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RESEARCH ARTICLE

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Incidence and risk factors of myocarditis in hospitalized patients with COVID-19

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Abstract

Myocarditis as cardiac involvement in coronavirus disease 2019 (COVID-19)-infection is well known. Real-world data about incidence in hospitalized COVID-19-patients and risk factors for myocarditis in COVID-19-patients are sparse. We used the German nationwide inpatient sample to analyze all hospitalized patients with confirmed COVID-19-diagnosis in Germany in 2020 and stratified them for myocarditis. Overall, 176 137 hospitalizations (52.3% males, 53.6% aged ≥70 years) with confirmed COVID-19-infection were coded in Germany in 2020 and among them, 226 (0.01%) had myocarditis (incidence: 1.28 per 1000 hospitalization-cases). Absolute numbers of myocarditis increased, while relative numbers decreased with age. COVID-19-patients with myocarditis were younger (64.0 [IQR: 43.0/78.0] vs. 71.0 [56.0/82.0], $p < 0.001$). In-hospital case-fatality was 1.3-fold higher in COVID-19-patients with than without myocarditis (24.3% vs. 18.9%, $p = 0.012$). Myocarditis was independently associated with increased case-fatality (OR: 1.89 [95% CI: 1.33–2.67], $p < 0.001$). Independent risk factors for myocarditis were age <70 years (OR: 2.36 [95% CI: 1.72–3.24], $p < 0.001$), male sex (1.68 [95% CI: 1.28–2.23], $p < 0.001$), pneumonia (OR: 1.77 [95% CI: 1.30–2.42], $p < 0.001$), and multisystemic inflammatory COVID-19-infection (OR: 10.73 [95% CI: 5.39–21.39], $p < 0.001$). The incidence of myocarditis in hospitalized COVID-19-patients in Germany was 1.28 cases per 1000 hospitalizations in 2020. Risk factors for myocarditis in COVID-19 were young age, male sex, pneumonia, and multisystemic inflammatory COVID-19-infection. Myocarditis was independently associated with increased case-fatality.

KEYWORDS

COVID-19, incidence, infection, myocarditis, SARS-CoV-2

1 | INTRODUCTION

In December 2019, first patient cases of pneumonia caused by a previously unknown virus were detected in Wuhan, China.[1–3] This was the starting point of the coronavirus disease 2019 (COVID-19)-pandemic with a never seen infectious disease burden and impact on the healthcare systems worldwide.[3] The first severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections in Germany were reported on January 27, 2020.[4–6] From this initial cluster in Bavaria, a sustained transmission of SARS-CoV-2 was followed by a substantial spread of COVID-19 in the German population.[5,7]

COVID-19 is frequently accompanied by symptoms like fever, cough, sore throat, malaise, myalgias, and dyspnea.[6,8–10] The infection affects the lungs primarily and can result in pneumonia, respiratory failure, and other lung manifestations.[5,8,9,11] Besides the lung as the primary localization, COVID-19 might also lead to acute cardiac, kidney, and liver injury.[8] Cardiac complications, particularly myocarditis, and pericarditis, were associated with SARS-CoV-2 infection.[5,10,12,13] Viral infections are frequent causes of myocarditis, an inflammation of the myocardium, which may result in hospitalization, and heart failure, and can be followed by sudden death.[10,14,15]

Before the COVID-19 pandemic, the estimated global incidence of myocarditis ranged between 1 and 10 cases per 100 000 persons per year, with the highest risk for people aged between 20 and 40 years.[10,15–17] The growing use of cardiac MRI during the last decades led to an increase in the detection regarding the incidence of myocarditis in the United States.[10] During the COVID-19 pandemic, one multicenter study including centers of different European countries and the US showed a prevalence of myocarditis ranging between 2.4 cases of definite or probable myocarditis and 4.1 cases of definite, probable or possible myocarditis per 1000 patients hospitalized for COVID-19.[13] [1,1] One previously published study focusing on in-hospital mortality of myocarditis patients in Germany described that the burden of patients with myocarditis and COVID-19 in 2020 was low. Still, in-hospital mortality was more than sixfold higher in patients with myocarditis and COVID-19 compared to those with myocarditis but without COVID-19.[18] In contrast, the Center of Disease Control (CDC) reported a 42.3% increase in myocarditis in hospitalized patients during the year 2020 in comparison to 2019, analyzing the US hospital-based administrative database of healthcare from more than 900 hospitals during March 2020 and January 2021.[14] Data for Europe comparing COVID-19 patients with and without myocarditis are sparse.[19–21] In addition, it is of high interest to identify risk factors and predisposing parameters for the development of myocarditis caused by SARS-CoV-2.

2 | METHODS

2.1 | Data source

The statistics were computed on our behalf by the Research Data Center (RDC) of the Federal Bureau of Statistics in Wiesbaden, Hessen (Germany). Aggregated statistical results were provided from RDC based on our generated SPSS codes (IBM Corp.; Released 2011; IBM SPSS Statistics for Windows; Version 20.0.; IBM Corp.) for analyzing the German nationwide inpatient sample (NIS) (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2020, own calculations).[22,23]

With this data analysis of the German nationwide inpatient sample (NIS), we aimed to analyze the incidence of myocarditis in all hospitalized patients with a confirmed COVID-19 diagnosis (ICD-code U07.1) during the observational period between January 1 and December 31 of the year 2020 and identify independent predictors of myocarditis in this vulnerable patient group.

2.2 | Study oversight and support

No commercial support and no funding were received for the present study and no foreign influence regarding the preparation of this paper/report was detected. Since our study did not comprise a direct access by us investigators on individual patient data (but only an access to summarized results provided by the RDC), approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law.[22,23]

2.3 | Coding of diagnoses, procedures, and definitions

Since the introduction of the diagnosis- and procedure-related remuneration system in the year 2004 in Germany, German hospitals have to code patients' data on diagnoses, coexisting conditions, and surgeries as well as on procedures/interventions according to the German Diagnosis Related Groups (G-DRG) system and transfer these codes to the Institute for the Hospital Remuneration to get their remuneration.[9,10] Patients' diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, with German modification (ICD-10-GM). In contrast, surgical, diagnostic, and interventional procedures were coded according to OPS codes (Operationen- und Prozedurenschlüssel).[9,10] For our present analysis, we selected and included all hospitalized patients with a confirmed COVID-19 diagnosis (ICD-code U07.1) in Germany during the year 2020 (COVID-19 as main or secondary diagnosis) and stratified these included patient cases for the presence of acute myocarditis (ICD code I40).

2.4 | Study outcomes

The primary study outcome was detected myocarditis and its calculated incidence related to the total number of hospitalizations. In addition, death of any cause during the hospital stay (in-hospital death) was defined as the further main study outcome.

2.5 | Definitions

In Germany, making the myocarditis diagnosis is based on the recommendation of the current ESC guidelines.[24,25] Obesity was defined as a body mass index ≥30 kg/m² as recommended by the WHO (World Health Organization). Major adverse cardiac and cerebrovascular events (MACCE, including in-hospital death, myocardial infarction [ICD code I21], and/or ischemic stroke [ICD code I63]). Stroke comprised both stroke entities: ischemic and hemorrhagic stroke. Post-COVID was defined as a status of a previously survived COVID-19 infection before the patient's hospitalization with the recurrent COVID-19 infection.

2.6 | Statistical analysis

Differences in patient characteristics between the groups of hospitalized Covid-19-patients with and without myocarditis were calculated with Wilcoxon–Whitney *U* test for continuous variables and Fisher's exact or χ^2 test for categorical variables, as appropriate. Temporal trends regarding myocarditis cases in COVID-19 patients over time and with increasing age were estimated using linear regression analyses. Results were presented as β-estimates and 95% confidence intervals (CI). Logistic regression models were calculated to investigate associations between patients' characteristics as well as adverse events and myocarditis. In addition, logistic regression models were used to identify associations between myocarditis in COVID-19 patients with in-hospital case fatality. Results of the logistic regression models were presented as odds ratios (OR) and 95% CI. To ensure that the results of the mentioned logistic regressions are not substantially influenced by biasing factors (guarantying a wide independence of different important cofactors), the multivariable logistic regressions were adjusted for age, sex, diabetes mellitus, cancer, heart failure, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, chronic renal insufficiency (glomerular filtration rate <60 mL/min/1.73 m²), atrial fibrillation/flutter, hyperlipidaemia, and obesity.

All statistical analyses were carried out using SPSS software (IBM Corp.; Released 2011; IBM SPSS Statistics for Windows; Version 20.0.; IBM Corp.). Only *p* values of <0.05 (two-sided) were considered to be statistically significant.

3 | RESULTS

In total, 176 137 hospitalizations (52.3% males, 53.6% aged ≥70 years) with confirmed COVID-19 infection were coded in Germany in 2020. Among them, 226 (0.01%) were diagnosed with myocarditis (Table 1), corresponding to 1.28 cases per 1000 hospitalization cases.

The highest absolute number of myocarditis cases was seen during spring (March/April) and winter (November/December), with monthly numbers of more than 40 cases per month (Figure 1). Taking all months into consideration, the total numbers decreased over time (*β*: −1.778 [95% CI: −2.192 to −1.365], $p < 0.001$). The highest relative monthly numbers of myocarditis were found during summer (June), with 0.4% of all hospitalized COVID-19 patients (Figure 1). During March and October, ≥50% of the treated COVID-19 patients with myocarditis were admitted to an intensive care unit, whereas in the other months, relative numbers were lower. The case fatality rate of hospitalized COVID-19 patients with myocarditis was 34.8%, highest in November and 30.2% in March, and lowest during December at 15.9%.

Absolute numbers of hospitalized COVID-19 patients with myocarditis increased distinctly, whereas relative numbers decreased with age decades and were highest during the first two decades of life (Figure 1). The in-hospital case-fatality rate increased substantially with age from 0% in the second, third, and fourth decade to 70% in the tenth decade of life (*β*: 2.060 [95% CI: 1.406–2.713], $p < 0.001$) with the highest admission rate of hospitalized COVID-19 patients with myocarditis on intensive care in the sixth age-decade (Figure 1).

COVID-19 patients with myocarditis were in median 7 years younger than those without (64.0 [IQR: 43.0/78.0] vs. 71.0 [56.0/82.0], $p < 0.001$) (Table 1). The proportion of male COVID-19 patients was with 65.9% higher in those patients with myocarditis than in those without (53.3%). As expected, the length of in-hospital stay was longer in myocarditis patients than in non-myocarditis patients (11.0 [IQR: 6.0/20.3] vs. 8.0 [4.0/14.0], $p < 0.001$). The severe respiratory manifestations of SARS-CoV-2 infection like pneumonia and acute respiratory distress syndrome were both more frequent in patients with myocarditis.

The Charlson comorbidity index showed a similar comorbidity profile ($p = 0.845$), whereby important cardiac comorbidities such as coronary artery disease (19.9% vs. 14.5%, $p = 0.021$), heart failure (34.5% vs. 15.5%, $p < 0.001$), and atrial fibrillation/flutter (24.8% vs. 19.4%, $p < 0.040$) were more common in COVID-19 patients with myocarditis than in those COVID-19 patients without (Table 1). Regarding the interventional diagnostic approach, COVID-19 patients with myocarditis underwent more frequent endomyocardial biopsy (2.65% vs. 0.02%, $p < 0.001$).

COVID-19 patients with myocarditis were more often admitted to the intensive care units (44.2% vs. 15.3%, $p < 0.001$), has more often to be ventilated (19.9% vs. 6.9%, $p < 0.001$) and more frequently treated with extracorporeal membrane oxygenation (ECMO) and dialysis (Table 1). Tocilizumab was more often administered in COVID-19-patients with compared to those without myocarditis (2.2% vs. 0.1%, $p < 0.001$).

The in-hospital case fatality rate was 1.36-fold higher in COVID-19 patients with than without myocarditis (24.3% vs. 18.9%, $p = 0.012$). MACCE, venous thromboembolism, myocardial infarction occurred all more often in COVID-19 patients with myocarditis (Table 1).

The logistic regressions revealed that myocarditis was associated with an increase of case-fatality in COVID-19 patients

TABLE 1 Patients' characteristics, medical history, presentation, and adverse in-hospital events of the 176 137 hospitalized patients with confirmed COVID-19 infection in Germany in the year 2020 stratified for myocarditis.

Parameters	COVID-19 without myocarditis (*n* = 175 911; 99.9%)	COVID-19 with myocarditis (*n* = 226; 0.01%)	*p* Value
Age	71.0 (56.0/82.0)	64.0 (43.0/78.0)	**<0.001**
Age ≥ 70 years	94 239 (53.6%)	90 (39.8%)	**<0.001**
Female sex	83 872 (47.7%)	77 (34.1%)	**<0.001**
In-hospital stay (days)	8.0 (4.0/14.0)	11.0 (6.0/20.3)	**<0.001**
Cardiovascular risk factors			
Obesity	9366 (5.3%)	17 (7.5%)	0.141
Diabetes mellitus	45 178 (25.7%)	54 (23.9%)	0.539
Essential arterial hypertension	82 394 (46.8%)	86 (38.1%)	**0.008**
Hyperlipidaemia	27 552 (15.7%)	21 (9.3%)	**0.008**
Comorbidities			
Coronary artery disease	25 529 (14.5%)	45 (19.9%)	**0.021**
Heart failure	27 041 (15.4%)	78 (34.5%)	**<0.001**
Peripheral artery disease	5636 (3.2%)	4 (1.8%)	0.339
Atrial fibrillation/flutter	34 104 (19.4%)	56 (24.8%)	**0.040**
Chronic obstructive pulmonary disease	12 143 (6.9%)	11 (4.9%)	0.294
Chronic renal insufficiency (glomerular filtration rate < 60 mL/min/1.73 m²)	27 332 (15.5%)	40 (17.7%)	0.370
Cancer	8993 (5.1%)	8 (3.5%)	0.363
Charlson comorbidity index	4.0 (2.0/6.0)	4.0 (1.0/6.0)	0.845
Respiratory manifestations of COVID-19			
Pneumonia	106 754 (60.7%)	159 (70.4%)	**0.003**
Acute respiratory distress syndrome	11 529 (6.6%)	65 (28.8%)	**<0.001**
Myocardial biopsy			
Myocardial biopsy	30 (0.02%)	6 (2.65%)	**<0.001**
Treatment			
Intensive care unit	26 953 (15.3%)	100 (44.2%)	**<0.001**
Mechanical ventilation	12 097 (6.9%)	45 (19.9%)	**<0.001**
Extracorporeal membrane oxygenation (ECMO)	1449 (0.8%)	5 (2.2%)	**0.041**
Dialysis	5548 (3.2%)	27 (11.9%)	**<0.001**
Adverse events during hospitalization			
In-hospital case-fatality	31 552 (17.9%)	55 (24.3%)	**0.012**
MACCE	34 958 (19.9%)	66 (29.2%)	**<0.001**
Cardio-pulmonary resuscitation	2843 (1.6%)	16 (7.1%)	**<0.001**
Venous thromboembolism	4970 (2.8%)	17 (7.5%)	**<0.001**
Acute kidney failure	21 996 (12.5%)	79 (35.0%)	**<0.001**
Myocardial infarction	2739 (1.6%)	14 (6.2%)	**<0.001**
Transfusion of blood constituents	13 823 (7.9%)	51 (22.6%)	**<0.001**

Note: *p* values of <0.05 were considered to be statistically significant.

Abbreviations: COVID-19, coronavirus disease 2019; MACCE, major adverse cardiac and cerebrovascular events.

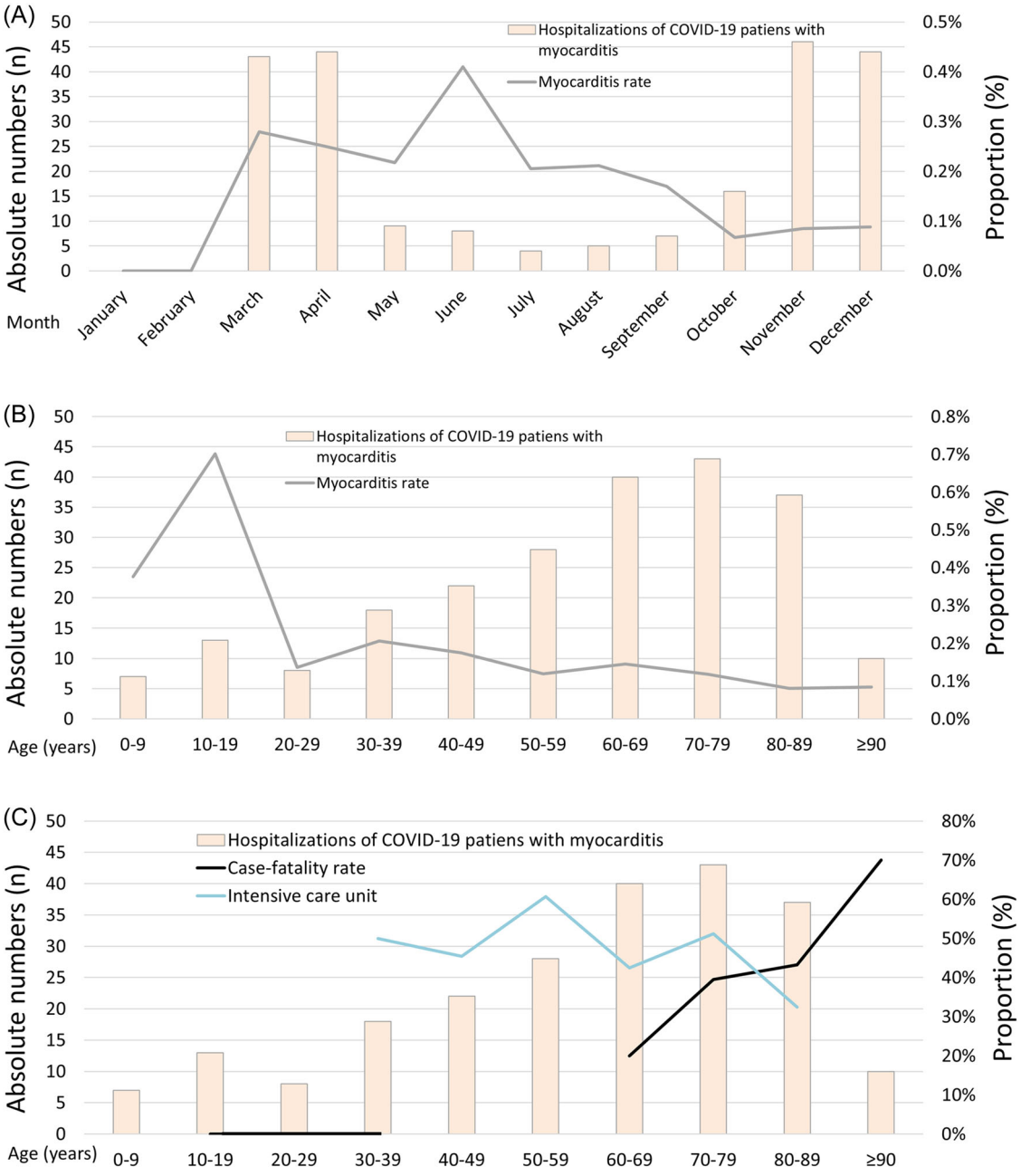

FIGURE 1 Temporal trends regarding absolute and relative numbers of hospitalized patients with COVID-19-infection and myocarditis in Germany 2020. (A) Temporal trends regarding absolute and relative numbers of hospitalized patients with COVID-19-infection and myocarditis stratified for months. (B) Temporal trends regarding absolute and relative numbers of hospitalized patients with COVID-19-infection and myocarditis for age decades. (C) Temporal trends regarding absolute numbers of hospitalized patients with COVID-19-infection and myocarditis, rate of intensive care unit admissions as well as case-fatality rate for age decades. COVID-19, coronavirus disease 2019.

independently of age, sex, and comorbidities (univariate regression: OR: 1.472 [95% CI: 1.086–1.995], $p = 0.013$, multivariate regression: OR: 1.887 [95% CI: 1.325–2.686], $p < 0.001$). In addition, myocarditis was independently related to the occurrence of venous thromboembolism (univariate regression: OR: 2.798 [95% CI: 1.705–4.590], $p < 0.001$, multivariate regression: OR: 2.569 [95% CI: 1.561–4.229], $p < 0.001$).

Independently associated factors with myocarditis in COVID-19 patients were age <70 years (OR: 2.364 [95% CI: 1.724–3.236], $p < 0.001$), male sex (1.683 [95% CI: 1.276–2.227], $p < 0.001$), coronary artery disease (OR: 1.479 [95% CI: 1.013–2.159], $p = 0.043$), heart failure (OR: 4.536 [95% CI: 3.207–6.414], $p < 0.001$), pneumonia (OR: 1.774 [95% CI: 1.303–2.415], $p < 0.001$), and multisystemic inflammatory

COVID-19 infection (OR: 10.734 [95% CI: 5.388–21.386], $p < 0.001$) (Table 2).

4 | DISCUSSION

In the present study, we sought to determine the incidence of myocarditis in hospitalized COVID-19 patients in Germany and to identify risk factors and predisposing parameters for the development of myocarditis caused by SARS-CoV-2.

The key results of the analyses can be summarized as follows: (I) The incidence of myocarditis in hospitalized COVID-19 patients was 1.28 cases per 1000 hospitalizations. (II) We detected seasonal differences regarding the incidence of myocarditis, with the highest relative numbers in the summer. (III) The highest necessity of intensive care unit admissions of COVID-19 patients with myocarditis was seen during spring. In contrast, the highest case-fatality rate of this vulnerable patient group was detected in March and November and the lowest during December. (IV) The relative numbers of myocarditis in COVID-19 patients were highest during the first two decades of life, whereas the in-hospital case-fatality rate increased substantially with age. (V) COVID-19 patients with myocarditis had more often intensive care unit and ventilation treatment. (VI) The in-hospital case-fatality rate was 1.36-fold higher in COVID-19 patients with than without myocarditis. (VII) Myocarditis was associated with a 1.5-fold increase of case-fatality in COVID-19 patients independently of age, sex, and comorbidities and with a 2.8-fold increase regarding the occurrence of venous thromboembolism. (VIII) Independently associated factors with myocarditis in COVID-19 patients were age <70 years, male sex, coronary artery disease, heart failure, pneumonia, and multisystemic inflammatory COVID-19 infection.

Viral infection is a frequent cause of myocarditis leading to hospitalizations, heart failure, and can be followed by sudden

TABLE 2 Risk factors for myocarditis in COVID-19-patients (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model[a]	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age (per year)	0.983 (0.977–0.988)	**<0.001**	0.972 (0.965–0.979)	**<0.001**
Age ≥70 years	0.574 (0.439–0.749)	**<0.001**	0.423 (0.309–0.580)	**<0.001**
Female sex	0.567 (0.431–0.747)	**<0.001**	0.594 (0.449–0.784)	**<0.001**
Cardiovascular risk factors				
Obesity	1.446 (0.882–2.372)	0.144	1.234 (0.746–2.040)	0.413
Diabetes mellitus	0.908 (0.669–1.234)	0.539	0.922 (0.661–1.286)	0.633
Essential arterial hypertension	0.697 (0.533–0.912)	**0.009**	1.022 (0.759–1.377)	0.884
Hyperlipidaemia	0.552 (0.352–0.864)	**0.009**	0.497 (0.309–0.801)	**0.004**
Comorbidities				
Coronary artery disease	1.465 (1.056–2.030)	**0.022**	1.479 (1.013–2.159)	**0.043**
Heart failure	2.901 (2.205–3.818)	**<0.001**	4.536 (3.207–6.414)	**<0.001**
Peripheral artery disease	0.544 (0.202–1.464)	0.228	0.434 (0.159–1.188)	0.104
Atrial fibrillation/flutter	1.370 (1.012–1.853)	**0.041**	1.335 (0.934–1.907)	0.113
Chronic obstructive pulmonary disease	0.690 (0.376–1.265)	0.230	0.605 (0.326–1.123)	0.111
Chronic renal insufficiency (glomerular filtration rate <60 mL/min/1.73 m²)	1.169 (0.831–1.645)	0.371	1.081 (0.734–1.593)	0.692
Cancer	0.681 (0.336–1.380)	0.286	0.750 (0.369–1.523)	0.426
Charlson comorbidity index	1.005 (0.961–1.050)	0.843	-	
Respiratory manifestations of COVID-19				
Pneumonia	1.537 (1.155–2.046)	**0.003**	1.774 (1.303–2.415)	**<0.001**
Multisystemic inflammatory COVID-19 infection	14.909 (7.609–29.212)	**<0.001**	10.734 (5.388–21.386)	**<0.001**
Post-COVID-19 status	1.402 (0.196–10.012)	0.736	1.384 (0.193–9.908)	0.746

Note: *p* values of <0.05 were considered to be statistically significant.

Abbreviation: COVID-19, coronavirus disease 2019.

[a]Adjusted for age, sex, diabetes mellitus, cancer, heart failure, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, chronic renal insufficiency (glomerular filtration rate <60 mL/min/1.73 m²), atrial fibrillation/flutter, hyperlipidemia, and obesity.

death.[10,14,15] Regarding COVID-19-infection, cardiac involvement, including myocarditis, is a well-known phenomenon and complication in patients suffering from COVID-19.[5,8,10,12,13] We detected an incidence of 1.28 myocarditis cases per 1000 hospitalized COVID-19 patients, which is slightly lower than the reported 2.4 cases of definite or probable myocarditis and 4.1 cases of definite, probable, or possible myocarditis per 1000 patients hospitalized for COVID-19 in a multicenter study of centers of different European countries and the US.[10,13] This higher incidence of myocarditis might be explained by differences in patient characteristics between both studies, in particular by the lower age of hospitalized COVID-19 patients in the study of Ammirati et al. (median age: 38 vs. 64 years) and maybe also by higher use of cardiac MRI in the United States.[10,13] Another important difference between the previously published studies and our study is that myocarditis incidence of COVID-19 patients in the studies of Ammirati et al.[13] and McNamara et al.[26] might be already influenced by the rising vaccination program during the study period (study period: February 1, 2020 and April 30, 2021—since the vaccination program against SARS-CoV-2 started in most European countries, including Germany, and the US in December 2020).[26] In contrast, since the observational period of our study, comprised the entire year 2020, we analyzed the risk for myocarditis in an almost entirely vaccinated-naïve population, and a significant impact on the myocarditis risk can be neglected, which is a strength of our study.[27] Regarding the influence of vaccination, an extensive nationwide study of more than 23 million residents vaccinated with SARS-CoV-2 mRNA vaccines revealed an only small impact of vaccination on myocarditis development.[19] Karlstad et al. reported that both first and second doses of mRNA vaccines were associated with an increased risk of myocarditis as well as pericarditis.[19] For individuals receiving two doses of the same mRNA vaccine, risk for myocarditis was highest in young males after the second dose.[19] SARS-CoV-2 mRNA vaccination with use of a mRNA vaccine was attributed to an excess of 4–7 events in 28 days per 100 000 vaccines after BNT162b2 (Pfizer–BioNTech), and between 9 and 28 excess events per 100 000 vaccines after mRNA-1273 (Moderna).[19] In line with the mentioned study, Oster et al. described results of a very large study including more than 192 400 000 persons receiving 354 100 845 mRNA-based COVID-19 vaccinations between December 2020 and August 2021 in the United States of America.[28] The authors reported that the large majority of myocarditis cases occurred after the second vaccination dose, and in younger and male individuals.

The relative numbers of myocarditis cases after the second vaccination with BNT162b2 (Pfizer–BioNTech) was 0.97 per 100 000 vaccines and 0.51 after the second vaccination with mRNA-1273 (Moderna) during the first 7 days after the vaccination.[28] Thus, an impact of vaccination-associated myocarditis cases in the studies of Ammirati et al.[13] and McNamara et al.[26] has to be suggested, especially in light of increasing vaccination numbers during early 2021.[26] These mentioned incidences of myocarditis after SARS-CoV-2 vaccination[19,28] are distinctly lower than the detected 1.28 myocarditis cases per 1000 hospitalized COVID-19 patients observed in our study. Similarly, authors of a large systematic review and meta-analysis reported that the risk of myocarditis is more than sevenfold higher in individuals infected with the SARS-CoV-2 than in those who received a SARS-CoV-2 vaccine, which supports the CDC and WHO recommendations to continue COVID-19 vaccination program.[20,29]

As expected, absolute numbers of COVID-19 patients suffering from myocarditis increased with growing numbers of hospitalization cases in older age decades, while the relative age-dependent incidence of myocarditis was highest in the first two decades of life. Remarkably, the in-hospital case-fatality rate of COVID-19 patients with myocarditis increased substantially with age. This age-dependency of myocarditis in COVID-19 patients was also seen for myocarditis in the general population[10,14,30] of other studies as well as postvaccination myocarditis.[19,28,31–35] Significantly young male individuals were affected by myocarditis after SARS-CoV-2-vaccination.[33,34] The observation of our study strengthens the hypothesis that younger COVID-19 patients have a higher risk of developing a myocarditis, but myocarditis has a higher harmfulness in older patients with COVID-19.

The proportion of female COVID-19 patients with myocarditis was similar to that reported by Ammirati et al. (34.1% vs. 38.9%)[13] and comparable to myocarditis caused by other pathogens than SARS-CoV-2.[15,36–38]

Our study demonstrated that the highest absolute numbers of myocarditis cases were seen during spring (March/April) and in winter (November/December), along with the highest numbers of hospitalized COVID-19 patients[5,18] and thus, following the seasonal variations of viral infections.[18,27] In this context, the highest relative numbers of myocarditis, in turn, were identified in the summer, suggesting that in summer was the risk of developing myocarditis at its maximum. COVID-19 patients with myocarditis were more frequently treated in intensive care units and had to be ventilated compared to COVID-19 patients without myocarditis. The highest necessity of intensive care unit treatment was seen in patients with myocarditis during the spring 2020. It is well known that the highest case-fatality rate of COVID-19 patients treated in intensive care units was seen during the spring and winter of year 2020, when intensive care unit demands were highest.[27,39,40] This finding is not only of great interest for adequate pandemic management,[27] but might explain a higher rate of detected myocarditis in hospitalized COVID-19 patients during the summer months. Since a lower in-hospital mortality rate during the first 2 days of the in-hospital course of these critically ill patient-group of COVID-19 patients on ICUs and more diagnostic and timing options during periods with lower intensive care unit demands in the summer might be related to higher rate regarding identification of myocarditis in the summer months.

Tocilizumab, as a treatment approach for adults with severe COVID-19 and/or with high levels of systemic inflammatory indices in light of rapidly worsening clinical condition, was administered 22.1-fold more commonly in COVID-19-patients with than without myocarditis.[41–43] This treatment seems to be in this critically ill patient-group of COVID-19 patients with myocarditis of outstanding importance since myocarditis might a sign of systemic inflammation

in COVID-19 patients. Studies have demonstrated that tocilizumab improved survival and other clinical outcomes in hospitalized COVID-19 patients with hypoxia and systemic inflammation.[44] These benefits were observed regardless of the intensity of respiratory support and were added to the benefits of systemic corticosteroids.[44]

ECMO as a rescue treatment for acute respiratory failure was 2.8-fold more often used in COVID-19 patients than without myocarditis.[9]

The in-hospital case-fatality rate was 1.3-fold higher in COVID-19 patients with than without myocarditis. We identified a case-fatality rate of 24.3% in patients with confirmed COVID-19 diagnosis by laboratory test and myocarditis, which is lower than in the in-hospital mortality rate of COVID-19-patients with myocarditis in the United States (31.5%),[45] but higher than the previously published 13.5% in the study of Bemtgen et al.[18] (also examining the German nationwide inpatient cohort) but including in contrast to our analysis not only patients with confirmed COVID-19 diagnosis by laboratory test (but also patients with suspicion of COVID-19 and typical symptoms without definite confirmation of COVID-19) as well as post-COVID myocarditis.[18] The laboratory confirmation of COVID-19 is an important criteria of this study and a key strength of our and the study of the US.[45] Our results were supported by an analysis of the NIS from the US, revealing that in-hospital mortality of COVID-19 patients with myocarditis was higher in comparison to those COVID-19 patients without myocarditis (OR: 1.59 [95% CI: 1.27–1.90])[45] and that in-hospital mortality of patients with COVID-19 and myocarditis was higher compared to those patients with myocarditis, but without COVID-19 infection (30.7% vs. 6.4%, OR: 4.8, 95% CI: 3.7–6.3, $p < 0.001$).[46]

In accordance with other studies,[45] our study demonstrated that myocarditis was associated with a 1.5-fold increase of case-fatality in COVID-19 patients independently of age, sex, and comorbidities and with 2.8-fold in-crease regarding occurrence of venous thromboembolism. It is well known that COVID-19 is associated with venous thromboembolism,[47–51] myocarditis seems to increase this risk further.

The most important key finding of our study was the identification of independent risk factors for the development of myocarditis, which comprises age <70 years, male sex, pneumonia, and multisystemic inflammatory COVID-19 infection. Several studies showed that younger age, as well as male sex, are risk factors for the development of myocarditis in COVID-19.[13,14,18] In addition and in concordance with our findings, previously published literature also points to an interaction between other infections, such as pneumonia as well as multisystemic inflammatory COVID-19 infection and myocarditis.[14,52] This is an important finding since mortality in COVID-19 patients has been linked to a "cytokine storm" induced by the SARS-CoV-2. Excessive production of proinflammatory cytokines might result in acute respiratory distress syndrome and widespread tissue damage, including myocardium, and may be followed by multiorgan failure and death.[9,53] It might be one treatment approach to target involved cytokines while managing COVID-19 patients to reduce mortality.[9,53] Further associated factors with myocarditis in COVID-19 patients were coronary artery disease and heart failure. Although coronary artery disease is not mechanistically related to myocarditis and the presence of coronary artery disease might instead reflect a sicker patient population, some studies revealed that global biventricular dysfunction in patients with severe asymptomatic coronary artery disease but without evidence of previous myocardial infarction may be caused by myocarditis.[54]

This detection of risk factors for the development of myocarditis in COVID-19 patients is essential to identify patients who might benefit from further examinations or treatments.

4.1 | Limitations

Some limitations of our study require consideration: First, one major limitation is that the mentioned study results are based on ICD discharge codes, which might result in incomplete data set due to under-reporting or under-coding. Second, clinical data like information about troponins, echocardiograms, or most concomitant medications are not available and therefore missing for additional analyses. Third, although it has to be suggested that myocarditis diagnosis was made according the recommendation of the current ESC guidelines,[24,25] nevertheless, since we had only access to aggregated data provided by the RDC and the authors didn't have direct access to individual patient charts, the exact parameters on which the myocarditis diagnosis was based on could not be assessed. This had to be considered as a major limition of our study.

5 | CONCLUSION

The incidence of myocarditis in hospitalized COVID-19 patients in Germany was 1.28 cases per 1000 hospitalizations during 2020, not influenced by the SARS-CoV-2-vaccination program. Relative numbers of myocarditis in COVID-19 patients were highest during the first two decades of life, whereas the in-hospital case fatality rate increased substantially with age. Myocarditis was independently associated with a 1.5-fold increase in case fatality in COVID-19 patients. Risk factors for myocarditis in COVID-19 patients were younger age, male sex, pneumonia, and multisystemic inflammatory COVID-19 infection.

AUTHOR CONTRIBUTIONS

Karsten Keller and Lukas Hobohm designed this study. Karsten Keller led the data analysis with support from Lukas Hobohm. Karsten Keller wrote the draft of the paper. All authors had full access to all the data, revised the manuscript for important intellectual content, and edited the final manuscript. All authors had final responsibility for the decision to submit for publication.

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CONFLICTS OF INTEREST STATEMENT

S. K. reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional

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DATA AVAILABILITY STATEMENT

The data is available at the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2020, and own calculations).

ETHICS STATEMENT

Since our study did not comprise direct access by the investigators to individual patient data but only an access to summarized results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law.

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