	**72 ± 30**	70 ± 34	78 ± 14	0.48
Signs of decompensation cordis [No. (%)]	**1 (2)**	1 (3)	0	1.00
Blood test results at six months follow-up				
CK, median (IQR) (U/l)	**84 (70–149)**	97 (73–143)	75 (64–174)	0.43
Elevated [No. (%)]	**4 (10)**	2 (7)	2 (17)	0.57
NTproBNP, median (IQR) (pmol/l)	**8 (4–14)**	7 (4–11)	13 (6–31)	0.04
Elevated [No. (%)]	**6 (14)**	3 (10)	3 (25)	0.33
CRP, median (IQR) (mg/l)	**2 (0–24)**	2 (0–4)	2 (0–33)	0.77
Elevated [No. (%)]	**3 (7)**	0	3 (25)	0.02
hs-TnT, median (IQR) (ng/l)	**10 (7–16)**	7 (6–10)	22 (16–39)	<0.001
Minimum–maximum (ng/l)	**4–114**	4–14	15–114	
Coronary artery disease detection				
Detection of CAD performed [No. (%)]	**10 (24)**	1/30 (3)	9 (75)	<0.01
No CAD [No. (%)]	**2/10 (20)**	0	2/9 (22)	0.11
Nonsignificant CAD [No. (%)]	**6/10 (60)**	0	6/9 (67)	
Significant CAD [No. (%)]	**2/10 (20)**	1/1 (100)	1/9 (11)	
PCI [No. (%)]	**2/10 (20)**	1/1 (100)	1/9 (11)	1.00
Electrocardiography				
Rhythm				
Sinus rhythm [No. (%)]	**41 (98)**	29 (97)	12 (100)	1.00
Atrial fibrillation [No. (%)]	**1 (2)**	1 (3)	0	
Atrial flutter [No. (%)]	**0**	0	0	
Atrial tachycardia [No. (%)]	**0**	0	0	
Escape rhythm [No. (%)]	**0**	0	0	
Paced rhythm [No. (%)]	**0**	0	0	
Conduction times				
PR time, mean ± SD (ms)	**161 ± 23**	159 ± 24	167 ± 20	0.35
High-degree atrioventricular-block [No. (%)]	**0**			
QRS duration, mean ± SD (ms)	**93 ± 13**	91 ± 10	98 ± 18	0.11
QT time, mean ± SD (ms)	**384 ± 29**	283 ± 28	388 ± 30	0.55
QTc time, mean ± SD (ms)	**431 ± 27**	428 ± 22	437 ± 38	0.32
Extended QTc time [No. (%)]	**0**			
RR interval, mean ± SD (ms)	**805 ± 143**	807 ± 143	801 ± 150	0.90
Left bundle branch block [No. (%)]	**2 (5)**	1 (3)	1 (8)	0.50
Right bundle branch block [No. (%)]	**0**	0	0	-

TABLE 1 (*Continued*)

	All ($n = 42$)	Normal hs-TnT ($n = 30$)	Elevated hs-TnT ($n = 12$)	*P* value
ST-deviation	**13 (31)**	8 (27)	5 (42)	0.46
ST-elevation in at least two leads [No. (%)]	**7 (17)**	3 (10)	4 (33)	0.09
ST-depression in at least two leads [No. (%)]	**11 (26)**	7 (23)	4 (33)	0.70
T-wave abnormalities [No. (%)]	**24 (57)**	16 (53)	8 (77)	0.51
T-wave inversion in at least two leads [No. (%)]	**7 (17)**	4 (13)	3 (25)	0.39
Flat T-waves in at least two leads [No. (%)]	**18 (43)**	13 (43)	5 (42)	1.00
Biphasic T-waves in at least two leads [No. (%)]	**3 (7)**	2 (7)	1 (8)	1.00
Signs of hypertrophy [No. (%)]	**6 (14)**	4 (13)	2 (17)	1.00
Echocardiography				
Left ventricular ejection fraction, mean ± SD (%)	**57 ± 5**	58 ± 5	56 ± 5	0.15
Left ventricular end-diastolic diameter, indexed, mean ± SD (mm/m^2)	**24 ± 3**	24 ± 2	24 ± 3	0.30
Left ventricular end-systolic diameter, indexed, mean ± SD (mm/m^2)	**15 ± 9**	16 ± 4	12 ± 16	0.18
Interventricular septal thickness, mean ± SD (mm)	**8.6 ± 1.0**	8.5 ± 1.0	8.8 ± 1.0	0.48
Left ventricular posterior wall thickness, mean ± SD (mm)	**8.4 ± 1.1**	8.3 ± 0.9	8.7 ± 1.5	0.39
Relative wall thickness (mean ± SD)	**0.36 ± 0.06**	0.36 ± 0.05	0.37 ± 0.08	0.69
Left ventricular mass index (mean ± SD) (g/m^2)	**69 ± 15**	67 ± 14	75 ± 16	0.17
Left atrial volume index (mean ± SD) (ml/m^2)	**18.6 ± 2.6**	18.4 ± 2.6	19.1 ± 2.7	0.53
Right atrial volume index (mean ± SD) (ml/m^2)	**24.9 ± 9.2**	23.5 ± 8.1	27.9 ± 10.9	0.21
Vena cava inferior, diameter (mean ± SD) (mm)	**15.9 ± 4.8**	15.8 ± 5.1	16.3 ± 3.6	0.81
Vena cava inferior, collapse (mean ± SD) (%)	**73 ± 14**	73 ± 16	72 ± 8	0.88
Estimated right ventricular pressure (mean ± SD) (mmHg)	**27.6 ± 5.8**	27.9 ± 6.1	26.7 ± 5.2	0.66
Mitral early filling (E) (mean ± SD) (cm/s)	**62.5 ± 13.3**	64.2 ± 13.5	58.1 ± 12.4	0.18
Mitral active filling (A), (mean ± SD) (cm/s)	**71.5 ± 16.7**	72.2 ± 17.9	69.8 ± 13.8	0.69
Mitral *E/A* ratio (mean ± SD)	**0.91 ± 0.29**	0.94 ± 0.32	0.84 ± 0.19	0.30
E/e (mean ± SD)	**7.99 ± 2.21**	7.98 ± 2.23	8.00 ± 2.27	0.98
Diastolic function				
Normal [No. (%)]	**27 (64)**	19 (63)	8 (67)	0.78
Type 1 (abnormal) [No. (%)]	**12 (29)**	8 (27)	4 (33)	
Type 2 (pseudo normal) [No. (%)]	**1 (2)**	1 (3)	0	
Type 3 (restrictive) [No. (%)]	**0**	0	0	
Mitral early deceleration time (mean ± SD) (ms)	**195 ± 35**	189 ± 36	205 ± 34	0.40
Tricuspid regurgitation (mean ± SD) (ms)	**2.37 ± 0.27**	2.38 ± 0.27	2.33 ± 0.27	0.69
Global longitudinal strain (GLS) (mean ± SD) (%)	**-20 ± 5**	-21 ± 5	-20 ± 4	0.55
Abnormal GLS [No. (%)]	**9/38 (24)**	5/26 (19)	4/12 (33)	0.42

Reference values of blood test parameters in our center: hs-TnT less than 14 ng/l, CK less than 225 U/l, NTproBNP less than 35 pmol/l, CRP less than 10 mg/l. Numbers in bold are the descriptives of the total study population. The *P*-value depicts the significance of the difference between patients with normal and elevated hs-TnT. CAD, coronary artery disease; CK, creatin kinase; CRP, C-reactive protein; hs-TnT, high-sensitivity troponin; NTproBNP, natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

obesity, smoking) was present in 21 patients (50%). NYHA class III or IV was reported by 11 (26%) of patients, and one (2%) patient had signs of decompensation cordis. Thirty (71%) patients had one or more cardiac symptoms, such as chest pain, dyspnea d'effort or palpitations. Data stratified for sex are reported in Online Tables 1–4, http://links.lww.com/HJH/B900.

Laboratory findings

During ICU admission, most of the patients had elevated hs-TnT values [$n = 38$ (90%), median 35 ng/l, IQR 23–74] but maximum hs-TnT values during admission were significantly higher in the patients who had remaining elevated hs-TnT values at follow-up ($P = 0.03$, Table 1). At 6 months follow-up, median concentrations of hs-TnT, CK and NTproBNP and CRP were 10 (IQR 7–16) ng/l with a maximum of 114 ng/l, 84 (70–149) U/l, 8 (4–14) pmol/l, and 2 [0–24] mg/l, respectively (Table 1). NTproBNP was elevated (≥35 pmol/l) in six patients (14%), and in five of these patients, HF medical therapy was initiated [i.e. diuretics, angiotensin-converting enzyme inhibitor (ACE-i), angiotensin receptor blocker (ARB)]. Hs–TnT was elevated (≥ 14 ng/l) in 12 patients (29%). Patients with elevated hs-TnT were slightly older, had more often elevated CRP, more often ST-segment deviation, although not matching ST-elevation myocardial infarction, and significantly higher LVMI but within normal ranges (Tables 1 and 2).

Electrocardiographic findings

All but one patient were in sinus rhythm. Atrial fibrillation was present in one patient (2%). LBBB was present in two patients (5%, Table 1). ST-segment deviation was present in 30 (71%) patients. Signs of LV hypertrophy were present in six patients (15%).

Coronary artery disease detection

Of the 12 patients with elevated hs-TnT, we performed CAD detection in nine patients that were all suffering from typical chest pain or ECG abnormalities. Three patients with elevated hs-TnT did not have any complaints associated with CAD nor ECG abnormalities, therefore, no CAD detection was performed in these patients. One patient with very typical angina pectoris and ECG abnormalities but normal hs-TnT, underwent CAD detection. Thus, 10 out of 42 patients (24%) underwent CAD detection with either CTA and/or CAG. Six patients (14% of total population) showed

TABLE 2. Cardiac magnetic resonance parameters of all patients 6 months after ICU admission

	All ($n = 38$)	Normal hs-TnT ($n = 27$)	Elevated hs-TnT ($n = 11$)	*P* value
Functional parameters				
LVEF, mean ± SD (%)	**60 ± 6**	60 ± 6	59 ± 5	0.59
LVEDVi, mean ± SD (ml/m^2)	**75 ± 15**	74 ± 16	79 ± 10	0.27
LVESVi, mean ± SD (ml/m^2)	**30 ± 7**	29 ± 8	32 ± 5	0.30
LVmass, indexed, mean ± SD (g/m^2)	**49 ± 11**	46 ± 9	55 ± 12	0.03
LV stroke volume, mean ± SD (ml)	**90 ± 24**	89 ± 25	93 ± 21	0.63
Late gadolinium enhancement (LGE)				
LGE present [No. (%)]	**8 (21)**	7 (26)	1 (9)	0.40
LGE distribution (% of patients with LGE) [No. (%)]				
Ischemic (subendocardial/transmural) [No. (%)]	**1 (13)**	1 (14)	0	1.00
Nonischemic (sub)epicardial [No. (%)]	**4 (50)**	4 (57)	0	0.31
Nonischemic midmyocardial [No. (%)]	**8 (100)**	7 (16)	1 (100)	0.25
Pericardial enhancement [No. (%)]	**2 (25)**	2 (7)	0	1.00
Patchy [No. (%)]	**2 (25)**	1 (14)	1 (100)	0.50
LGE location (% of patients with LGE) [No. (%)]				
Septal [No. (%)]	**3 (38)**	3 (43)	0	0.38
LV lateral wall [No. (%)]	**3 (38)**	3 (43)	0	
Both [No. (%)]	**0**	0	0	
Other [No. (%)]	**2 (25)**	1 (14)	1 (100)	
Tissue characterization				
T1 relaxation time, mean ± SD (ms)	**987 ± 31**	989 ± 33	983 ± 27	0.62
Elevated T_1 [No. (%)]	**0**	0	0	1.00
T2 relaxation time, mean ± SD (ms)	**50.8 ± 5.6**	49.2 ± 4.3	54.3 ± 6.7	0.01
Elevated T2 [No. (%)]	**5/36 (14)**	2/25 (8)	3/11 (27)	0.15
T2 weighted imaging abnormal (%)	**1 (3)**	1 (4)	0	0.64
Signs of pericarditis [No. (%)]	**2 (5)**	2 (7)	0	1.00
Signs of (previous) myocarditis [No. (%)]	**3 (8)**	3 (11)	0	1.00
Left ventricular strain parameters				
Global longitudinal strain (GLS), mean ± SD (%)	**-15 ± 4**	-16 ± 4	-14 ± 3	0.20
Abnormal GLS [No. (%)]	**4/33 (12)**	2/24 (8)	2/9 (22)	0.30
Global circumferential strain (GCS), mean ± SD (%)	**-15 ± 3**	-15 ± 3	-13 ± 2	0.09
Abnormal GCS [No. (%)]	**24/33 (73)**	16/24 (67)	8/9 (89)	0.38

EDVi, end-diastolic volume, indexed; EF, ejection fraction; ESVi, end-systolic volume, indexed; LGE, late gadolinium enhancement; LV, left ventricular.

nonsignificant CAD, whereas two patients (5% of total population) showed significant CAD followed by a PCI (the other patients were treated conservatively with medication (Table 1).

Echocardiography findings

All echocardiographic parameters are presented in Table 1. Mean LVEF was 57 ± 5%. A mildly reduced LVEF (<50%) was present in two patients (45 and 48%, respectively). No patients presented with LV dilation, and no patients fulfilled the criteria for diastolic dysfunction. STE GLS was measured in 38 patients. In four patients, image quality was too bad (≥2 segments, not visual). Mean GLS was −20 ± 5%. GLS was abnormal in nine of 38 patients (24%), all of whom were men. Two male patients had signs of mild LV hypertrophy (LVMI109 and 94 g/m^2), accompanied by hypertension without elevated NTproBNP or other structural or functional abnormalities. Only one patient had signs of increased filling pressure combined with elevated NTproBNP (despite normal LVEF and GLS) and was treated with heart failure (HF) therapy. No clinically relevant valvular disease was observed on echocardiography.

Cardiac MRI

In total, 38 out of 42 (90%) patients underwent CMR (Table 2). Mean LVEF on cardiac MRI was 60 ± 6%. Only one patient had a mildly reduced LVEF (49%) on CMR. LV dilation or LV hypertrophy was absent (Fig. 2). In eight (21%) patients, LGE was present. Most patients had LGE in the septal or lateral LV wall ($n = 6$) with a predominant nonischemic, mid-myocardial pattern (Table 2). Intriguingly, the presence of (predominantly nonischemic) LGE was only seen in patients who were not evaluated for CAD and did not have elevated hs-TnT. In total, five (13%) patients had signs of inflammatory cardiac disease (myocarditis or pericarditis as defined in the methods), accompanied by LGE presence. Of the patients with LGE, qualitative CMR analyses revealed signs of healed myocarditis in two male patients and active myocarditis in one male patient [21]. Interestingly, none of these patients had elevated troponins suggesting myocardial damage at six months follow-up. These patients did have elevated hs-TnT during their initial ICU admission (maximum values of 20, 25 and 49 ng/l, respectively); however, these values were not substantially higher compared with the patients without signs of myocarditis. Also, no important ECG abnormalities (i.e. ST-elevation or ST-depression and T-wave inversion) were found on the ECGs of patients with myocarditis signs during ICU admission.

Of the 36 patients examined with T_2 mapping, 33 were analyzed using the images that were acquired during a breath-hold. Three patients were analyzed using the images that were acquired with a navigator, two because of poor image quality in the breath-hold acquisition, and one because of the absence of a breath-hold T_1 map. None

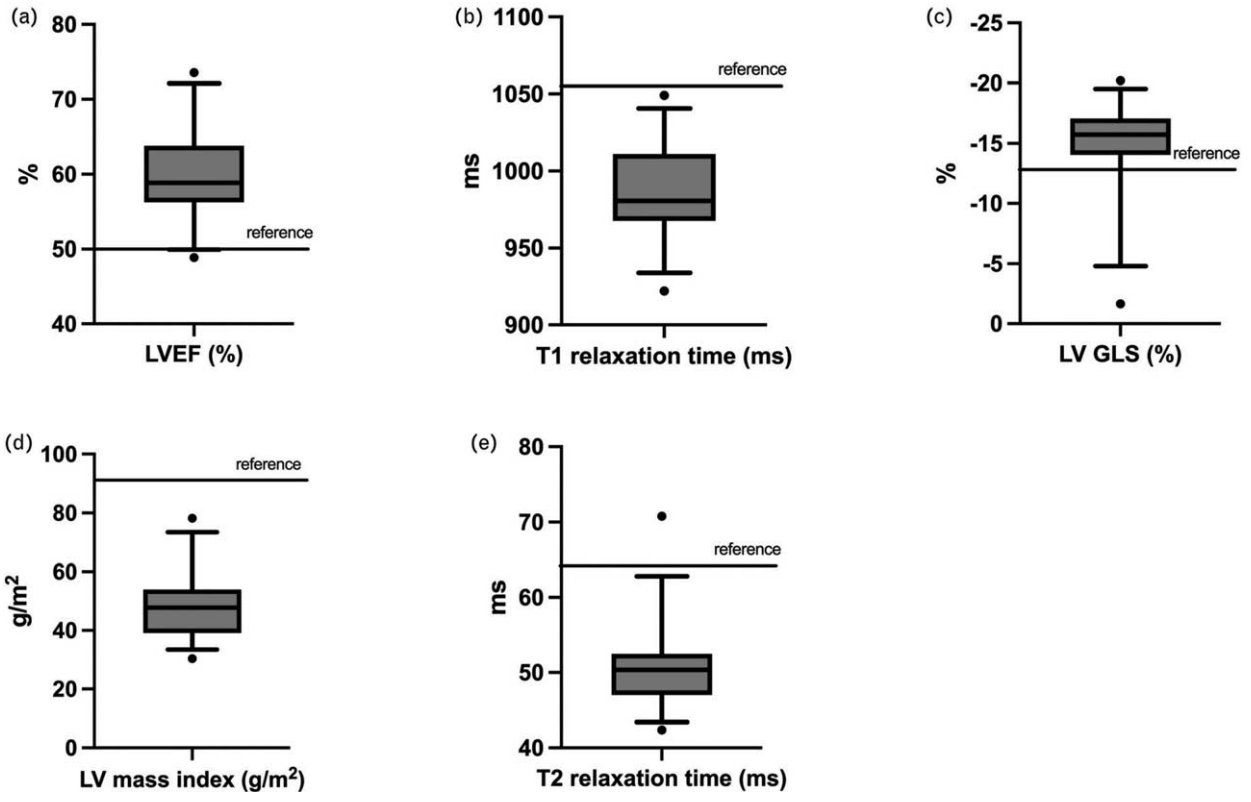

FIGURE 2 Boxplots of cardiac magnetic resonance tissue characterization parameters. (a) LVEF was normal in almost all patients, (b) T1 relaxation time was elevated in 0% of the patients, (c) CMR-derived LV GLS was abnormal in 12% of the patients, (d) no patients showed signs of LV hypertrophy based on LV mass index, (e) T2 relaxation time was elevated in two patients showing signs of myocarditis. CMR, cardiac magnetic resonance; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular.

of the patients showed elevated T_1 relaxation times and elevated T_2 relaxation times was found in 5 of the 36 patients (14%). Two male patients had signs of active pericarditis, including pericardial enhancement, accompanied with dyspnea d'effort but not chest pain. None of these patients had elevated hs-TnT at 6 months follow-up.

Myocardial strain assessment was performed in 33 of the 38 patients with MRI. Images were not available for offline analysis in two patients, and in three patients, the image quality was too poor to perform strain analysis. Mean GLS was $-15 \pm 4\%$ and was abnormal in four out of 33 (12%) of the patients, based on previously published sex-specific reference values (cutoff point for abnormality was defined as worse than −2SD) [20]. None of the four patients with abnormal CMR-derived GLS had LGE presence or elevated T_1 relaxation time and one patient had elevated T_2 relaxation time.

Interventions after cardiac screening

The cardiac screening resulted in the following interventions: in 11 patients (26%), antihypertensive medication was initiated in the context of cardiovascular risk management, one patient (2%) received diuretics for HF signs and symptoms (without echocardiographic signs of HF), in 10 patients (25%) statin therapy was initiated, and seven patients (17%) started with anti-ischemic therapy of which five only pharmacological therapy and two a combination of medication and PCI.

DISCUSSION

We performed a comprehensive clinical cardiac diagnostic work-up in post-COVID-19 patients 6 months after discharge from the ICU as a prospective follow-up on the MaastrICCht cohort study [22,25–27]. First, we found that approximately one-third ($n = 12$) of the patients had elevated cardiac troponins, resulting in newly diagnosed CAD in two-third of these cases ($n = 8$, 19% of total population). Second, 42% of the patients had abnormal CMR findings, including regional myocardial LGE ($n = 8$, 24%) with predominantly a nonischemic distribution pattern, of which two patients had CMR signs of pericarditis, and three patients had CMR signs of myocarditis. Although elevated cardiac troponins were indicative for CAD, it did not relate to the imaging diagnosis of (peri)myocarditis. Third, subclinical systolic dysfunction measured by echocardiographic GLS was present in 24% and whenever measured by CMR-derived feature tracking in 12%.

Myocardial injury during and after coronavirus disease 2019

For the past year, multiple studies [28–33] focused on the incidence of cardiac complications during the initial hospitalization for COVID-19 infection, whereas studies on the long-term cardiac sequelae, especially in severe COVID-19 patients requiring ICU admission, are scarce [34]. In most COVID-19 studies, myocardial injury was defined as a

concentration of troponin above the 99th centile and is reported to be elevated in up to 30%, especially in patients admitted to the ICU [2,5,35]. Elevated cardiac troponins in hospitalized COVID-19 patients are associated with a 10-fold higher mortality rate compared with patients with normal cardiac troponin levels and are among the most important mediators of in-hospital mortality [7,29,36]. Nevertheless, the prognosis of patients with underlying CVD but without myocardial injury was relatively favorable [36]. This suggests a cumulative role for myocardial injury over sole preexistent CVD.

Left ventricular hypertrophy, systolic and diastolic dysfunctions

It has been hypothesized that the downregulation of ACE-2 by SARS-CoV-2 may lead to increased microvascular damage, myocardial hypertrophy, atrial dilatation, and diastolic dysfunction during COVID-19 infection [37,38]. In our study, the prevalence of LV hypertrophy (4%), atrial dilatation (0%) and diastolic dysfunction (0%) were low. Our findings suggest that the 'swollen heart' observed during acute infection [39] may regress at longer term after discharge in ICU survivors. However, this hypothesis may still be relevant during active infection and in those that did not survive the disease [40].

Only two out of 42 patients had reduced LVEF at 6 months follow-up. Importantly, echocardiographic GLS was impaired in 24% of the patients [18], whereas CMR-derived GLS is impaired in 12% [20]. Previous studies showed that 80% of patients hospitalized with COVID-19 had reduced GLS during active infection, and that this is associated with worse outcome [41,42]. However, an overall improvement of GLS was observed 2 months after COVID-19 infection [43]. Still, GLS values were lower compared with a healthy control group at 4 months post-COVID-19 infection [44].

In addition to impaired GLS, Puntmann *et al.* [9] reported abnormal CMR findings in 79% of the cases 3 months after infection, including myocardial inflammation, regional LGE and pericardial enhancement. Although 50% of their study population did not require hospitalization and we, by contrast, studied the most severely affected patients, we found a significantly lower prevalence of CMR characteristics, such as elevated T_1, T_2 or presence of LGE, indicating inflammation or fibrosis. In our cohort, the prevalence of LGE was 24%, which is lower than 58% reported by Puntmann *et al.* [9] and lower than 32% reported by Huang *et al.* [45]. Differences may be explained by the timing of follow-up and the higher incidence of cardiovascular medical history in the previous studies compared with our study. Intriguingly, myocardial inflammation was seen in 60% 1–3 months after COVID-19 infection [9], whereas in our study, a much lower incidence of active myocardial inflammation was observed (2%). The same accounts for elevated T_1 relaxation times, which were found in 73% of the COVID-19 patients, 3 months after infection [9], whereas at 6 months follow-up, we did not find elevated T_1 values in our study population, suggesting that presence of diffuse fibrosis might disappear during recovery. This difference might also be explained by the fact that internal reference ranges for T_1 mapping were used.

In addition to structural abnormalities, we did find elevated cardiac troponins in one-third of the study population, of which 70% had CAD requiring pharmacological and/or percutaneous interventions. This number is much higher compared with Kotech *et al.*, who found ischemic heart disease in 25% of 148 COVID-patients with elevated troponins 2 months after infection [32]. However, in the latter, ischemic heart disease was only based on CMR imaging, and no CAG was performed in these patients. Also, only one-third required ICU admission for ventilation support, so their study population likely reflects a less severe patient population compared with our study population.

It is unknown to which extent these cardiac complications are related to COVID-19 disease rather than critical illness or even a reflection of preexisting comorbidities that could make patients prone to a more severe course of disease [46]. Nevertheless, a recent report investigating the 6 months' consequences of COVID-19 concerning functional complaints and pulmonary function showed that more severely ill patients had an increased risk of post-COVID medical complications and that this severely ill patient population should be the main target population for long-term follow-up [47].

Strengths and limitations

We present a comprehensive long-term cardiovascular follow-up, 6 months postinfection embedded within a prospective cohort study. Moreover, we assessed a population with a homogenous severity of the disease being the most severely affected COVID-19 patients that required invasive mechanical ventilation. Our study's limitation is the lack of pre-COVID measurements and a control group, hampering comparison with a study population with comparable comorbidities. Therefore, we could not elaborate on whether these abnormalities are induced by COVID-19 infection, critical illness or partly preexistent. Nevertheless, the high prevalence of inflammatory (subclinical) LV impairment and CAD in this specific (seemingly recovered) population emphasizes the importance of cardiovascular follow-up in COVID-19 patients [34]. CAD detection was performed in a minority of patients at 6 months follow-up, when there was biochemical or clinical suspection. Nonetheless, one can assume that amongst the rest there will also be an incidence of asymptomatic CAD that might be disproportionately high compared with other less severe COVID groups. However, we cannot draw firm conclusions as most of the patients did not undergo CAD detection. We could not perform extracellular volume mapping on CMR as hematocrit values were not determined at the same day as the CMR and a derivation cohort to estimate synthetic ECV was not available. Nineteen percentage of the patients was lost-to-follow-up between ICU discharge and 6 months follow-up. Most of these patients attended follow-up in their regional hospital as they were transferred to our ICU during their hospitalization. No significant or clinically relevant differences in ICU admission characteristics were seen between lost-to-follow-up patients and patients that underwent cardiac screening (Supplemental Table 5, http://links.lww.com/HJH/B900). Therefore, either underestimation or overestimation of cardiac consequences because of loss-to-follow-up seems unlikely.

Perspectives

Over 35% of invasively mechanically ventilated survivors of severe COVID-19 had cardiac abnormalities after extensive cardiovascular follow-up, stressing the need for long-term cardiovascular follow-up. Although these results indicate that a substantial part of ICU-survivors after COVID-19 had cardiac abnormalities, data on the long-term cardiovascular effects of COVID-19 disease are still scarce. New (long-term) clinical observational studies and trials are needed and will lead to better understanding of which patients should be screened for post-COVID-19 myocardial injury and dysfunction.

In conclusion, at 6 months after COVID-19 infection, one out of five invasively mechanically ventilated survivors of COVID-19 had CAD, a quarter of the patients had subclinical left ventricular dysfunction defined as reduced echocardiographic GLS, and 42% of the patients had CMR abnormalities (reduced LVEF, reduced GLS, LGE presence, or elevated T_2). In a substantial part of these patients, interventions, such as initiation of cardiac medication and PCI followed on findings of the cardiac screening. Our findings reveal that cardiac injury, whether subclinical present before COVID-19 infection, is common in patients that were admitted to the ICU because of severe COVID infection. Our findings stress the need for long-term cardiovascular follow-up after ICU admission. Nevertheless, studies evaluating the possible causal relation between COVID-19 infection and cardiovascular involvement are still needed.

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Conflicts of interest

There are no conflicts of interest.

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