Cardiovascular diseases challenges in COVID-19 pandemic.

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Abstract

On 31st December, when the world was getting ready for the New year celebration, China reported its first case of a novel SARS-CoV2 virus. Within months of the outbreak, it has spread to the entire globe, with affected numbers reaching million. Like other Medical fields, Cardiologists both as physician and interventionalist are finding themselves in the middle of a battle where the enemy is unknown. In such uncertain times, this paper looks at various issues that we, as Cardiologists, will be confronted with and how we will have to change our practice.

Keywords: Severe acute respiratory syndrome, Coronavirus-2, Cardiovascular disease, Respiratory disease.

Introduction

COVID-19 is the clinical manifestation of infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2). Presentation can vary from asymptomatic (30%-35%), mild disease (35%-40%), Moderate (15%) to severe disease (2%-5%). It mostly presents with respiratory symptoms and, in some patients, leads to pneumonia and acute respiratory distress syndrome and subsequently shock. Mortality is around 3%-5% in major studies [1]. Cardiovascular Disease (CAD) along with obesity, hypertension and diabetes, is an important risk factor for poor prognosis [2].

COVID-19 patients have a prevalence rate of pre-existing CAD in a range of 6% to 25% in various studies [3]. Among patients admitted to ICU, the prevalence was much higher. Patients with cardiovascular comorbidity were more likely to develop cardiac complications. Acute cardiac injury and heart failure were more common in deceased patients. Cardiac biomarkers such as cardiac troponin I, N-terminal pro-brain natriuretic peptide and D-dimer were markedly higher in deceased patients than in recovered patients [4].

Various mechanisms have been postulated for cardiovascular complications in COVID19. Inflammatory myocarditis, systemic pro-inflammatory cytokine responses that directly contributes to plaque rupture through local inflammation, Type II myocardial ischemia as a result of high cardiac demand in severe respiratory disease, elevated D-dimer concentrations indicative of heightened coagulopathy and microvascular thrombosis can be seen [5].

Materials and Methods

Acute coronary syndrome

Acute Coronary Syndrome (ACS) can present as ST-Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI) or unstable Angina [6]. It can be a COVID 19 patient or a patient whose status to COVID 19 is not known. The first step should be to decide whether a conservative or aggressive approach is to be adopted. Chinese cardiovascular society has published a guideline to divide the patient into two groups (Tables 1 and 2).

Table 1. *Patients with severe emergent cardiovascular diseases for whom hospitalization and conservative medical treatment is recommended during COVID-19 epidemic (Source; Chinese cardiovascular society permission taken).*

S.no	Patients with serve emergent cardiovascular diseases
1	Patients with STEMI for whom thrombolytic therapy is indicated*.
2	STEMI patients presenting after exceeding the optimal window of time for revascularization but yet with worsen symptomes , such as severe chest pain, continuous ST-segment elevation or myocardial infaraction-related mechanicals complications.
3	High risk NSTE-ACS patients (GRACE score ≤ 140).
4	Patients with uncomplicated stanford type B aortic dissection#.
5	Patients with acute pulmonary embolism.
6	Patients with acute exacerbation of heart failure.
7	Patients with hypertensive emergency.

Note: STEMI, ST-Segment Elevation Myocardial Infraction; NSTE-ACS, non-ST elevationacute coronary syndrome;GRACE Global Registary of Acute Coronary Events; * The third- generation thrombolytic agents are preferred.
For stanford type A arotic dissection, surgirical treatment is recommended.

Table 2. *Severe cardiovascular diseases requiring urgent or emergent intervention or surgery (Source: Chinese Cardiovascular Society permission taken).*

S.no	Patients with serve cardiovascular diseases
1	Acute STEMI with hemodynamic instability.
2	Life- threating NSTEMI indicated for urgent revascularization.
3	Standford type A or complex type B acute aortic dissection.
4	Bradyarrhythmia complicated with syncope or unstable hemodynamics mandating implantaition of a temporary (beside implantation as far as possible) or if indicated, permanent pacemaker.
5	Pulmonary embolisim presenting with hemodynamic instability for whomregular intravenous thrombolytic therapy might lead to excessively risk of intracarnial bleeding, trans-catheter low-dose thrombolysis in the pulmonary artery may be required.
Note: STEMI, ST-segment elevation myocardial infraction; NSTEMI, Non-ST Segment Elevation Myocardial Infraction.	

ACS patients with suspected/confirmed COVID19 status who need to be taken to cardiac catheterization labs (Cath lab) should be taken with all precaution as aerosol ingestion can occur during intubation or cardiopulmonary resuscitation in any unforeseen situation. Chinese cardiovascular society has recommended

- Self-protection of medical staff following the directives of the infection control department of local hospitals and local health commissions.
- Patient risk assessment of both infection and cardiovascular issues.
- Preferential use of conservative medical therapeutic approaches to minimize disease spread.13 and most importantly preventing Nosocomial Infection which can be as high as 41%. 14 It is also essential to adopt a more conservative strategy in which outcome is already poor [7].

STEMI: Hemodynamically stable STEMI patients, consider thrombolysis (preferably tenecteplase or reteplase) as the treatment of choice. Cardiac catheterization should be considered with proper precaution and PPE only for rescue PCI. High-risk STEMI patients (hemodynamically stable, recurrent arrhythmia, intractable failure) should be considered for primary PCI.

NSTEMI/Unstable Angina (hemodynamically stable) conservative management for patients is recommended.

For patients who cannot be ruled out of COVID 19, a consent from COVID 19 expert panel is a must. Intervention should be done in emergent indication. ACS (hemodynamically stable) with unknown COVID-19 status are treated as potential COVID-19 patients and testing for COVID-19 is recommended [8].

There is no societal decision for asymptomatic or COVID19 status unknown patients; however, the current situation is different from overloaded hospitals and scarce advance care trained health professionals. Whether doing rapid testing in stable or semi-urgent patients is a cost-effective measure (as the supposed risk of transmitting to high-risk hospital patient and valuable scarce qualified personal will be a challenge) will be a debatable issue. Aggressive testing is a policy matter and will have to be considered for an area where residual community transmission is high.

Stable coronary artery disease: Elective revascularization should be delayed. If needed, a heart team should be sought to keep in mind that percutaneous coronary intervention will have a shortened course of hospital stay as compared to coronary artery bypass grafting. No drug therapy is modified. Drug interaction is discussed later [9].

Myocarditis: It can be caused by direct infiltration of the virus but can also be secondary to severe hypoxia and the “cytokine storm” mounted in response to the systemic infection. Some of these manifestations might be, in part, attributable to metabolic disarray, hypoxia, neurohormonal or inflammatory stress. For a confirmed COVID-19 patient, a critical differential to be kept in mind is whether it is myocarditis or Type II myocardial ischemia due to increased demand as a result of respiratory distress. Diagnosis is made by; elevated troponin-I or T, raised NT Pro BNP, sinus tachycardia, extensive QRS/ ST-T changes with no localization, enlarged left ventricle with low Left Ventricular Ejection Fraction (LVEF) and global LV dysfunction on echocardiography. Management is goal-directed standard heart failure medications, ventilatory support and ECMO if needed. Isolated case studies with prednisolone has shown benefit but is not recommended.

Cardiogenic shock: COVID19 patients have responses similar to viral illness-induced Systemic Inflammatory Response Syndrome (SIRS). The primary disorder is hypoxia-related respiratory failure. Some patients develop systemic hyperinflammatory response and vasodilatory shock as the viremia clears. This phase of illness may be accompanied by simultaneous myocardial suppression and cardiogenic shock. This mixed etiology of shock can be challenging to manage. Option of advanced life support, including extra corporeal membrane oxygenation, becomes important [10].

Results and Discussion

Cardiac catheterization labs

For years, there have always been priorities in the cath lab; radiological protection of the team and acting as fast as possible: 'time is life' was the mantra. Today, the first priority is the safety of the organization; a team in quarantine means the inability to save many more patients. Radiological protection is

needed, but it is not enough. It should be combined with adequate protection from the virus.

Two relevant societal statements have come, first from the American college of cardiology and other from Chinese cardiovascular society. Most importantly, cath lab should be equipped with negative-pressure ventilation. If not, available centralized ventilation should be switched off. One lab should be designated for COVID-19 confirmed or suspected cases. Proper PPE should be available. Each lab should have basic stuff like workhorse wire and catheter inside, so the number of entry and exit is restricted. Staff should be limited inside the lab and proper PPE dressing protocol should be there. Infection control committee should be regularly monitoring the protocol. Post-procedure terminal disinfection of the catheterization lab should be performed. Ultraviolet light, exposure to 56°C for 30 min, as well as lipid solvents, such as diethyl ether, 75% ethanol, chlorine-containing disinfectants, peracetic acid and chloroform can all effectively inactivate COVID-19. Chlorhexidine is ineffective [11]. Hydrogen peroxide (3%) spray should be used for air disinfection after the procedure and instruments should be cleaned with 2000 mg/L chlorine-containing disinfecting solution. After 30 minutes, clean water should be used to wipe off the tools.

NT pro-BNP (Brain Natriuretic Peptide) is also a similar nonspecific biomarker when myocarditis, shock and various other factors that come in acute viral illness (Figure 1 and Table 3).

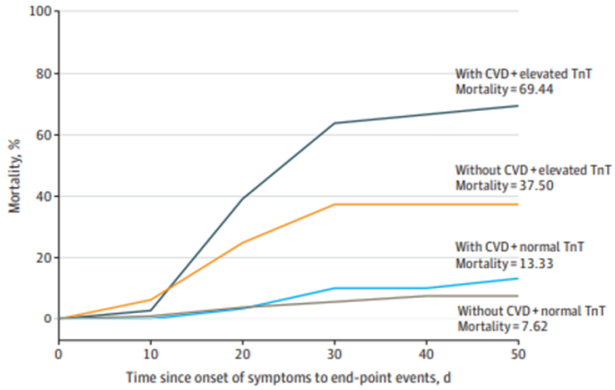

Figure 1. *Mortality of patients with Coronavirus disease 2019 (COVID-19) with/without Cardiovascular Disease (CVD) and with/without elevated Troponin T (TnT) levels. Note:*

Without CVD+normal TnT Mortality=7.62, Without CVD +normal TnT Mortality=13.33,

Without CVD+elevated TnT Mortality=37.50, Without CVD +elevated TnT Mortality=69.44.

Table 3. *Cardiovascular implications of fatal outcomes of patients with Coronavirus disease 2019 (COVID-19) permission taken.*

No. at risk					
without CVD +normal TnT (n=105)	102	86	41	10	0
without CVD +elevate TnT (n=16)	15	12	7	1	0
with CVD +normal TnT (n=30)	29	25	10	4	0
with CVD +elevate TnT (n=36)	34	20	8	2	0

Cardiac biomarker and their importance as a prognostic marker; the fourth universal definition of myocardial infarction states that myocardial injury is characterized by elevated Troponin T (Tn T). Trop T because of inherent nonspecific nature cannot be relied upon in COVID 19 as there can be myocarditis or respiratory compromise, in turn causing myocardial injury. But the important question is what prognostic value it carries? Guo has studied 181 patients in Wuhan. 27% of patients had myocardial injury, which resulted in cardiac dysfunction and arrhythmias. Myocardial injury was significantly associated with worse prognosis in those having high Trop T. This indirectly led to the hypothesis that this group of patients should be subjected to aggressive treatment (Figures 2 and 3).

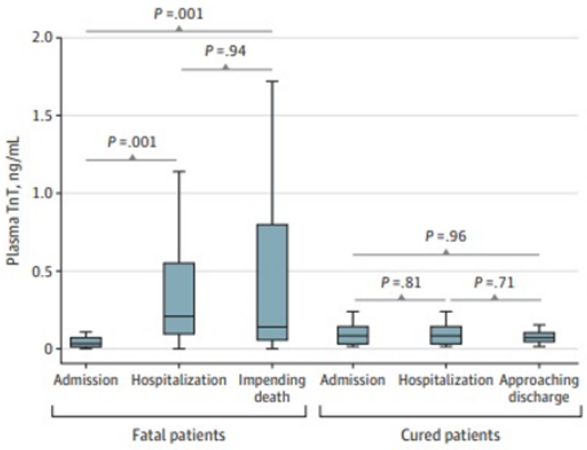

Figure 2. *Dynamic changes of TnT during hospitalization.*

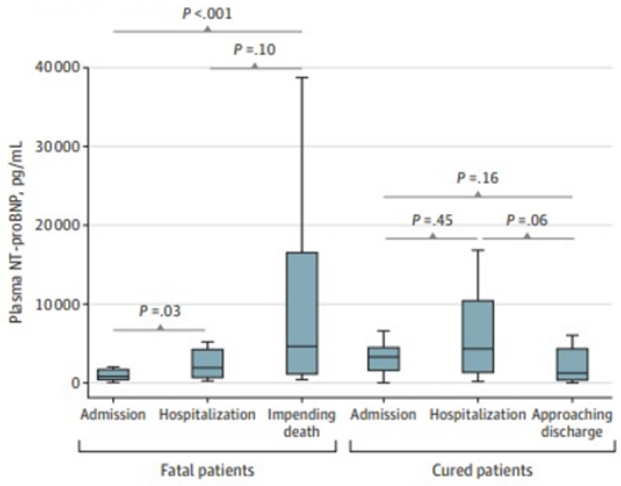

Figure 3. *Dynamic changes of NT-proBNP during hospitalization.*

Renin-angiotensin system inhibitors and COVID19: SARS-CoV2 is a single-strand RNA coronavirus, which enters human cells mainly by binding the Angiotensin-Converting Enzyme 2 (ACE2), which is highly expressed in alveolar cells, cardiac myocytes, the vascular endothelium. (Figure 4).

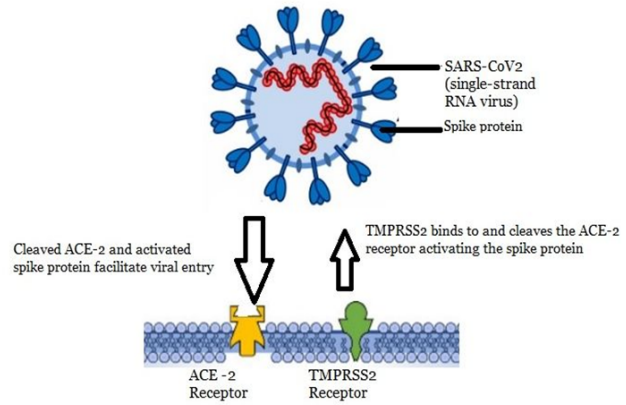

Figure 4. *Spike proteins on the surface of the coronavirus bind to Angiotensin-Converting Enzyme 2 (ACE-2) receptors on the surface of the target cell; the type II Transmembrane Serine Protease (TMPRSS2) binds to and cleaves the ACE-2 receptor. In the process, the spike protein is activated cleaved ACE-2 and activated spike protein facilitates virus entry. TMPRSS2 expression increases cellular uptake of the coronavirus*.

Cardiopulmonary resuscitation: American college of cardiology recommended protocol for COVID19 suspect or confirmed patient will be comprising the same basic and advance life support with few exceptions. PPE is recommended for the person giving CPR. Minimum persons should be ensured, video laryngoscope guided intubation should be preferred, so it does not take much time. For out-of-hospital resuscitation efforts, lay rescuers should perform chest compression-only CPR while wearing a face mask or cloth covering.

Venous Thromboembolic Disease (VTE): COVID-19 may predispose patients to be arterial and venous thrombosis. Hospitalized patients with COVID-19 should undergo risk stratification for VTE prophylaxis. For hospitalized patients (immobilized) with COVID-19 and not in the Disseminated Intravascular Coagulation (DIC) phase, prophylactic doses of anticoagulation can be administered to prevent VTE if pharmacological prophylaxis is contraindicated, as in severe thrombocytopenia it is reasonable to consider intermittent pneumatic compression.

For hospitalized patients with COVID-19 with suspected or confirmed DIC, but no overt bleeding, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH [13].

Drug interaction and patient on antiplatelet; for patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g., percutaneous coronary intervention within the past three months or recent myocardial infarction) in the absence of evidence, decisions for antiplatelet treatment need to be individualized. This also holds for suspected or confirmed DIC without overt bleeding. In general, it is reasonable to continue dual antiplatelet therapy if platelet count >50,000, reduce to single antiplatelet therapy if 25,000 and withhold if below 25000. Drug interactions between antiplatelet agents and investigational therapies is also to be kept in mind while prescribing drugs (Table 4).

Table 4. *Potential drug interactions between antiplatelet agents and investigational therapies for COVID-19.*

Investigational therapies for COVID-19	Mechanism of action	Clopidogrel	Prasugrel	Ticagrelor
Lopinavir/ Ritonavir	Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A4 metabolism increasing lopinavir levels.	CYP 3A4 inhibition (minor pathway): Reduction in clopidogrel active metabolite. Utilize P2Y12 platelet function assays	CYP3A4 Inhibition: Decreased active metabolite but maintained platelet inhibition	Increased effects of ticagrelor. Do notco-administer or, if available, utilize P2Y12 monitoring or consider dose educed ticagrelor.
Remdesivir	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	No dose adjustment	No dose adjustment	No dose adjustment

Other drugs being studied to treat COVID-19 include azithromycin, interferon, methylprednisolone, pirfenidone and ribavirin. Drug-drug interactions between these medications and antiplatelet agents are yet to be identified.

Cangrelor, aspirin, dipyridamole and glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, abciximab) are not known to interact with investigational therapies for COVID-19.

Chloroquine/hydroxychloroquine is being recently promoted in some countries; it alters the endosomal pH required for

virus/cell fusion [14]. It can cause Direct myocardial toxicity and exacerbation of underlying cardiomyopathy altered cardiac conduction AV block, bundle branch block, torsade de pointes, ventricular tachycardia/ fibrillation can occur. It is recommended to get the baseline ECG for seeing QT interval in all patients where it is prescribed.

Conclusion

COVID 19 infection is an evolving global pandemic with significant cardiovascular complications and in times where every hour guidelines are being changed. Cardiology will not remain untouched. The majority of patients admitted with COVID-19 will have underlying Coronary Artery Disease (CAD) or will have a direct or indirect effect of COVID19 infection. Challenge will be thrown if there is residual community infection and a patient reaches for routine or emergent cardiology issues. We do not change our general management of CAD in patients with COVID-19 disease with one exception; we attempt to delay elective revascularization procedures.

Sources of Funding

None.

Disclosures

No disclosures pertinent to this work.

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