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Cardiovascular injuries and SARS-COV-2 infection: focus on elderly people

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ABSTRACT The novel coronavirus disease (COVID-19) has hit the healthcare system worldwide. The risk of severe infection and mortality increases with advancing age, especially in subjects with comorbidities such as cardiovascular disease, hypertension, diabetes, obesity and cancer. Moreover, cardiovascular complications such as myocardial injury, heart failure and thromboembolism are frequently observed in COVID-19 cases, and several biomarkers (troponin, NTproBNP and D-Dimer) have been identified as prognostic indicators of disease severity and worst outcome. Currently, there is no specific therapy against SARS-CoV-2, although many medications are under investigation. The aim of this review will be to explore the intertwined relationship between COVID-19 disease and the cardiovascular system, focusing on elderly population. The available supportive treatments along with the related concerns in elderly patients, due to their comorbidities and polypharmacotherapy, will be explored.

The novel coronavirus type 2 (SARS-CoV-2) infection, which leads to severe acute respiratory syndrome in its most severe forms, has been first reported in December 2019 in the Chinese province of Hubei and subsequently designated as a pandemic by the World Health Organization (WHO) on March 11th 2020. Globally, as of 13 January 2021, there have been 90,054,813 confirmed cases of COVID-19, including 1,945,610 deaths, reported to WHO.[1] After the Chinese outbreak, Europe overtook China with the highest number of reported cases and deaths. The pandemic now is propagating across Americas, where over 25,958,213 cases and 717,028 deaths has been reported in November 2020.[1]

The case-fatality rate (CFR, i.e., number of deaths/number of diagnosed cases) differ significantly around the world, showing increased prevalence with advancing age. In particular, the CFR is < 1% for patients < 50 years of age, 1.3% for 50-year-old patients, 3.6% for 60-year-old patients, 8% for 70-year-old patients, and 14.8% for octogenarians.[2]

A number of key comorbidities are associated with worse clinical outcomes and CFR in patients with COVID-19. While CFR in patients with no medical history is low (0.9%), it raises to 5%-10% when frailty conditions are present [10.5% for cardiovascular disease (CVD), 7.3% for diabetes mellitus (DM), 6.3% for chronic obstructive pulmonary disease, 6% for arterial hypertension, and 5.6% for cancer].[2]

Among the predictors of outcome, age has consistently been reported as an independent and strong covariate associated with mortality.[3] Focusing on elderly patients, a recent cohort study of nursing home residents with COVID-19 has found impaired cognitive physical function as independent predictors of mortality in this population.[4]

COVID-19 AND CARDIOVASCULAR SYSTEM

A number of studies suggest an association between pre-existing CVD and severe COVID-19,[3,5–7] but the viral infection leads itself to CV complications or exacerbation of pre-existing CVD.[6,7] particularly in the geriatric population.[8]

PATHOPHYSIOLOGY

COVID-19 and Cardiovascular System: Hypothesis of Interaction and Mechanisms of Damage

COVID-19 interacts with various systems, being responsible for a wide spectrum of clinical manifestations. Angiotensin converting enzyme-2 (ACE2) has been demonstrated to be the SARS-CoV-2 cell entry receptor, after activation of the viral surface spike protein S by transmembrane protease serine 2 (TMPRSS2).[9] ACE2 is highly expressed in the lung (principally type II alveolar cells), but has also been found in multiple tissues, including heart, intestinal epithelium, vascular endothelium and kidneys.[6] Relevantly, by cleaving angiotensin II (Ang II), ACE2 generates Ang 1-7, which counteracts the pro-inflammatory and pro-oxidant effects of Ang II.[10,11]

Beyond direct cell damage due to viral infiltration, SARS-CoV-2 seems to downregulate ACE 2 expression and Ang 1-7 production, leading to increased levels of Ang II.[12] Consequently, alveolar apoptosis and fibrosis together with cytokine storm and systemic inflammation can result in acute respiratory distress syndrome (ARDS) and multiorgan dysfunction.[13]

Cardiovascular complications are often observed in patients with COVID-19, especially those with severe manifestations. The mechanisms of cardiac injury remain under investigation, but it has been supposed to involve three possible mechanisms: direct myocardial infection through ACE2 receptors expressed in myocardial tissue, indirect injury due to the systemic inflammatory response and increased cardiac stress due to hypoxemia (Figure 1).[14–16]

Evidence suggests that ACE2 plays a double role in cardiovascular complication of COVID-19. First, ACE2 is largely expressed by myocardial pericytes,[17] therefore representing a potential portal of viral entry, resulting in cellular death and inflammation. On the other hand, viral replication seems to induce ACE2 downregulation.[18] This may alter the ACE/ACE2 balance leading to hyperactivation of the ACE/Ang II/AT1 system, responsible of vasoconstrictive, pro-inflammatory and pro-oxidant effects, potentially culminating in acute heart failure, endothelial dysfunction and intravascular coagulopathy.[19]

The cardiovascular damage mediated by SARS-CoV-2 can also result from the immune-mediated pathway caused by activated T and B cells, leading to a cytokine storm (i.e., interleukin-1 (IL-1), IL-6, and TNF-a)[20] that can exert a negative inotropic ef-

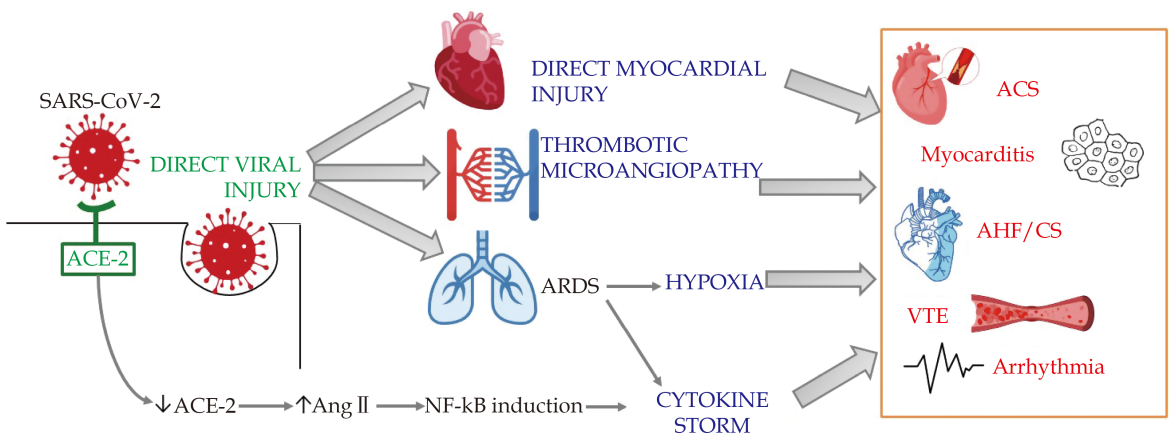

Figure 1 Possible mechanisms of cardiovascular injury due to COVID-19. ACE-2: angiotensin converting enzyme-2; ACS: acute coronary syndrome; AHF: acute heart failure; Ang II: angiotensin II; ARDS: acute respiratory distress syndrome; CS: cardiogenic shock; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VTE: venous thromboembolism.

fect, promote cardiomyocyte apoptosis and fibrosis and induce the release of pro-coagulant factors.[21–23] Generally, the rise in cardiac biomarkers tracks with inflammatory markers elevation, suggesting the relationship between cytokine storm and myocardial injury.[24]

Even though Tavazzi, *et al*.[25] published a case of acute cardiac injury directly linked to SARS-CoV-2 myocardial localization, needs to be clarify if myocardial localization implies a viraemic phase or, alternatively, the migration of infected alveolar macrophages in extra-pulmonary tissues. Regardless the underlying mechanism, inflammatory infiltrates and necrosis were observed in cardiomyocytes of patients with COVID-19 and suspected myocarditis.[26,27]

In addition, prolonged hypoxia due to respiratory failure leads to cardiomyocytes apoptosis,[28] pulmonary hypertension,[29] and pressure overload of the right ventricle. Finally, the endothelial damage caused by SARS-CoV-2 causes vascular injury with severe consequences as acute release of cytokines, plasminogen activator (responsible for high levels of D-dimers) and von Willebrand factor, leading to a pro-thrombotic status and to a thrombotic microangiopathy.[30–33]

Interestingly, older adults and subjects with diabetes and pre-existing CVD have lower levels of ACE2.[34,35] The ACE2 downregulation with subsequent increased levels of Ang II and proinflammatory state predisposes older individuals with cardiovascular comorbidities to experience a more aggressive SARS-CoV2 infection, which can explain the higher CFR reported in the studies.[36] Moreover, aging leads to a disruption of the immune system and to a vascular pro-inflammatory state with dysregulated production of cytokines and other inflammatory mediators, that can further explain the worst outcome of patients affected by COVID-19 disease.[37,38]

Myocardial Injury and Myocarditis

Myocardial injury is generally defined by the elevation of cardiac troponin (cTn) above the 99th percentile of its upper limit of normal (ULN). It can occur in the context of myocardial ischemia (type 1 or type 2 myocardial infarction according to fourth universal definition) or non-ischemic myocardial processes (myocarditis, stress-induced cardiomyopathy or cytokine release syndrome).[39] Irrespectively from the underlying mechanism, cTn elevation was observed in 7.2% to 17% of hospitalized patients with COVID-19.[6,40] and has important prognostic implications. Indeed, as showed in several observational studies (Table 1) troponin elevation among patients hospitalized with COVID-19 is associated with higher risk of mortality, especially in elderly with an history of CVD.[41] The pattern in the rise of cTn levels is also significant: various reports from China showed that cTn values for survivors did not change significantly during follow-up, while they continued to rise until death in non-survivors.[6,28]

In absence of obstructive coronary artery disease, whether the myocardial injury is secondary to oxygen supply-demand imbalance (Type 2 MI), acute myocarditis, stress cardiomyopathy or cardiac involvement in cytokine release syndrome is a challenging issue. Despite some argued that up to 7% of COVID-19– related deaths were attributable to myocarditis,[42] the prevalence of acute myocarditis among COVID-19 patients is still unclear.[43] The Chinese National Health Commission firstly reports autopsy specimens characterized by degenerated and necrotized cardiomyocytes and monocytes, lymphocytes and/or neutrophils in the myocardium,[44] making a diagnosis of suspected myocarditis. Considering that in the clinical scenario of COVID-19 patients cardiac magnetic resonance or endomyocardial biopsy are rarely feasible, the diagnosis of myocarditis is mainly based on troponin elevation in association with echocardiographic abnormalities and ECG changes compatible with acute myocarditis.[45] Cases of acute cardiomyopathies with clinical, echocardiographic and ECG features of Tako-Tsubo syndrome have also been reported, especially in elderly individuals and in critically ill patients with prolonged mechanical ventilation.[46,47]

Acute Coronary Syndrome

Despite the effects of COVID-19 on acute coronary syndromes (ACS) is still under investigation, it is known that profound systemic inflammatory responses may contribute to destabilize plaques in COVID-19 patients.[48] In this regard, Kwong *et al*.

Table 1 Studies exploring relationship between myocardial injury and mortality in patients with COVID-19.

First Author	Number of patients myocardial injury/total (%)	Definitionof myocardial injury	Age, mean ± SD or median (IQR)	Impact of myocardial injuy on outcomes
Aquino[105]	73/254 (29%)	Hs-cTnI > 99th URL	53.8 ± 12.7	Multivariate cox proportional hazards analysis showed that primary endpoint (mortality) is determined by several variables including myocardial injury (OR = 3.764, 95% CI: 1.307–10.838; *P* = 0.014).
Arcari[106]	39/103 (38%)	Hs-cTnI > URN	79 ± 13	In-hospital death is 11% in patients with Hs-troponine < URN and 31% in patients with Hs-Troponine > URN (*P* = 0.012).
Barman HA[27]	150/607 (24.7%)	Hs-cTnI > 99th percentile URL	68.5 ± 13.4	Mortality rate is higher in patients with cardiac injury *vs.* patients without myocardial injury (42% *vs.* 8%; *P* < 0.01).
Cipriani[107]	41/109 (38%)	Hs-cTnI > 99th URL	71 (60–81)	Compared with survivors, non-survivors presented with higher median levels of Hs-cTnI (64 *vs.* 6 ng/L, *P* < 0.001).
Du[108]	NA/179 (NA)		57.6 ± 13.7	Univariate and multivariate logistic regression analysis revealed that cardiac troponin I ≥ 0.05 ng/mL (OR = 4.077, 95% CI: 1.166–14.253; *P* < 0.001) is associated with an increase in risk of mortality.
Guo[109]	52/187 (27.8%)	TnT > 99th percentile URL	58.5 ± 14.66	TnT elevation is associated with increased risk of mortality (59.6% *vs.* 8.9%, *P* < 0.001).
Lala[41]	985/2,736 (36%)	TnI > 0.03 ng/mL	66.40 ± 15.80	TnI > 0.03 to 0.09 ng/mL (*n* = 455; 16.6%) → significantly associated with death (adjusted HR: 1.75; 95% CI: 1.37 to 2.24; *P* < 0.001). TnI > 0.09 ng/dL; *n* = 530; 19.4%) → significantly associated with higher risk (adjusted HR = 3.03; 95% CI: 2.42 to 3.80; *P* < 0.001).
Li[24]	181/2068 (9%)	Hs-cTnI > 99th URL	63 (51- 70)	When compared to non-critically ill patients critically ill have more frequent cardiac injury on admission (30.3% *vs.* 2.3%, *P* < 0.001), with increased mortality during hospitalization (38.4% *vs.* 0%, *P* < 0.001).
Lombardi[110]	278/614 (45.3%)	TnT or TnI > 99th percentile URL	64±13.6	Elevated troponin levels were associated with an increased in-hospital mortality (37% *vs.* 13%; HR = 1.71 [95% CI: 1.13–2.59]; *P* = 0.01 via multivariable Cox regression analysis), and this is independent from concomitant cardiac disease.
Lorente-Ros[111]	147/700 (21%)	TnI > 99th percentile URL	66.76 ± 15.7	cTnI is associated with worse clinical outcomes, including all-cause mortality within 30 days (45.1% *vs.* 23.2%; *P* = 0.005).
Karbalai[112]	118/386 (30%)	Hs-cTnI > 99th URL	59 ± 16	The development of cardiac injury is significantly associated with a higher in-hospital mortality rate compared to those with normal troponin levels (40.9% *vs.* 11.1%, *P* < 0.001).
Majure[113]	1821/6247 (29%)	Hs-cTnI > 99th URLTnT > 99th percentile URLHs-cTnI > 99th URL	66 (56–77)	Patients with elevated troponin have significantly increased odds of death for mildly elevated compared with normal troponin (adjusted OR = 2.06; 95% CI: 1.68–2.53; *P* < 0.001).
Nie[114]	103/311 (33%)	TnI > 99th percentile URL	63 (54–70)	Multivariable logistic regression analysis identified cTNI concentration (OR = 1.92 [95% CI: 1.41–2.59]) as one of the independent risk factors for death in patients with COVID-19.
Qin[115]	95/1462 (6.5%)	Hs-cTnI > 99th percentile URL	57 (45–66)	Elevation of hs-cTnI is associated with increased 28 days mortality (adjusted HR 7.12 ([95% CI: 4.60–11.03]; *P* < 0.001).
Stefanini[116]	90/397 (23%)	Hs-TnI > 99th percentile URL	67 (55–76)	The rate of mortality is higher in patients with elevated hs-TnI (22.5%, OR = 4.35, 95% CI: 1.72 to 11.04).
Shi[69]	106/671 (15.8%)	TnI > 99th percentile URL	63 (50–72)	TnI > 0.026 ng/mL is associated with increased risk of in-hospital mortality (adjusted OR = 4.56; 95% CI: 1.28–16.28).
Shi[117]	82/416 (19.7%)	TnI > 99th percentile URL	64 (21–95)	TnI elevations is associated with increased mortality (51.2% *vs.* 4.5%, *P* < 0.001) also after multivariable adjustment (adjusted HR = 3.41; 95% CI: 1.62–7.16).
Tan[118]	NA/115 (NA)	NA	63 (55–70)	Troponin [HR = 9.02 (95%CI, 3.02, 26.97)] is an independent predictors for patients' prognosis.
Wei[119]	16/101 (16%)	Hs-TnT > 99th percentile URL	49 (34–62)	Log hs-TnT is associated with disease severity (OR = 6.63, 95% CI: 2.24 to 19.65.
Woo[120]	NA/415 (NA)	Hs-cTnI > 99th URLHs-cTnI > 99th URL	66 (54–77)	Elevated troponin is associated with a higher rate of mortality (37.2% *vs.* 14.8%, *P* < 0.001).
Yang[121]	45/463 (10%)	Hs-cTnI > 99th URL	60 (50-69)	Multivariable regression showed increasing odds of in-hospital critical-ill events associated with hypersensitive cTnI greater than 0.04 ng/mL (OR = 20.98,95% CI: 3.51–125.31).

Hs-TnI: high sesnitive troponone I; NA: not available; TnI: Troponine I; TnT: troponine T; URL: upper range limit; URN: upper range normality.

demonstrated that patients with acute respiratory infections are more prone to develop acute MI after influenza and after non-influenza viral illnesses including other coronavirus species.[49] Moreover, inflammation promotes a prothrombotic state, which could further increase the risk of microangiopathy[50] and coronary thrombosis at sites of plaque disruption.[51] As already mentioned, although reports suggest that cTn elevation in COVID-19 may be related more to myocardial injury or type 2 MI than to type 1 MI, more data are needed to properly understand all mechanisms that may induce ACS in SARS-CoV-2 infection.[52] On the other hand, as a side effect of COVID-19, the ongoing pandemic has stressed the public opinion and the emergency system to the point that activation of the Emergency Services and reperfusion therapy have been systematically delayed in STEMI, leading to increased rates of out of hospital cardiac arrest[53] and increased mortality across the ACS spectrum.[54]

Arrhythmia

Viral infections are associated with metabolic dysfunction, myocardial inflammation, and activation of the sympathetic nervous system, all of which predispose to cardiac arrhythmia. In a report on 138 hospitalized COVID-19 patients, the incidence of arrhythmia is about 17%, which ranked only second among serious complications after ARDS.[40] Arrhythmia was observed in 7% of patients who did not require ICU treatment and in 44% of subjects who were admitted to an ICU.[50] A study from Bhatla, *et al*.[55] concluded the cardiac arrests and arrhythmias are likely the consequence of systemic illness and not solely the direct effects of COVID-19 infection.

In the setting of supraventricular arrhythmias, as assessed by Colon *et al*, compared with patients without atrial tachyarrhythmias, those with atrial fibrillation, flutter, or tachycardia tended to be older with higher concentrations of CRP and D-dimer (55 ± 17 vs. 64.6 ± 12.8, $P = 0.028$).[56]

Heart Failure

Although few data exists on incidence of heart failure in COVID-19 patients, as reported by Zhou, *et al*.,[6] acute heart failure (AHF) was observed in 23.0% of infected patients and was more common in patients who died compared to survivors (51.9% *vs.* 11.7%). Similar rates were observed in other studies.[57] Whether AHF is most commonly due to exacerbation of pre-existing cardiovascular disease or to new cardiomyopathy (such as myocarditis or stress cardiomyopathy) is not clear. In elderly individuals with left ventricular (LV) dysfunction, coronary artery disease, hypertension or diabetes, AHF is more likely to result from the exacerbation of these conditions, sometimes previously undiagnosed.[58] Moreover, diastolic LV dysfunction is a common condition related to senescence,[59] particularly in patients with hypertension, overweight and chronic obstructive pulmonary disease (COPD). These patients are prone to develop heart failure with preserved ejection fraction (HFpEF), triggered by fever, tachycardia and impaired renal function.[58] Routine monitoring of N-terminal pro-brain natriuretic peptide (NTproBNP) or BNP levels may be helpful to timely detection of patients with LV systolic or diastolic dysfunction, which is essential to avoid aggressive fluid replacement.[42] However, since natriuretic peptides circulation levels are significantly influenced by age,[60,61] their diagnostic and prognostic accuracy may be limited in the elderly population.[61,62] Therefore, diagnostic age-adjusted cutoff values have been proposed[62,63] and should be taken into account in the management of these patients.

Coagulation Abnormalities

COVID-19 patients are at increased risk of thrombotic complications such as venous and arterial thromboembolism and microvasculature thrombosis. Data suggests that rates of thrombotic complications may involve almost 1/3 of critically ill patients.[64] Hypercoagulability in COVID-19 is primary the results of direct effects of the virus able to infect endothelial cells and cause perturbation of the cellular homeostasis,[65] leading to plasminogen activator release, and high molecular size multimeric von Willebrand factor causing thrombotic microangiopathy.[30] Furthermore, severe inflammatory response, critical illness, and underlying traditional risk factors may all predispose to thrombotic events, similar to prior coronavirus outbreaks.[66] Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in critically ill

patients with COVID-19, especially when admitted to ICU (Table 2). Case series of hospitalized patients with COVID-19 reported VTE in 20% to 85% of ICU-patients and in 2% to 15% of non-ICU patients.[67–72] In some studies, VTE was associated with an increased mortality rate[73,74] and longer duration of mechanical ventilation.[75] Whereas prophylactic anticoagulation is generally effective in preventing DVT, many patients experienced PE despite adequate prophylaxis, usually without evidence of DVT.[64] This evidence, together with autopsy studies descriptions of thrombotic microangiopathy in pulmonary and systemic vessels,[33] suggest that pulmonary thrombi, rather than emboli from peripheral veins, may be the hallmark of severe COVID-19.[76,77]

Table 2 Prevalence of VTE in hospitalized patients with COVID-19.

First Author	Patient population	VTE *n*/total (%)	Age, mean ± SD or median (IQR)	All cause mortality, *n*/total(%)
Bilaloglu[73]	ICU and non-ICU	ICU: 113/829 (13.6%) Non-ICU: 90/2505 (3.6%)	64 (51–57)	817/3334 (24.5%)
Criel[122]	ICU and non-ICU	ICU: 4/30 (13.3%) Non-ICU: 2/52 (3.8%)	ICU: 64.5 ± 11.8 Non-ICU: 63.6 ± 14.4	NR
Cui[123]	ICU	20/81 (24.7%)	VTE: 68.4 ± 9 Non-VTE: 57.1 ± 14	8/81 (10%)
Demelo-Rodriguez[124]	Non ICU, with D-dimer > 1000 and CUS screening	23/198 (11.6%)	DVT: 66.7 ± 15.2 Non-DVT: 68.4 ± 14.4	NR
Desborough[125]	ICU	10/66 (15.2%)	VTE: 54 (45–63) Non-VTE: 59 (52–57)	20/66 (30.3%)
Dubois-Silva[126]	Non ICU	8/171 (4.9%)	PE: 67 (58–74)	NR
Fraissè[127]	ICU	31/92 (33.7%)	VTE: 62 (54–71) Non-VTE: 61 (55–69)	38/92 (41%)
Helms[128]	ICU	28/150 (18.7%)	63 (53–71)	NR
Hippensteel[75]	ICU	24/91 (26.1%)	VTE: 55 ± 13 Non-VTE: 57 ± 17	39/91 (42.9%)
Klok[64]	ICU	68/184 (37%)	64 ± 12	41/184 (22%)
Kolelait[129]	ICU and non-ICU, all underwent to LE venous duplexes	18/135 (13.3%)	DVT: 59 (49–64) No-DVT: 64 (53–73)	DVT: 2/18 (11.1%) Non-DVT: 18/117 (15.4%)
Llitjos[72]	ICU	18/26 (69%)	68 (51.5–74.5)	3/26 (12%)
Lodigiani[71]	ICU and non-ICU	ICU:8/61 (13%) Non-ICU: 12/327 (3.7%)	ICU: 61 (55–69) Non-ICU: 68 (55–77)	92/388 (23.7%)
Longchamp[130]	ICU	8/25 (32%)	68 ± 11	5/25 (20%)
Mestre-Gomez[131]	Non-ICU	PE: 29/452 (6.4%)	PE: 65 (56–73)	PE: 1/29 (3.4%)
Middeldorp[132]	ICU and non-ICU	ICU: 39/75 (52%) Non-ICU: 4/123 (3.3%)	VTE: 62 ±10 Non-VTE: 60 ±15	NR
Nahum[133]	ICU	27/34 (79%)	VTE: 62.9 ±7.9 Non-VTE: 59.9 ±11.2	NR
Poissy[134]	ICU	PE: 22/107 (20.6%)	PE: 57 (29–80)	NR
Soumagne[135]	ICU	79/375 (21%)	PE: 61.1 ± 9.1 Non-PE: 63.9 ±10.3	PE: 16/55 (29%) Non-PE: 118/320 (37%)
Tavazzi[136]	ICU	12/54 (22.2%)	VTE: 68 ± 7	NR
Thomas[137]	ICU	6/63 (9.5%)	59 ±13	NR
Wang[138]	ICU and non-ICU	DVT: 19/88 (21.6%)	61.5 (55–68.8)	DVT: 5/19 (26.3%) Non-DVT: 13/69 (18.8%)
Zhang[74]	Non-ICU	67/159 (42.1%)	VTE: 67 ± 12 Non-VTE: 59 ± 16	VTE: 23/67 (34%) Non-VTE: 9/92 (9.7%)

DVT: deep vein thrombosis; ICU: intensive care unit; LE: lower extremities; NR: not reported; PE: pulmonary embolism; VTE: Venous thromboembolism.

Arterial thrombosis was also reported as a complication of COVID-19. A large case series from New York, including 3 334 patients, reported stroke in 1.6%, myocardial infarction in 8.9% and other arterial thrombotic events (i.e., acute limb ischemia, upper extremity arterial thrombosis, renal and splenic infarcts) in 1%. As predictable, arterial thrombotic events were associated with increased mortality (adjusted HR = 1.99; 95% CI: 1.65–2.40).[73]

The most common laboratory test abnormalities found in COVID-19 patients are thrombocytopenia and increased D-dimer levels, which are associated with a higher risk of requiring mechanical ventilation, ICU admission, or death.[66] In a multicenter retrospective cohort study from China, elevated D-dimer levels (> 1 g/L) were strongly associated with in-hospital death, even after multivariable adjustment.[6] As assessed by Tang, *et al*.[78] in a retrospective study of 183 COVID-19 patients, those who died presented levels of D-dimer and fibrin degradation products significantly increase (3.5- and ~1.9-fold increase, respectively) and PT prolongation. In addition, 71% of patients who died fulfilled the International Society on Thrombosis and Hemostasis criteria for DIC, compared with only 0.6% among survivors.

TREATMENT CONSIDERATIONS

Currently, there is no specific therapy against SARS-CoV-2, although many medications are under investigation. Therefore, we focused our review on supportive treatments and the related concerns in elderly COVID-19 patients, due to their comorbidities and polypharmacotherapy.

Glucocorticoids

Glucocorticoids are indicated for severely ill patients receiving respiratory support, as they counteract the immune system hyperactivation and mitigate the inflammatory multiorgan damage due to COVID-19.[79] This recommendation originates from several clinical trials, especially the RECOVERY Trial,[80] which showed that treatment with dexamethasone at a dose of 6 mg once daily reduced mortality in COVID-19 patients on supplemental oxygen or ventilatory support. Data are lacking about the possible role of glucocorticoids in preventing and treating the cardiovascular complications of COVID-19, which may constitute a supplemental indication to this treatment. Of note, in elderly patients, the benefits of a steroid therapy may be outweighed by higher risk of superinfections, induction or worsening of underlying psychiatric disorder and metabolic side effects (i.e., fluid retention, hypertension and hyperglycemia), which can precipitate pre-existing comorbidities including cardiovascular disease.[81] Caution should be used about corticosteroid administration in elderly STEMI patients with subacute admission, not a rare case during the current pandemic, due to the increased risk of myocardial rupture.[82]

Anticoagulants

Due to the high rate of venous and arterial thromboembolism, anticoagulation is a cornerstone in the management of COVID-19 patients. According to current guidelines,[83] all hospitalized patients should receive low-molecular-weight heparin (LMWH) at doses registered for prevention of venous thromboembolism, the only which have demonstrated an association with reduced risk of death.[84] LMWH is also known to exert anti-inflammatory and immunomodulant properties, by protecting glycocalyx from shedding.[85]

Anticoagulant interventions at increased doses (intermediate or therapeutic) have been proposed and used in patients hospitalized for COVID disease,[64] based on the hypothesis that higher dose of heparin could reduce mortality and morbidity by improving anti-inflammatory activity and decreasing the incidence of local thrombosis in vital organs, therefore preventing their disfunction.

Comparisons between different anticoagulant dosing strategies are under investigation in several randomized controlled trials (RCTs), which have been described in a recent scoping review.[86] Of note, in three trials (REMAP-CAP, ACTV-4 and ATTAC) investigating therapeutic doses of anticoagulant drugs in COVID-19 patients, enrollment of ICU patients has been recently paused because of futility and safety concerns.[87]

Since high-quality data from randomized controlled trials will provide consistent evidence, any different approach compared to a thromboprophylaxis regimen, should be avoided in patients without a clear indication to full dose anticoagulant therapy.

An algorithm for the antithrombotic management of patients with SARS-CoV2 infection, with and without pre-existing indications to antithrombotic treatment, is suggested in Figure 2.

Currently, there is no sufficient evidence to recommend for or against intermediate and therapeutic dose regimens, which are obviously affected by a higher risk of bleeding.

COVID-19 Specific Treatments and CV System: Side Effects and Drug-Drug Interaction

Several clinical trials on antiviral and immunomodulant agents are currently ongoing. Advanced age is generally not an exclusion criterion *per se*, but patients with severe comorbidities (i.e., advanced liver, heart, or kidney disease) are usually excluded. Potential interactions of these therapies with the cardiovascular system and with other cardiovascular medications are summarized in (Table 3).

Cardiovascular Drugs and COVID-19: Role of RAAS Inhibitors

Besides the cardiovascular effects of SARS-COV-2 treatments, early concern had been raised about the potential involvement of some cardiovascular drugs in the natural history of COVID-19. In particular,

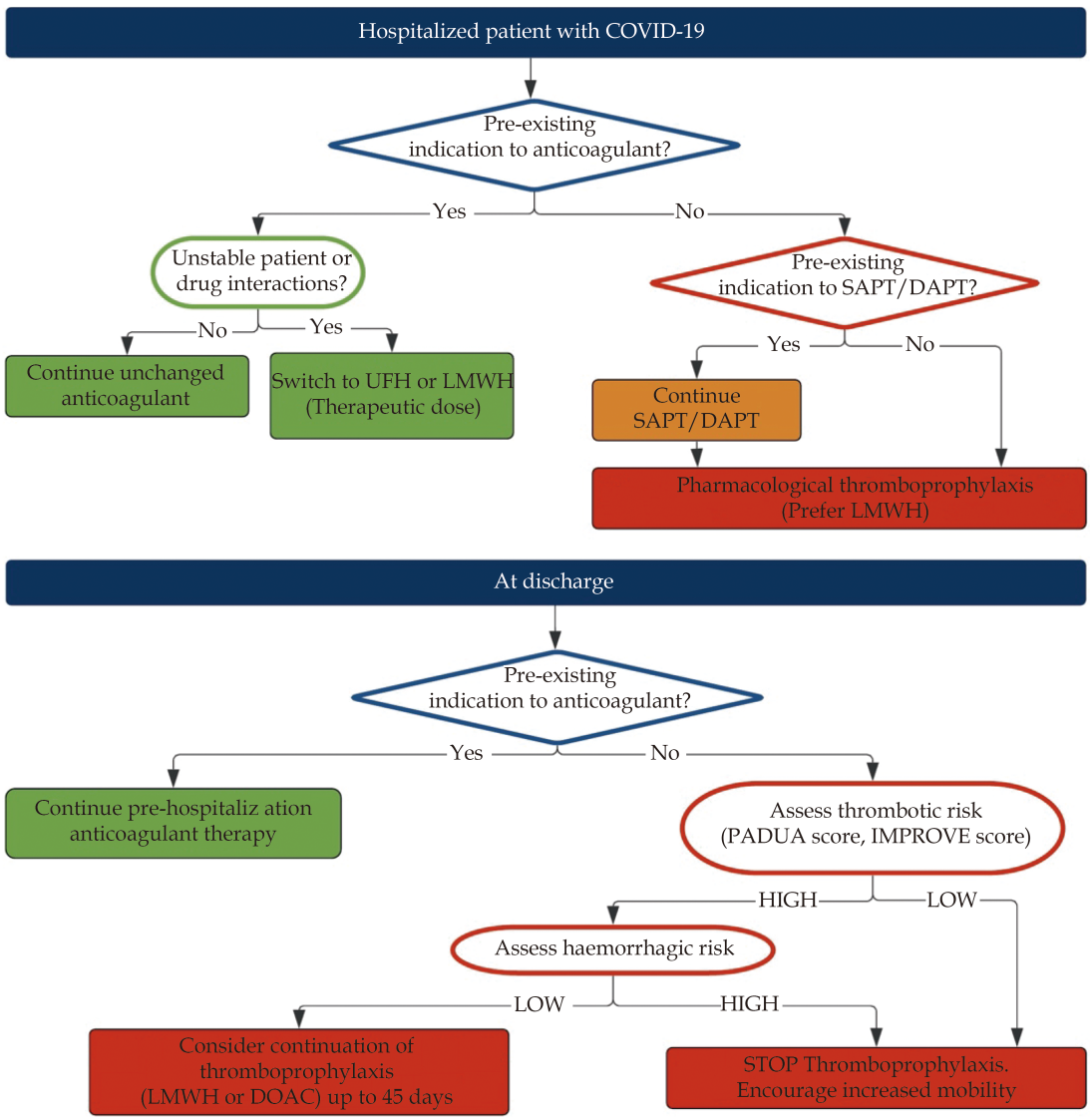

Figure 2 Flow chart of antithrombotic therapy in patients with COVID-19. Proposed algorithm for the management of antithrombotic therapy during hospitalization and after discharge of patients with COVID-19. DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; SAPT: single antiplatelet therapy; UFH: unfractioned heparin.

Table 3 Proposed COVID-19 treatment: concluded RCTs' population age and CV interactions.

Drug	Clinicaltrials.gov identifier	Age, mean ± SD or median (IQR)	Mechanism of action	CV side effects	CV drug interactions	Recommendations
Chloroquine/ hydroxychloroquine	NCT04316377 NCT04328961 NCT04332991 NCT04323527 NCT04322123 NCT04491994	62 (50-73) 39 (27–51) 57 (44–68) 51.1 ± 13.9 50.3 ±14.6 18–65	Blockade of virus cell entry by changing endosomal pH	QTc prolongation, ventricular arrhythmias, AV/bundle branch blocks, direct cardiotoxicity/ worsening of underlying cardiomyopathies	↑Concentration Beta-blockers (CYP2D6 inhibition), and Digoxin (P glycoprotein inhibition), QTc-prolonging antiarrhythmics	Monitor ECG Monitor digoxin levels Avoid in case of cardiomyopathy, conduction disorders, ventricular arrhythmias, prolonged QTc, concomitant QTc/PR-prolonging drugs
Lopinavir/Ritonavir	NCT04276688 NCT04252885	52 (32–62) 49.4 ± 14.7	Protease inhibition	QTc prolongation, AV blocks, ↑ serum cholesterol	↑Concentration DOACs, statins, ticagrelor, ranolazine, ivabradine (CYP3A4 inhibition); ↓ concentration Warfarin (CYP2C9 induction); ↑concentration digoxin (P glycoprotein inhibition)	Monitor ECG; avoid in case of structural heart disease and conduction disorders. Dabigatran and Warfarin: administer with caution; Apixaban half dose (do not administer if required 2.5 mg bid); edoxaban/rivaroxaban contraindicated; avoid statins; monitor digoxin level; antiplatelets: prefer prasugrel if not contraindicated
Ribavarin	NCT04276688	52 (32–62)	RdRP inhibition	Hemolytic anemia	↓Concentration of Warfarin	Use with caution in ischemic heart disease. Monitor INR
Remdesivir	NCT04280705 NCT04292899 NCT04292730 NCT04401579	58.9 ± 15 61 (50-70) 57 (46–66) 55.4 ± 15.7	RdRP inhibition	Unknown	Unknown	-
Tocilizumab	NCT04356937	59.8 (45–69)	IL-6 receptor inhibition	Hypertension, ↑ serum cholesterol	↑ Metabolism of anticoagulants, statins, amiodarone, antiplatelets	Monitor ECG Monitor INR No dose adjustment required
Sarilumab	NCT04324073 NCT04327388 NCT04322773		IL-6 receptor inhibitor	Unknown	↑ Metabolism of anticoagulants, statins, amiodarone, antiplatelets	Monitor ECG Monitor INR No dose adjustment required
Bevacizumab	NCT04275414		VEGF inhibition	Direct cardiac toxicity vs worsening of cardiomyopathy, hypertension, thromboembolic events	None	Avoid in case of cardiomyopathy/heart failure
Interferon	NCT04276688 NCT04521400	52 (32–62)	Immune system activation	Direct cardiac toxicity vs worsening of cardiomyopathy, conduction disorders	↑ Concentration of Warfarin	Avoid in case of structural heart disease/conduction disorders. Monitor INR
Glucocorticoids	NCT04327401 NCT04381936	61 ± 14 66.9 ± 15.6	Reduce inflammation	Fluid retention, hypertension,	↑ Concentration of Warfarin	Monitor BP and INR
Heparins (LMWH or UFH)	NCT04362085 NCT04409834 NCT04444700 NCT02735707 NCT04377997 NCT04372589 NCT04401293 NCT04406389 NCT04394377 NCT04373707 NCT04366960 NCT04360824 NCT04367831 NCT04351724	All RCTs are still recruiting (no concluded RCTs available)	Anticoagulant (Inhibits factor Xa through ATIII activation) + anti-inflammatory (prevents glycocalyx shedding)	Bleeding; HIT	Other anticoagulants; antiplatelets (risk of bleeding)	Prophylactic doses in all hospitalized patients; Continue concomitant antiplatelet drugs; Monitor blood cell count and renal function

ACS: acute coronary syndrome; ADHF: acute decompensated heart failure; ATIII: antithrombin III; AV: atrio-ventricular; BP: blood pressure; CV: cardiovascular; CYP: cytochrome; DOAC: direct oral anticoagulant; ECG: electrocardiogram; HIT: heparin-induced thrombocytopenia; INR: international normalized ratio; IL-1: interleukin-1; IL-6: interleukin-6; LMWH: low molecular weight heparin; QTc: corrected QT interval; RCT: randomized clinical trials; RdRP: RNA-dependent RNA polymerase; VEGF: vascular endothelial growth factor.

since ACEi and ARBs have been shown to upregulate ACE2 expression in animal models,[88] it had been supposed that these drugs might cause a higher susceptibility and/or a more aggressive course of COVID-19.[89,90] On the other hand, RAAS inhibitors could exert a beneficial effect by counteracting the pro-inflammatory role of Angiotensin II, as previously discussed, despite lack of evidence from clinical studies. Based on available data,[90–92] major cardiology scientific societies recommend the continuation or initiation of ACEi/ARBs when indicated.[93,94]

Therapeutic Antibodies

Antibodies taken from the blood of recovered patients serve as a therapeutic alternative that is currently under study. One of the first studies on the use of plasma in the treatment of patients with SARS-CoV2 infections was conducted on 5 COVID-19 patients[95] and followed by other studies, mostly on a small number of patients.[96] The main results of the observational studies conducted reported clinical and survival improvement in all patients after the end of the additional intervention with plasma and hyperimmune immunoglobulins. However, as recently demonstrated by RCTs, the use of convalescent plasma therapy in addition to standard treatment in patients with moderate to severe pneumonia due to COVID-19 did not reduce mortality or improve other clinical outcomes as compared with placebo.[97,98]

Vaccine

Several observations support the concept that vaccination has the potential to prevent SARS-CoV-2 infection. In non-human primate studies, infection with wild-type SARS-CoV-2 virus protected against subsequent reinfection, indicating that infection can result in protective immunity.[99] Vaccination of primates also protected against viral challenge allowing development of functional neutralizing antibodies correlated with protection.[100] Epidemiologic studies in humans have also suggested that neutralizing antibodies are associated with protection from infection.[101] SARS-CoV-2 vaccines are being developed using several different platforms.[102] Some of these are traditional approaches, such as inactivated virus or live attenuated viruses. Other approaches employ newer platforms, such as recombinant proteins and vectors.[102] Some platforms, such as RNA and DNA vaccines, have never been employed in a licensed vaccine. Recently mRNA vaccines BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) and 1 273 (Moderna COVID-19 Vaccine) have been granted emergency use authorization (EUA) for prevention of COVID-19. Of note, responses in participants ≥ 65 years old to mRNA vaccine (BNT162b2 Pfizer-BioNTech) were generally lower than in younger subjects, but still comparable to titers in convalescent plasma.[103] As well as mRNA 1 273 (Moderna COVID-19 Vaccine) vaccination in adults older than 55 years also elicited immune responses that were comparable to those seen in the younger populations.[104]

CONCLUSIONS

From the beginning of the COVID-19 outbreak, the scientific world devote attention to the cardiovascular implication of SARS-COV-2 infection. Since cardiovascular biomarkers are recognized as prognostic indicators, the effort to complete understand the mechanisms of this interaction is still crucial. Despite current evidence of several interaction between viral infection and cardiovascular disease, the consideration for treatments, including ACEI or ARB, immunosuppression/modulation and anti-coagulation continue to evolve. Elderly people have been the proportion with worst outcome among those affected by SARS-CoV-2 infection. However, the need of turn off the effects of the immune system hyperactivation by therapy should adequately counterbalance the excess of adverse effects in the elderly population.

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