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Cardiovascular Risk Assessment in COVID-19

Monika Zdanyte[1] Dominik Rath[1]

[1] Department of Cardiology and Angiology, University Hospital Tübingen, Tübingen, Germany

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Address for correspondence Dominik Rath, MD, Department of Cardiology and Angiology, University Hospital Tübingen, Otfried-Müller-Straße 10, Tübingen 72076, Germany (e-mail: dominik.rath@med.uni-tuebingen.de).

Zusammenfassung

COVID-19 bezeichnet eine der schlimmsten Krisen unserer Generation und stellt (nicht nur) für das Gesundheitssystem eine schwer bewältigbare Herausforderung dar. Mortalität und Morbidität sind im Vergleich zu anderen saisonalen Erkrankungen wie der Influenza deutlich erhöht. COVID-19 bedroht allerdings nicht die gesamte Bevölkerung in gleichem Maße. Hochrisikopatienten sind älter und leiden an kardiovaskulären Erkrankungen wie Bluthochdruck, Diabetes mellitus oder einer koronaren Herzerkrankung. Um das Risiko für einen schweren Erkrankungsverlaufs zu quantifizieren bedarf es einer multimodalen Herangehensweise. Verschiedene Risikostratifizierungssysteme stehen zu Verfügung um ungünstige Verläufe wie Intensivbehandlung oder Gesamtmortalität vorauszusagen. Biomarker wie Troponin-I, D-Dimere und NT pro-BNP kombiniert mit echokardiographischen Parametern wie links- und rechtsventrikulärer Pumpfunktion sowie pulmonalarteriellem Druck können hilfreich sein um Hochrisikopatienten zu identifizieren, die ein intensiviertes Monitoring und eine stringentere Behandlung benötigen. Da kardiovaskuläre Risikofaktoren und Komorbiditäten von großer Bedeutung zur Abschätzung des Verlaufs einer SARS-CoV-2 Infektion sind, könnten alle hospitalisierten COVID-19 Patienten von einer routinemäßigen kardiologischen Betreuung durch ein COVID-19-Heart-Team profitieren. Ein frühzeitiges Erkennen von (kardiovaskulären) Hochrisikopatienten könnte das Management erleichtern sowie die Prognose einer schweren SARS-CoV-2 Infektion verbessern.

Schlüsselwörter

- COVID-19
- kardiovaskuläres Risiko
- kardiovaskuläre Risikofaktoren
- Risikostratifizierung

Abstract

The COVID-19 pandemic represents one of the largest burdens of our generation with enormous consequences on socioeconomics and healthcare around the globe. COVID-19 is associated with increased morbidity and mortality. However, the course of disease differs among the population. Advanced age and a compromised immune system among others are associated with significantly worse outcomes. Furthermore, cardiovascular comorbidities are of utmost importance and may influence severity of SARS-CoV-2 infection to a considerable degree. This review aims to identify risk factors, biomarkers, and echocardiographic parameters associated with a severe course of SARS-CoV-2 infection and give a brief overview of the management of COVID-19 patients with cardiovascular comorbidities. Furthermore, available models identifying high-risk patients and their performance in prediction of severe outcomes of SARS-CoV-2 are addressed.

Keywords

- COVID-19
- cardiovascular risk
- cardiovascular risk factors
- risk assessment

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Cardiovascular Comorbidities and COVID-19

Current evidence indicates that SARS-CoV-2 infection is associated with serious adverse cardiovascular events. Preexisting cardiovascular risk factors and/or disease (CVRFs/CVD) may aggravate the course of COVID-19 due to increased thromboischemic risk and myocardial distress. Arterial hypertension, hyperlipidemia, diabetes, history of or current smoking, and coronary artery disease (CAD) have been identified as the most common comorbidities[1,2] in severe SARS-CoV-2 infection.[3] It is, however, difficult to identify independent associations of these CVRFs as most of them are more prevalent in advanced age, denoting probably the most important risk factor.

Arterial hypertension, diabetes mellitus (DM), and cardiovascular and respiratory diseases are associated with worse outcomes and increased all-cause mortality in COVID-19.[3–6] COVID-19 patients suffering from concomitant DM and CVD are more often hospitalized and treated in intensive care unit (ICU).[7] Furthermore, an adequate glycemic control seems to lower mortality in COVID-19.[8,9] A threefold higher risk of severe course of COVID-19 and a significantly longer intra-hospital stay were reported in obese patients.[10] Presence of CVD is linked to noncardiac comorbidities, for example, chronic obstructive pulmonary disease, chronic kidney disease, peripheral arterial disease, and cerebrovascular disease. These risk factors were found to be associated with increased mortality in COVID-19.[11]

Cardiac manifestations in COVID-19 include ischemic/nonischemic myocardial injury, congestive heart failure (HF), cardiogenic shock, and cardiac arrhythmias. Myocardial injury (myocarditis, stress cardiomyopathy, or myocardial infarction [MI]) in COVID-19 is significantly associated with preexisting CVRFs and leads to higher rates of adverse events, including mechanical ventilation and all-cause mortality.[12] Up to 17% of patients hospitalized due to COVID-19 suffer from concomitant myocardial injury.[2] Impaired myocardial function, both left and right ventricular, is associated with higher rates of mortality, mechanical ventilation, and longer intra-hospital stay.[13,14]

Pathophysiology of Myocardial Injury in COVID-19

The exact mechanisms of COVID-19-induced myocardial damage are not yet completely understood. Direct myocardial damage may be caused through angiotensin-converting enzyme 2 (ACE2) receptor-related signaling pathways, as the latter receptors are widely expressed in the cardiovascular system.[15] Myocardial damage may also arise in the course of the cytokine storm mediated by an inadequate response of immune T helper cells due to SARS-CoV-2 infection.[16] Furthermore, levels of creatine kinase-myocardial band (CK-MB), N-terminal pro-hormone of brain natriuretic peptide (NT pro-BNP), lactate dehydrogenase (LDH), D-dimer, and other coagulation factors are found elevated as part of the cytokine storm.[3,17,18] Finally, myocardial injury occurs as a result of respiratory distress and hypoxemia leading to excessive calcium influx into myocytes and their apoptosis.[16]

Prognostic Markers of Myocardial Injury in COVID-19

Troponin-I (TnI) as well as troponin-T (TnT), CK-MB, and NT pro-BNP are considered to be important biomarkers not only concerning cardiac injury associated with SARS-CoV-2 infection but also in predicting adverse events including mechanical ventilation and all-cause mortality.[14,19] 5% to 25% of COVID-19 in- and outpatients exhibit elevated troponin levels.[20] Elevated levels of CK-MB, high-sensitive TnI, and NT pro-BNP are associated with severe course of COVID-19.[21] Troponin is considered to be the strongest predictor associated with mortality, ICU treatment, and/or mechanical ventilation.[22] There is evidence showing a continuous rise of troponin levels in patients with severe course of SARS-CoV-2 infection.[18] However, although these biomarkers rather serve as prognostic tools in the context of COVID-19, one must not underemphasize the diagnostic importance of TnI and NT pro-BNP in e.g. acute MI, severe aortic stenosis when corresponding clinical signs and symptoms exist. Therefore, a thorough patient history, electrocardiography, transthoracic echocardiography, coronary angiography, magnetic resonance imaging (MRI), etc. combined with cardiac biomarkers are crucial for identifying patients in need of specific treatment.

Pathologic echocardiographic findings in COVID-19 include right ventricular dilation and/or dysfunction and impaired left ventricular systolic or diastolic function. Echocardiographic abnormalities are more common among patients with myocardial injury and lead to higher mortality.[14,23] Impaired right or left ventricular function and moderate or severe tricuspid regurgitation were found to be associated with higher mortality in COVID-19 patients.[14]

(Cardiovascular) Risk Assessment in COVID-19

Risk assessment in COVID-19 patients is a challenging process. Several groups tried to address this issue by generating risk assessment models. The Quick COVID-19 Severity Index (qCSI) uses three variables (respiratory rate, lowest documented peripheral oxygen saturation [SpO_2], and oxygen flow rate) to predict 24-hour all-cause mortality and ICU admission.[24] qCSI score performed better in predicting all-cause mortality than the established CURB-65 score validated for community-acquired pneumonia or Sequential Organ Failure Assessment (Quick) score for sepsis-related mortality (area under the curve [AUC]: 0.89, 0.66, and 0.76, respectively).[24–26] COVID-GRAM is currently one of the most widely used risk assessment systems in COVID-19 patients. This score uses 10 variables (chest radiography abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, levels of LDH, and direct bilirubin) to predict critical illness associated with SARS-CoV-2 infection.[27] COVID-

GRAM performed very well in predicting a combined endpoint including ICU admission, invasive ventilation, or death in both derivation and validation cohorts (AUC = 0.88 and AUC = 0.88, respectively). Another scoring system derived from a large prospective cohort of more than 57,000 patients in the United Kingdom aims to predict intra-hospital mortality in COVID-19 patients. The 4C Mortality Score uses eight parameters (age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, Glasgow coma scale, levels of urea, and C-reactive protein [CRP]) and reached an AUC of 0.79 in the derivation and an AUC of 0.77 in the validation cohort.[28]

The mentioned scores, however, do not include CVRFs for predicting an unfavorable outcome. On the other hand, due to high prevalence, CVD is indirectly considered under the variable "number of comorbidities" in COVID-GRAM and 4C Mortality Score calculation. Another recently generated risk score included DM and arterial hypertension which were the most prevalent compared with other variables (age > 40, male sex, non-white ethnicity, oxygen saturation < 93%, radiological severity score > 3, neutrophil count > 8.0×10^9/L, CRP > 40 mg/L, albumin < 34 g/L, creatinine > 100μμmol/L, and chronic lung disease) for the prediction of ICU treatment and all-cause mortality.[29] The Veterans Health Administration COVID-19 (VACO) Index for COVID-19 Mortality is a complex risk assessment model including, among others, DM, CHF, history of MI, and peripheral arterial disease to predict 30-day mortality in COVID-19 patients (AUC = 0.79, AUC = 0.81, and AUC = 0.84 in derivation, early, and late validation cohorts, respectively).[30] An overview of selected risk assessment models in COVID-19 is presented in ►Table 1.

To estimate the risk of cardiovascular adverse events in SARS-CoV-2 infection, established cardiovascular risk scores (e.g., GRACE 2.0, PREDICT-STABLE, and CALIBER) need to be validated in COVID-19 patient cohorts.[31–34] The second and third scores include CVRFs and CVD next to demographic variables. Therefore, some of the risk assessment scores generated for CAD patients could be applied for prediction of cardiovascular complications and all-cause mortality in COVID-19 patients due to evident association of CVRFs and COVID-19. Furthermore, no SARS-CoV-2 risk assessment models including echocardiographic parameters and/or cardiac-specific biomarkers are available to this day. As already mentioned, impaired myocardial function is associated with adverse outcomes in COVID-19 patients.[14,18] Thus, a risk assessment model based on myocardial function, cardiac biomarkers, and established CVRFs may differentiate high-risk COVID-19 patients with cardiovascular comorbidities even more reliably. According to our data, univariate and multivariate models including NT pro-BNP, TnI, and D-dimer levels deliver the most promising results in the prediction of 30-day mechanical ventilation and all-cause mortality. Echocardiographic parameters, however, fail to discriminate between favorable and adverse outcomes in patients hospitalized with COVID-19.[35] A hypothesis on how SARS-CoV-2 affects the cardiovascular system and preliminary data on cardiovascular biomarkers and echocardiographic parameters for the prediction of adverse events in COVID-19 are presented in ►Fig. 1.

Management of COVID-19 Patients with Cardiac Comorbidities

Due to overall higher risk of adverse events and all-cause mortality, SARS-CoV-2-positive patients with preexisting CVD should therefore be identified as high-risk COVID-19 patients, requiring intensified monitoring and specific therapeutic considerations.

In stable CVD outpatients, routine visits should be reevaluated and eventually substituted through telemedicine to reduce the infection risk.[36]

According to scientific evidence available to this day, antihypertensive therapy with ACE inhibitors and angiotensin receptor blockers should not be discontinued.[37] Suspicions that renin–angiotensin–aldosterone system inhibitors lead to increased severity of SARS-CoV-2 infection lack evidence and therefore need further investigation.[38]

In patients with congestive HF, intravenous fluid therapy should be carefully monitored and volume overload should be avoided.[36]

Therapy with acetylsalicylic acid in patients with chronic coronary syndrome should not be withheld as the anti-inflammatory effect is rather insignificant.[39]

Statin therapy may be paused due to occurrence of rhabdomyolysis and/or elevation of liver enzymes.[40]

Patients with ST-segment elevation MI and very-high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS; e.g., patients with hemodynamic instability, life-threatening arrhythmias, and acute HF) must receive appropriate therapy without further delay irrespective of SARS-CoV-2 status. NSTE-ACS patients with lower risk may be first tested for SARS-CoV-2 and eventually transferred to a COVID-19-equipped hospital.[20]

Establishing an experienced COVID-19 heart team that routinely assesses the cardiovascular status (e.g., electrocardiography, transthoracic echocardiography, myocardial biomarkers) of all hospitalized COVID-19 patients may improve the management and therefore outcomes of high-risk patients with cardiovascular comorbidities.

Summary

COVID-19 represents one of the greatest crises of our generation driving (not only) our healthcare system on the verge of collapse. Morbidity and mortality are higher compared with other seasonal respiratory infections like influenza. However, the course of disease differs in the population. Patients at high risk are older and suffer from cardiovascular comorbidities such as arterial hypertension, DM, and CAD. However, risk assessment in COVID-19 patients remains challenging and requires a multimodal approach. Several risk assessment systems have been generated to predict adverse events including ICU treatment or all-cause mortality in COVID-19. Biomarkers like troponin I, D-dimers, and NT pro-BNP both at baseline and during the course of disease—added to echocardiographic parameters like impaired left-ventricular and right-ventricular function as well as elevated pulmonary artery pressures—may help identify patients likely to suffer from serious adverse events and in need of intensified

Table 1 Overview of available COVID-19 risk assessment scores and included variables

	4C Mortality Score[26]	COVID-GRAM[25]	qCSI[24]	*Galloway et al*[29]	VACO Index[28]
Predicted outcome	Intra-hospital mortality	All-cause mortality, ICU admission, invasive ventilation	All-cause mortality, ICU admission	ICU admission, all-cause mortality	30-day mortality
Cohort	Derivation ($n = 35,463$), Validation ($n = 22,361$)	Derivation ($n = 1,590$), Validation ($n = 710$)	Derivation ($n = 932$), Validation ($n = 240$)	Derivation ($n = 1,157$)	Derivation ($n = 3,681$), Early validation ($n = 2,151$), Late validation ($n = 7,491$)
Included variables					
Age	+	+		+	+
Sex	+			+	+
Non-white ethnicity				+	
Chest radiography		+		+	
O2 flow rate			+		
Peripheral oxygen saturation (SpO2)	+		+	+	
Dyspnea		+			
Respiratory rate	+		+		
Hemoptysis		+			
Impaired consciousness	+	+			
Albumin				+	
C-reactive protein	+			+	
Creatinine				+	
Direct bilirubin		+			
Lactate dehydrogenase		+			
Neutrophil count				+	
Neutrophil-to-lymphocyte ratio		+			
Urea	+				
Number of comorbidities	+	+			
Comorbidities[a]		+		+	+

[a]Comorbidities: COVID-GRAM (malignancy); *Galloway et al* (arterial hypertension, chronic lung disease, diabetes mellitus); VACO Index (asthma, arterial hypertension, AIDS, malignancy, cerebrovascular event, chronic pulmonary disease, congestive heart failure, diabetes mellitus, dementia, liver disease, myocardial infarction, peptic ulcer disease, peripheral artery disease, paralysis, renal disease, rheumatologic disease).

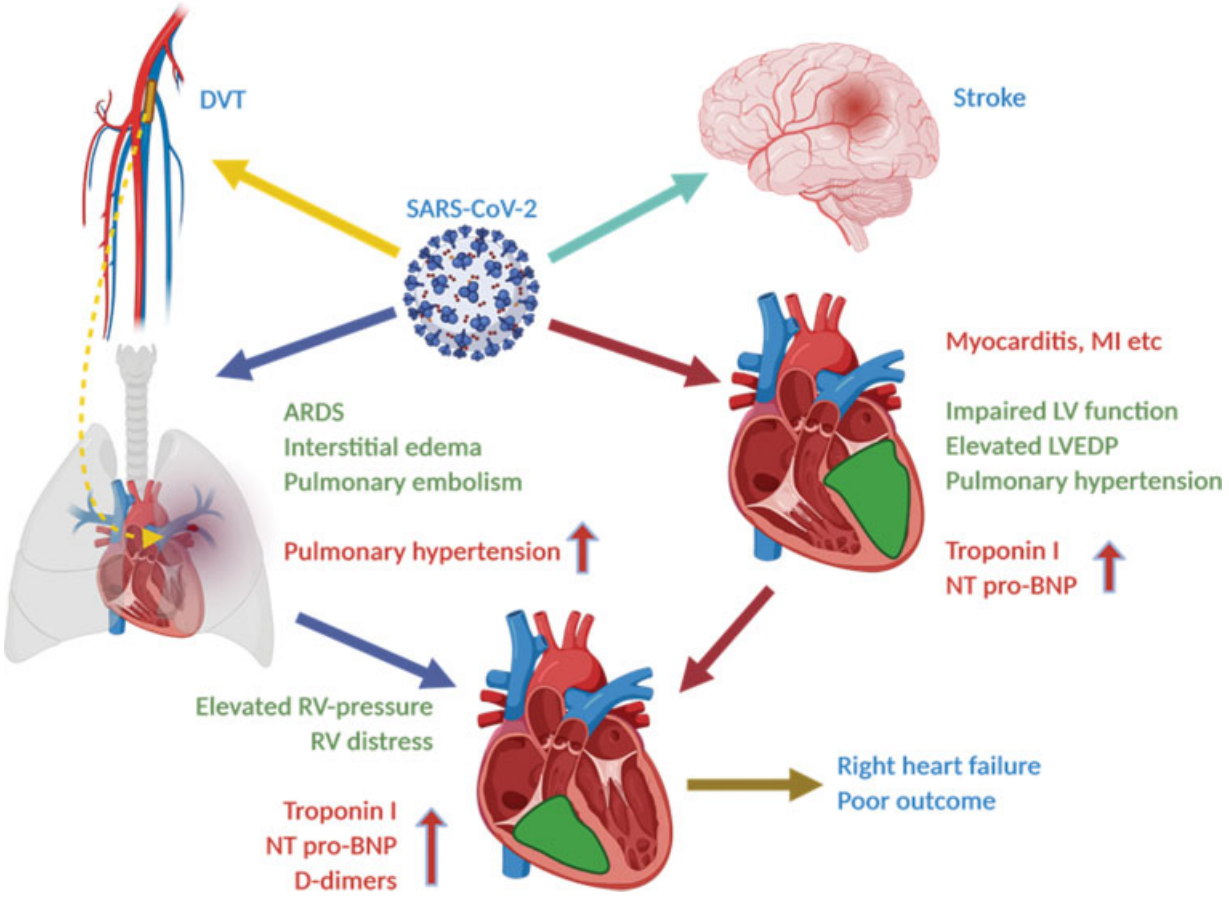

Fig. 1 Simplified hypothesis on how SARS-CoV-2 affects the cardiovascular system. SARS-CoV-2 affects the lungs, leading to acute respiratory distress syndrome (ARDS) and interstitial edema. COVID-19-induced myocarditis leads to myocardial damage. Due to enhanced thrombogenicity, SARS-COV-2 may lead to deep vein thrombosis and/or pulmonary embolism as well as MI. These complications trigger left and right ventricular myocardial distress. Due to hypercoagulability and myocardial distress, levels of TnI, NT pro-BNP, and D-dimer become elevated. At the end of the cascade, we suggest acute right heart failure to be one of the critical factors resulting in poor prognosis. Created with BioRender.com.

monitoring and treatment. As the cardiovascular burden is of critical importance for severity of SARS-CoV-2 infection, all hospitalized COVID-19 patients in our opinion benefit from a routine assessment by a competent COVID-19 heart team. Early identification of high-risk patients may optimize the management and improve the outcomes of COVID-19.

Conflict of Interest

The authors declare that they have no conflict of interest.

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