SARS-CoV-2 Infection and Heart Disease

Infeção SARS-CoV-2 e Doença Cardíaca

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Abstract

Coronavirus disease 2019 (COVID-19) rapidly became a world pandemic disease constituting a strong burden on health systems, with a devastating impact on social and economic living.

Primarily affecting the respiratory system, producing severe pneumonia and respiratory failure evolving into an ARDS like presentation, COVID-19 has shown to substantially impact patients with pre-existing cardiovascular comorbidities. Also, cardiac manifestations directly related to COVID-19 have been acknowledged successively contributing to the high morbidity associated with this viral infection.

This review will focus on the cardiovascular manifestations related to SARS CoV2 infection.

Keywords: Cardiovascular Diseases; Coronavirus Infections; COVID-19; Heart Diseases; SARS-CoV-2

Resumo

A infeção por Coronavírus 2019 (COVID-19) rapidamente evoluiu para uma pandemia, constituindo um elevado peso nos sistemas de saúde com um impacto devastador na vida social e económica.

Afetando primariamente o sistema respiratório, causando uma pneumonia grave e insuficiência respiratória e evoluindo para uma síndrome semelhante à da ARDS, a COVID-19 demonstrou ter um impacto substancial nos doentes com comorbilidades cardiovasculares pré-existentes. Também as manifestações cardíacas, diretamente relacionadas com a COVID-19, têm sido reconhecidas contribuído sucessivamente para a elevada morbilidade associada a esta infeção viral.

Esta revisão irá focar-se nas manifestações cardiovasculares associadas à infeção por SARS CoV2.

Palavras-chave: COVID-19; Doenças Cardiovasculares; Doenças do Coração; Infeções por Coronavírus; SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a member of the genus betacoronavirus like the two other coronaviruses that have caused pandemic diseases (severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[1-4]

COVID-19 was first reported in Wuhan, China, in late December 2019.[1-3] Since then, COVID-19 has spread rapidly worldwide and has become a global pandemic affecting > 200 countries and territories, with an unprecedented effect not only on public health, but also social and economic activities.[5]

Since then, in Portugal 76 396 cases of COVID-19 patients have been confirmed as of 2 October 2020 with 1977 reported dea-

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ths (data obtained from the General Directorate of Health site – www.dgs.pt).

So far, the USA, India and Brazil account for the countries most affected by this disease.

It is acknowledged that patients infected with COVID-19 with pre-existent cardiac comorbidities such as hypertension, cerebrovascular disease and diabetes have worse clinical outcomes[6]. Cardiac manifestations on the other hand include myocardial injury, acute coronary syndromes, acute heart failure, arrhythmias, and thromboembolism.

This article will focus on the impact of COVID-19 infection in the cardiovascular spectrum.

Epidemiology

As of the first week of October, Russia, Spain, and France gather the highest number of patients infected with COVID-19 in Europe – see Table 1. Portugal is currently on the 18th position.

Older population is frequently more affected, and few cases are identified below 20 years old. In Portugal, the aging distribution is like the pattern observed in EU countries – see Fig. 1. In fact, most patients with a confirm diagnosis are between 20 and 59 years old.

Also, a mild female predominance is noted (55% female vs 45% male, according to General Directorate of Health/Direcção Geral da Saúde, in Portugal).

Ethnic minorities may display a higher propensity to acquire infection and eventually with the final outcome.[7,8]

Finally, health professionals, particularly those working in the frontline (emergency department, intensive care, respiratory units) are at increased risk of reporting positive for SARS- CoV-2 infection.[9]

Cardiovascular manifestations

Clinical presentation

Fever, dry cough and shortness of breath are among the most common symptoms in patients presenting with COVID-19.[10] Anosmia, hyposmia, and dysgeusia have also been associated to the usual clinical presentation, and digestive symptoms such as diarrhoea, although less common, can also appear.[10,11] Severe respiratory failure and COVID-19-associated acute respiratory distress syndrome (ARDS) accounts for the most serious respiratory manifestations – its prevalence has been recorded in around 3% of cases but its Laboratory blood results present lymphopenia, increased C reactive protein, D dimers, LDH, ferritin, ALT and AST. An elevation of cardiac troponins has been shown in up to 20% of patients hospitalised for COVID-19 infection.[12] The lung is usually the most affected organ and thoracic radiographs can be normal to presenting ground glass bilateral opacities.[11]

Table 1. Epidemiology of COVID-19 infection in Europe.

		Cases - cumulative	Cases - cumulative per 1 million habitants	Deaths - cumulative
1	Russion Federation	1 260 112	8634,78	22 056
2	Spain	835 901	17 878,41	32 562
3	France	626 502	9598,1	32 211
4	The United Kingdom	32 211	8017,54	42 515
5	Italy	42 515	5523,15	36 061
6	Turkey	329 138	3902,56	8609
7	Germany	310 144	3701,71	9578
8	Israel	273 460	31593	1765
9	Ukraine	244 734	5596	4690
10	Netherlands	149 817	8743,4	6509
	....			
18	Portugal	81 256	7968,85	2040

Source: Data extracted from the https://covid19.who.int/ on the 9th October 2020.

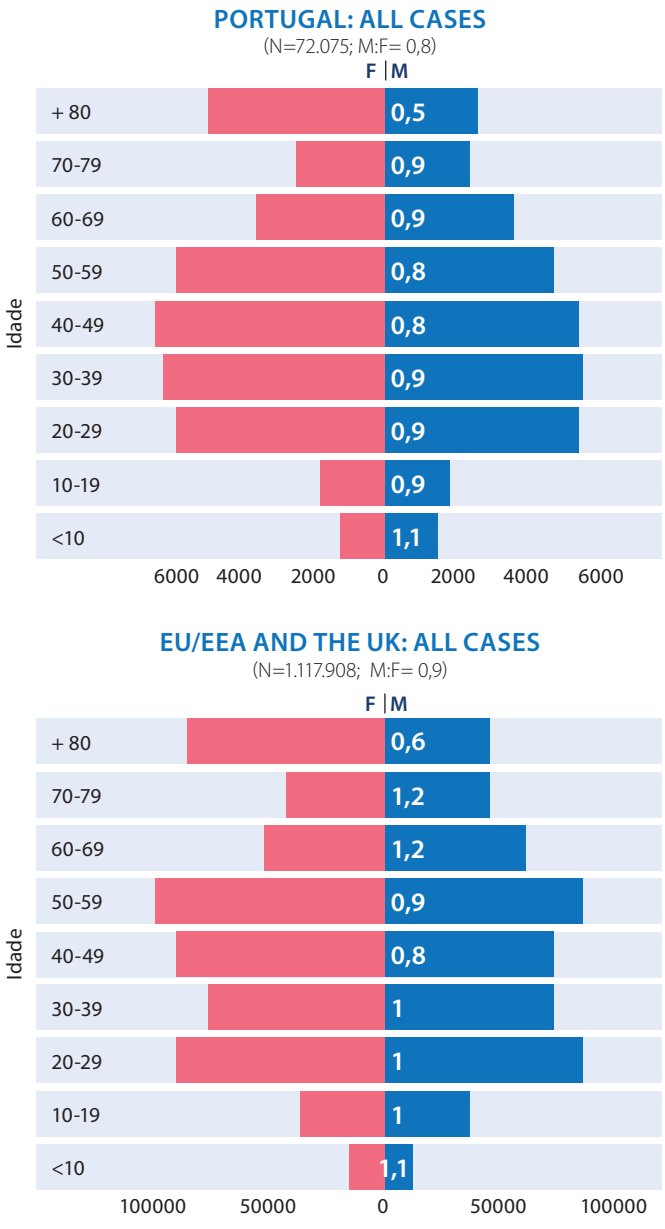

Figure 1. Age/sex distribution in the EU countries and in Portugal.
Source: Data extracted from the https://covid19-surveillance-report.ecdc.europa.eu/ on the 9th October 2020.

Cardiovascular comorbidities in patients with COVID-19

Cardiovascular comorbidities are significant among patients that develop severe forms of COVID-19 presentation. In China, regarding a metanalysis that included 1527 patients, hypertension, cardio and cerebrovascular and diabetes have a significant prevalence in COVID-19 infected patients (17.1%, 16.4%, and 9.7%, respectively) and increase twofold, threefold, and twofold in patients admitted to Intensive Care.[13]

In other countries besides China, the prevalence of cardiovascular (CV) comorbidities in patients hospitalized with COVID-19 was also high. In Italy, a cohort[14] with 1591 hospitalized COVID-19 patients 68% had at least one comorbidity and 49% had hypertension. In fact, hypertension weas significantly more prevalent in patients who died in the ICU.

Cardiovascular manifestations

Although respiratory manifestations are the cornerstone of COVID-19, several cardiac manifestations also occur such as myocardial injury, myocarditis, arrhythmias, acute coronary syndrome, and thromboembolism.

Myocardial injury presents clinically as elevated myocardial necrosis biomarkers and it was early reported in China with rates of 27.8%[15] among hospitalized patients, usually older, with more hypertension and more cardiovascular pathology, displaying a more malignant clinical evolution, with cardiac dysfunction and arrhythmias. Troponin elevation can have several causes, such as coronary plaque rupture, local inflammation, hypercoagulability and thrombosis, ischemia related to hypoxemia or infection induced myocarditis. Two presentations are seen such, one that presents as the systemic disease worsens and acute cardiac presentation associated with cardiac dysfunction.

Elevation of cardiac troponin has also been linked to the presence of myocarditis. Autopsy studies presented limited data on the presence of viral RNA in the heart.[16,17] Its prevalence in COVID-19 patients is still unknown. In a study involving cardiac magnetic resonance evaluation in patients recovered from COVID-19 infection, 78% presented cardiac involvement and 60% still had ongoing myocardial inflammation. Cardiac magnetic resonance or endomyocardial biopsy have a role in its diagnosis.

Heart failure incidence also depends on the severity of SARS--CoV-2 infection. In hospitalized patients can reach 30%.[18] Heart failure can arise from patients with previous heart failure just as in other viral infections or as a new manifestation in previously health individuals. Diagnosis can be made by the presence of elevated natriuretic peptides, compatible imaging such as chest radiography and thoracic computed tomography (CT) and point of care transthoracic echo. Heart failure guidelines[19] should orient the therapy as well as COVID-19 more specific treatment. Fluid status, heart rate, blood pressure and overall hemodynamic and respiratory function should be continuously monitored as well as drug interactions to help tailor medication.

Myocardial ischemia can arise from coronary thrombosis (acute coronary syndrome - ACS) or be secondary to hypoxia and cytokine storm. Important ST elevation can also be seen with unobstructed coronary arteries in a Takotsubo like pattern.[20] In ST elevation ACS, immediate reperfusion should be sought. All STEMI patients should be managed as if they potentially infected with SARS-CoV-2.[21] In non-ST elevation ACS clinical and stratification risk score may help prioritize the treatment strategy.[22] Very high risk should follow the same strategy as in STEMI patients with immediate reperfusion. The remaining should have SARS-CoV-2 excluded to define their approach and care in the cardiac care unit or catheterization lab.

Venous thromboembolism, including deep venous thrombosis and pulmonary embolism are challenging situations from the diagnosis and management point of view in patients with COVID-19. In fact, its incidence is significant in critically ill patients. Pulmonary thromboembolism's incidence has been reported in ranges varying from 8.3% in a multicentric French study[23] to around 22%.[24,25] The diagnosis was made through pulmonary CT angiography (CTPA).[26] Probably selection criteria in these studies contributed to this disparity. Autopsy findings also noted a high prevalence of thromboembolic events.[17] Male gender and obesity have been identified as factors associated with increased risk of thromboembolism.[23,27] D-dimers are probably less useful as a rule out criteria and CTPA crucial in the diagnosis. As an alternative, deep vein lower limbs Doppler or V/Q scan or only perfusion scintigraphy can be used.[28,29]

Imaging cardiovascular complications in COVID-19 patients

In a patient infected with SARS-CoV-2, identification of cardiovascular complications is critical because it can directly influence clinical management. Nevertheless, due to a high flow of patients and having into account the need to protect health personnel and patients, clinical prioritisation is essential.

Clinical history, electrocardiogram, chest radiography and cardiac and thrombosis biomarkers, such as troponin, natriuretic peptides and D-dimers play a pivotal role in the initial cardiovascular evaluation. Clinicians need to bear in mind that mild cardiac biomarkers elevation is noted in COVID-19 patients despite the absence of cardiovascular complications and no further evaluation need to be done in the absence of chest pain or electrocardiographic changes.[21] Hemodynamic instability or marked cardiac biomarkers elevation, though, needs to be further assessed with more specific cardiac imaging.[24] A POCUS (point of care ultrasound) echocardiogram should be performed,[25] including lung ultrasound to assess general cardiac involvement, volume status and help in the assessment

of lung congestion, as well as in the diagnosis of pneumonia, effusion or pneumothorax.

Multimodality imaging should be undertaken to further assess and stratify cardiovascular involvement in COVID-19 patients.

If further evaluation needs to be performed, a formal transthoracic echocardiography should be undertaken. Transesophageal echocardiogram, on the other hand, should be avoided, due to the high risk of aerosol concentration and risk of personnel and equipment contamination,[30] only to be performed if very specific cases such as poor echo imaging quality, intubated and critical patients with challenging positioning.

CT has been previously mentioned as essential in the evaluation of chest pain in COVID-19 patients such as on the diagnosis and evaluation of pneumonia and pulmonary embolism.[31] Advanced cardiac CT has also a fundamental role in the evaluation of coronary artery disease and myocardial and pericardial assessment.[30] Also, prior to atrial fibrillation cardioversion cardiac CT may be used to exclude intracardiac thrombus, replacing transesophageal echocardiogram in acutely ill COVID-19 patients.[21]

Cardiac magnetic resonance has a pivotal role in the evaluation of myocardial oedema and inflammation (COVID-19 related myocarditis)[32] and in the differential diagnosis with MINOCA[33] or stress induced cardiomyopathy.[34]

Exercise testing should be replaced by diagnostic tests that do not require exercise, in this pandemic era.

Finally, cardiac catheterization should not be postponed in ST elevation ACS patients, in non-ST elevation ACS with high risk stratification score and in patients with cardiogenic shock.[21]

Potential drug disease interactions

This is probably one of the most controversial topics. COVID-19 treatment has been relying on off label medication to treat a new disease – with that, drug interactions and adverse reactions can occur, and pharmacovigilance has a pivotal role.

Three situations arose in the last 9 months. Doubts concerning an increased risk in patients with SARS-CoV-2 infection on ACE inhibitors (ACEI) or angiotensin II receptor antagonists (ARA2) occurred. Also, the interaction of COVID-19 specific medication on cardia medication and clinical events also took place. Finally, the use of antithrombotic drugs in patients with SARS-CoV-2 infection.

1. ACEI and ARA2 effect on SARS-CoV-2 infection

The SARS-CoV-2 protein binds directly to the host cell surface ACE2 receptor to gain cell entry and replication,[35] increasing the susceptibility of cells with ACE2 receptors to COVID-19 infection. Nevertheless, and despite some conflicting evidence on the increased susceptibility of patients on ACEI or ARA2 to severe infection, such suggestion has been unproven. In fact, recent metanalysis have been conducted that revealed that such risk was not demonstrated and that ACEI and ARA2 should be maintained in hypertensive or heart failure patients[36,37] as per international scientific guidelines indication.

2. COVID-19 medication and cardiovascular interactions

Antibiotics, hydroxychloroquine, antivirals, monoclonal antibodies, and corticosteroids have been used in an off-label fashion on the empirical treatment of COVID-19 patients.

Clinicians had great expectation on the hydroxychloroquine alone or in combination with azythromicin[38] but this has so far been unfounded.[39] Nevertheless, cardiac toxicity, prolongation of QTc and cardiac conduction disorders have been linked to this therapy[40] which led to the creation of hospital protocols to evaluate and monitor such serious adverse reactions. Also, drug interactions with cardiovascular medications such as digoxin can occur. Azithromycin can increase the drug level of certain NOACs such as dabigatran and rivaroxaban and of warfarin and care should be taken for drug dose adjustment.[21]

Antivirals have also been used with limited evidence on its efficacy. Remdesivir has been used in the treatment of hospitalized COVID-19 patients,[41] although its efficacy has been questioned[42] and safety profile is still largely unknown as it is a new antiviral drug. QTC prolongation specially when associated with electrolytes prolongation can occur. Other antiviral combinations used such as lopinavir/ritonavir have shown no clinical advantage,[39] but increased QTc has also been demonstrated. Antiviral drugs can affect pharmacokinetics of cardiac medication such as eplerenone, digoxin, ivabradine, sacubitril, calcium channel antagonists and NOACs which mandates for careful monitoring. The use of lopinavir/ritonavir should lead to the discontinuation of apixaban or rivaroxaban and dabigatran should be used with caution.[21]

Steroids were initially contraindicated in COVID-19 patients, due to a fear of increasing viral propagation. In the Recovery trial,[43] a controlled open label on the use of steroids (dexamethasone) versus usual care, dexamethasone has demonstrated to be superior in patients receiving with either invasive ventilation or oxygen. In fact, and probably as a consequence of this trial, the evidence so far has been in favour of a protective role of steroids in severe cases of infection with COVID-19.[44] Steroids are known to aggravate the clinical status of patients with previous heart failure and several adverse effects are linked to this drug class related to dose and duration of treatment.

3. Antithrombotic medication in COVID-19 patients

The systemic inflammation noted in COVID-19 patients can result in low level intravascular clotting and platelets activation,[45] with increased susceptibility to intravascular thrombosis.

Special care should be taken when using antithrombotic drugs

in patients with COVID-19 infection due to possible drug interactions.

Parenteral anticoagulants are less prone to interact with COVID-19 investigational medications.[46] The ESC recommends that COVID-19 patients on oral anticoagulation should be switched over to parenteral anticoagulation with LMWH and UFH when admitted to an ICU with a severe clinical presentation.[21] On the other hand, oral anticoagulants should be used with caution in these patients as drug interactions may occur.

Regarding antiplatelet medication, lopinavir/ritonavir and darunavir/cobicistat can interact with CYT3A4, decreasing the antiplatelet efficacy of clopidogrel and increasing the concentration of ticagrelor contraindicating its use.[47] Nevertheless, the risk benefit should be individualized as the mentioned antivirals efficacy towards COVID-19 infection is dubious and the patients with acute coronary syndromes should have usual standard care therapy.

Conclusion

Contemporary medicine performs an evidence-based data. COVID-19 infection is a novel viral disease with a growing rate of patients worldwide and with a tremendous impact in public health, in the performance of health care institutions and individually in the clinical evaluation of patients. COVID-19 displays specificities regarding cardiovascular manifestations, imaging, and treatment.

The evidence is still quite tenuous regarding treatment and efforts should be taken as an individual to prevent further spreading. Researchers should globally work with the common goal of integrating biological and clinical aspects of this infection with the ultimate perspective of finding an effective immunization and treatment for this viral infection, improving its prognosis.

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